THE INFLUENCE OF AMBIENT TEMPERATURE ON BIRTH OUTCOMES IN BRISBANE, AUSTRALIA

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Bachelor of Nursing,

Master of Health Science (Environmental Health)

Submitted in fulfilment of the requirements for the degree of

Master of Applied Science (Research)

School of Public Health

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August 2011

Keywords

Climate change

Competing risks survival model

Pregnancy

Preterm birth

Stillbirth

Seasonality

Temperature

Time-dependent variables

Vulnerable periods

Abstract

Lately, there has been increasing interest in the association between temperature and adverse birth outcomes including preterm birth (PTB) and stillbirth. PTB is a major predictor of many diseases later in life, and stillbirth is a devastating event for parents and families. The aim of this study was to assess the seasonal pattern of adverse birth outcomes, and to examine possible associations of maternal exposure to temperature with PTB and stillbirth. We also aimed to identify if there were any periods of the pregnancy where exposure to temperature was particularly harmful.

A retrospective cohort study design was used and we retrieved individual birth records from the Queensland Health Perinatal Data Collection Unit for all singleton births (excluding twins and triplets) delivered in Brisbane between 1 July 2005 and 30 June 2009. We obtained weather data (including hourly relative humidity, minimum and maximum temperature) and air-pollution data (including PM_{10}, SO_2 and O_3) from the Queensland Department of Environment and Resource Management.

We used survival analyses with the time-dependent variables of temperature, humidity and air pollution, and the competing risks of stillbirth and live birth. To assess the monthly pattern of the birth outcomes, we fitted month of pregnancy as a time-dependent variable. We examined the seasonal pattern of the birth outcomes and the relationship between exposure to high or low temperatures and birth outcomes over the four lag weeks before birth. We further stratified by categorisation of PTB: extreme PTB (< 28 weeks of gestation), PTB (28–36 weeks

of gestation), and term birth (≥ 37 weeks of gestation). Lastly, we examined the effect of temperature variation in each week of the pregnancy on birth outcomes.

There was a bimodal seasonal pattern in gestation length. After adjusting for temperature, the seasonal pattern changed from bimodal, to only one peak in winter. The risk of stillbirth was statistically significant lower in March compared with January. After adjusting for temperature, the March trough was still statistically significant and there was a peak in risk (not statistically significant) in winter.

There was an acute effect of temperature on gestational age and stillbirth with a shortened gestation for increasing temperature from 15 °C to 25 °C over the last four weeks before birth. For stillbirth, we found an increasing risk with increasing temperatures from 12 °C to approximately 20 °C, and no change in risk at temperatures above 20 °C. Certain periods of the pregnancy were more vulnerable to temperature variation. The risk of PTB (28–36 weeks of gestation) increased as temperatures increased above 21 °C. For stillbirth, the fetus was most vulnerable at less than 28 weeks of gestation, but there were also effects in 28–36 weeks of gestation. For fetuses of more than 37 weeks of gestation, increasing temperatures did not increase the risk of stillbirth. We did not find any adverse affects of cold temperature on birth outcomes in this cohort.

My findings contribute to knowledge of the relationship between temperature and birth outcomes. In the context of climate change, this is particularly important. The results may have implications for public health policy and planning, as they indicate that pregnant women would decrease their risk of adverse birth outcomes by avoiding exposure to high temperatures and seeking cool environments during hot days.

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List of abbreviations

BMI:	Body Mass Index
°C:	Degrees Celsius
CI:	Confidence interval
CO:	Carbon oxide
df:	Degrees of freedom
g:	Grams
hPa:	Hectopascal
HR:	Hazard ratio
ELBW:	Extremely low birth weight
LBW:	Low birth weight
NO_2:	Nitrogen dioxide
O_3:	Ozone
PE:	Pre-eclampsia
PM:	Particular matter
PTB:	Preterm birth
ROP:	Retinopathy of prematurity
SGA:	Small for gestational age
SO_2:	Sulphur dioxide
VLBW:	Very low birth weight
VPTB:	Very preterm birth

Statement of original authorship

We have not previously submitted the work contained in this thesis to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Linn Beate Strand

Signature: Linn Beate Strand

Date: 16.08.2011

Acknowledgements

I would like to thank my two supervisors Professor Shilu Tong and Associate Professor Adrian Barnett. Shilu made sure I always stayed on track and encouraged me to work hard. His academic advice and prompt comments on my written work throughout this Master program was highly valuable for my study. For that, I will always be grateful. Adrian spent endless hours teaching me statistics and gave me more support and advice than I ever expected. I will be forever thankful for his patience, flexibility, and willingness to accept new challenges. My supervisors have provided me with an experience in Brisbane that I would never have had otherwise.

I would like to acknowledge School of Public Health and Institute of Health and Biomedical Innovation, QUT, for funding this research project and for all the support in my research.

I would also like to acknowledge Queensland Health Perinatal Data Collection unit for providing the birth files needed to do the analysis and the Department of Environmental and Resource Management for providing weather and air pollution data.

I would like to thank my family and friends for the encouragement and for believing in me, and my fiancée for patiently putting up with my temper during stressful periods and for his unconditional love and support.

Publications generated by the candidate

Strand, LB., Barnett, AG. and Tong, S. (2010). The influence of season and ambient temperature on birth outcomes: a review of the epidemiological literature. *Environmental Research* 111 (3); 451-462.

Strand, LB., Barnett, AG. and Tong, S. (2010). Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes. *BMC Medical Research Methodology* 11:49.

Strand LB, Tong S, and Barnett AG (2010). Maternal exposure to ambient temperature and the risk of preterm birth and stillbirth in Brisbane, Australia. *American Journal of Epidemiology* (in press).

Chapter 1: Introduction

1.1 BACKGROUND

There is broad scientific consensus that the Earth’s climate has recently changed and will continue to change (McMichael, Woodruff & Hales, 2006). The change has resulted in a warming of atmosphere and oceans, rise in sea levels, increased frequency and intensity of storms, droughts, heatwaves, and flooding (Epstein, 2005; IPCC, 2007). Australia is one of the developed nations most likely to be adversely influenced by climate change and the estimated warming by 2030 relative to 1990 is about 1 °C (CSIRO & Australian Bureau of Meteorology, 2007). In Australia, the frequency of hot nights has increased and the frequency of cold nights has declined (Queensland Government, 2008), and each decade since the 1940s has been warmer than the preceding (Australian Bureau of Meteorology, 2010).

Brisbane, the capital of Queensland, Australia, is a city with a subtropical climate that often experiences long periods of warm temperatures. As across the rest of Australia, Brisbane is predicted to have an increased intensity and frequency of heatwaves (Woodruff, McMichael, Butler & Hales, 2006). In addition, Queensland has a tradition of designing houses (Queenslanders) for increased airflow in summer. Houses often have windows that cannot be closed properly, and have poor wall and roof insulation. In 2005, only 43% of Queensland dwellings were insulated (Australian Bureau of Statistics, 2006). During extreme temperatures and heatwaves, airflow may be an insufficient cooling mechanism and encourage an increased reliance on air-conditioning. As a result, there has been a substantial rise in the use of air-conditioning from 33% of households in 1994 to 60% of households in 2005 (Australian Bureau of Statistics, 2007c).

Heatwaves around the world have caused excess mortality and morbidity, and several studies have reported high numbers of deaths and hospital admissions during heatwaves (Basu & Samet, 2002). There was a significant increase in non-external and cardiovascular mortality during a heatwave in Brisbane in February 2004 (Tong, Ren & Becker, 2010). In France, maximum temperatures during the 2003 heatwave were above 36 °C for 9 days causing 15,000 deaths (Fouillet et al., 2006). In Chicago, temperatures during the 1995 heatwave reached 42 °C causing 500–700 deaths (Whitman et al., 1997). Several studies have linked adverse birth outcomes with exposure to high temperatures during the pregnancy (Lajinian, Hudson, Applewhite, Feldman & Minkoff, 1997; Murray et al., 2000). In Greece, Flouris and colleagues reported that gestational age was negatively correlated with mean temperature (Flouris, Spiropoulos, Sakellariou & Koutedakis, 2009). In the United States, researchers reported a strong negative relationship between birth weight and temperature, particularly on days of more than 29.5 °C occurred in the second and the third trimester (0.008% and 0.009% decline in birth weight, respectively, $p < 0.01$) (Deschenes, Greenstone & Guryan, 2009).

One method to generate knowledge about possible environmental factors is to examine seasonal patterns. As early as 400 BC, one of the most important figures in the history of medicine, Hippocrates, suggested that season was associated with disease and the environment was an important factor in people's health and well-being. He was convinced that changes in the seasons, natural influences, and characteristics of climate and location influenced disease risks (Franco & Williams, 2000).

An early study in New York City reported a seasonal variation in stillbirths and fetal malformations between the years 1940 and 1954 (Hewitt, 1962) and numerous studies following Hewitt have found similar seasonal patterns in birth outcomes (Cooperstock & Wolfe, 1986; Keller & Nugent, 1983; Rayco-Solon, Fulford & Prentice, 2005). As seasonal variation has been thoroughly established, more recent research has focused on investigating factors contributing to the seasonality such as nutrition, work-load, air pollution, sunshine (which produces Vitamin D) and temperature (Hansen, Neller, Williams & Simpson, 2006; Tustin, Gross & Hayne, 2004; Wells & Cole, 2002).

On a global scale 9.6% of all births (12.9 million births) were preterm in 2005 (Beck et al., 2010). In Australia the rate of preterm birth (PTB) increased from 7% to 8% between 1991 and 2004 (Figure 1.1), and in 2007, 9% of all babies born in Queensland were premature (Queensland Government, 2009).

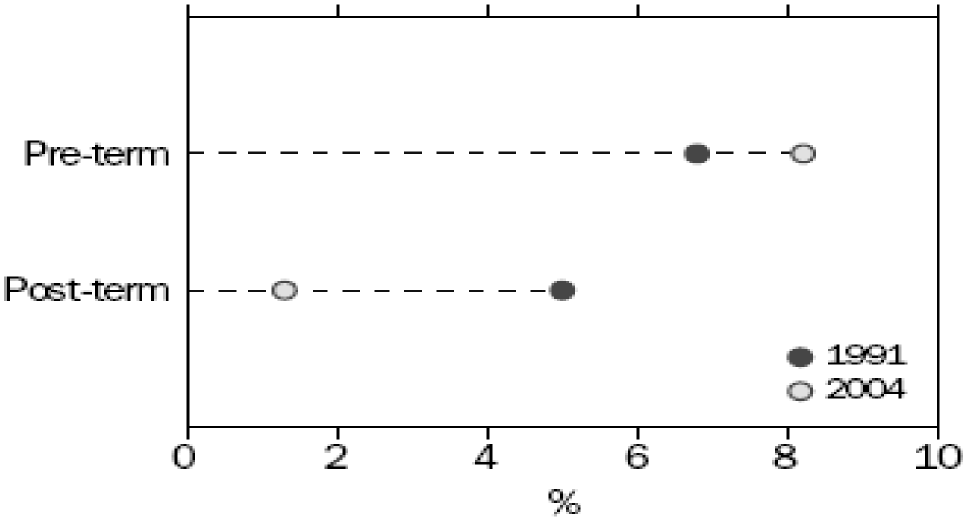


Figure 1.1. Gestation of Australian babies 1991 and 2004. The black dots represent percentage of babies born preterm or post-term in 1991 and the grey dots represent the percentage of babies born preterm or post-term in 2004. (Australian Bureau of Statistics, 2007b).

The World Health Organization, reported that among the 136 million births worldwide in 2004, three million were stillborn (Åhman & Zupan, 2004). Stillbirths account for two thirds of all perinatal deaths in Australia (Australian Institute of Health and Welfare, 2008). In addition, more than 2,000 babies are stillborn each year which corresponds to a rate of 7.4 per 1,000 births (Australian Institute of Health and Welfare, 2006). Stillbirth is a shattering event for the parents and families, and premature babies are at greater risk of poor health, death, require longer periods of hospitalisation after birth, and are more likely to develop disabilities (Goldenberg & Culhane, 2007). Adverse birth outcomes are traumatic for families, socially damaging, and they increase both the cost and demand on the health system (Lindstrom, Winbladh, Haglund & Hjern, 2007). Currently, 30% of stillbirths remain unexplained (Australian and New Zealand Stillbirth Alliance, 2010). In New South Wales, Australia, the main causes of stillbirth during 2002–2004 were unexplained antepartum death (see section 1.4), birth defects and preterm birth (Figure 1.2).

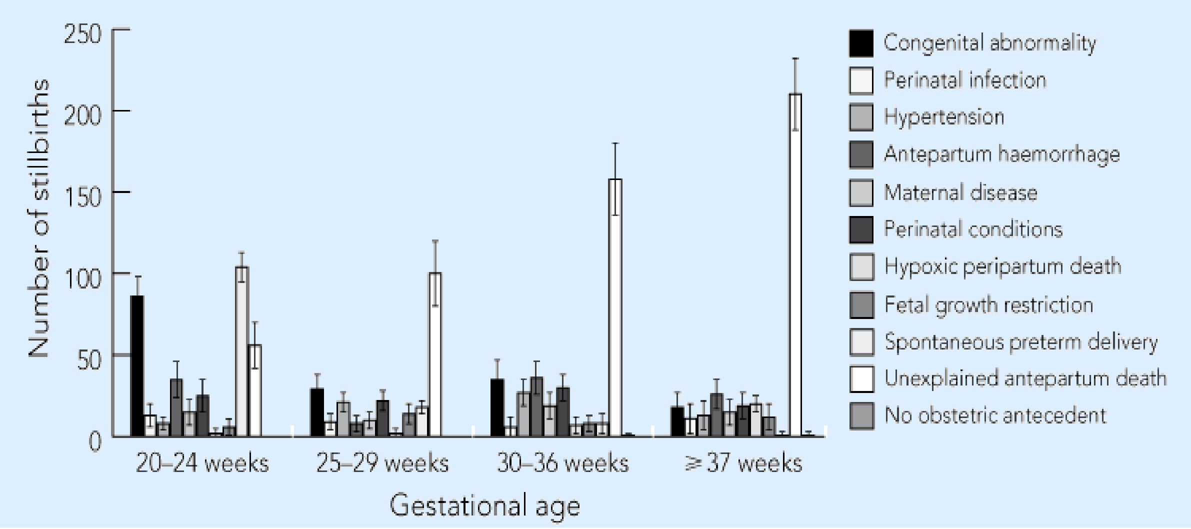


Figure 1.2. Causes of Stillbirth in New South Wales, 2002-2004 (Gordon & Jeffery, 2008).

It is therefore essential to identify the modifiable determinants of stillbirth to reduce the number of stillbirths in Australia. Despite the emotional distress and social cost of stillbirth, there has been little research into stillbirth prevention.

1.2 AIMS AND OBJECTIVES

1.2.1 AIMS

This study aims to identify and quantify the nature and magnitude of the association between temperature variation and birth outcomes after adjustment for the confounding effects of season, humidity and air pollutants in Brisbane, Australia.

1.2.2 OBJECTIVES

- To explore the temporal distribution and seasonal pattern of weather variables and birth outcomes in Brisbane.

- To estimate the associations between temperature and gestational age and stillbirth after adjustment for the confounding factors of season, humidity, air pollution, and important sources of variance including maternal age, previous pregnancies and smoking.

- To identify which gestational age the fetus is most vulnerable to temperature exposure.

1.3 SIGNIFICANCE AND SCOPE

Given the projected climate change worldwide, specifically Australia's expected accelerated change (CSIRO & Australian Bureau of Meteorology, 2007), and the burden of adverse birth outcomes, there is a great need to explore any associations between temperature and birth outcomes. This study will assess the association of exposure to temperature with PTB and stillbirth and it is the first study of its kind in Australia. Previous studies have investigated the effect of season and latitude on birth weight and gestational age (McGrath, Barnett & Eyles, 2005; Rousham & Gracey, 1998), and the influence of temperature variation and air-pollution on PTB (Hansen et al., 2006; Lajinian et al., 1997). No previous studies have investigated the influence of exposure to temperature during the pregnancy on the risk of stillbirth.

1.4 IMPORTANT DEFINITIONS

Abortion - All fetal deaths happening before 20 completed weeks of gestation.

Birth asphyxia - inadequate supply of oxygen immediately prior to, during or just after delivery.

Gestation - the period between conception and birth during which the fetus grows and develops inside the mother's womb.

Gestational age - the time measured from the first day of the woman's last menstrual period/date of conception to the current date/date of birth. It is measured in weeks. A normal pregnancy ranges from 37 to 42 weeks.

Infant mortality - the number of infant deaths (one year of age or younger) per 1,000 live births.

Live birth - The complete extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached (Queensland Health Perinatal Data Collection Unit, 2009).

Low birth weight (LBW) - a birth weight of less than 2,500 grams (World Health Organization, 2007). *Very low birth weight (VLBW)* is defined as < 1,500 grams and *extremely low birth weight (ELBW)* as < 1,000 grams.

Neonatal mortality - *Early neonatal mortality* refers to the death of a live-born baby within the first seven days of life, while *late neonatal mortality* refers to fetal death from seven to 28 days after birth. The sum of these two is the neonatal mortality.

Placental abruption - premature separation of the placenta (Oyelese & Ananth, 2006).

Preterm birth (PTB) - birth at a gestational age of less than 37 completed weeks or 259 days of gestation and *extreme preterm birth* as less than 28 completed weeks (less than 196 completed days) of gestation (World Health Organization, 2007). In addition, some studies use the term *very preterm birth (VPTB)* for gestational ages of less than 32 completed weeks of gestation.

Pre-eclampsia - hypertension arising after 20 weeks of gestation. In addition, the new onset of one of the following must be present: proteinuria or a spot urine protein; renal insufficiency; liver disease-raised serum transaminases and/or right upper quadrant pain; neurological problems (eclampsia), hyperreflexia with clonus, severe headaches with hyperreflexia, persistent visual disturbances; haematological problems-thrombocytopenia, disseminated intravascular coagulation, haemolysis; and fetal growth restriction (Brown et al., 2000).

Premature rupture of membrane - Spontaneous rupture of membranes before contraction begins and prior to 37 weeks of gestation (Yackerson, Piura & Sheiner, 2008).

Preterm labour - a term to describe contractions of the uterus that begin at 20–36 weeks of a pregnancy.

Small for gestational age (SGA) - a baby who is smaller than usual for the number of weeks of pregnancy. SGA babies usually have birth weights below the 10th percentile for babies of the same gestational age.

Stillbirth - in Australia, stillbirth is defined as the loss of a fetus that shows no signs of life at birth and is at least 20 weeks in gestation or 400 grams in birth weight (Australian Institute of Health and Welfare, 2008). Another word for stillbirth is fetal mortality. Fetal mortality is also be divided into death prior to labour, antenatal (antepartum) death, and death during labour, intranatal (intrapartum) death. Figure 1.3 illustrates the Australian definitions of abortion, stillbirth and neonatal mortality.

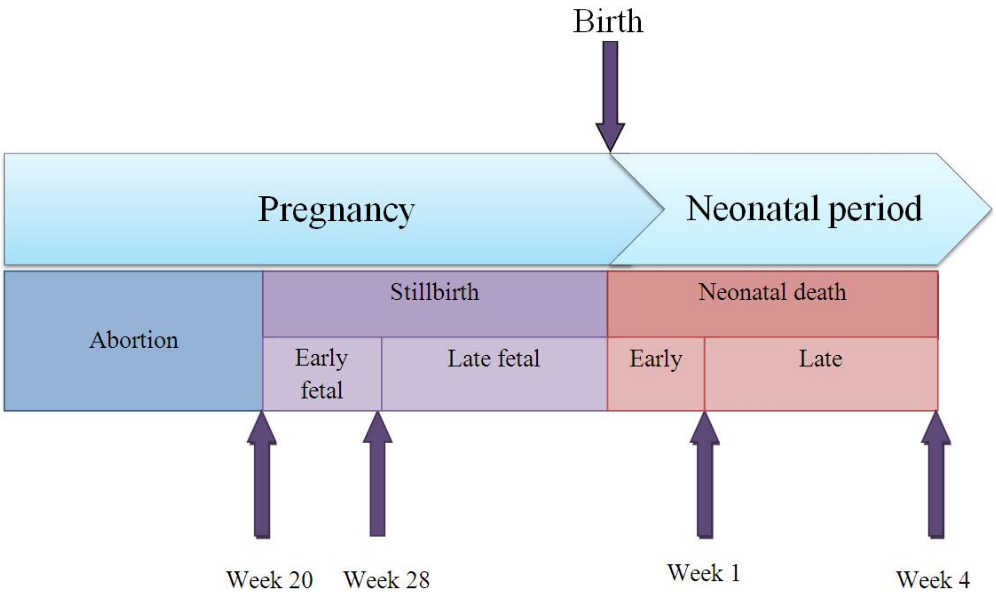


Figure 1.3. Flow chart showing the definitions of fetal and neonatal mortality.

1.5 THESIS OUTLINE

This thesis is presented in a traditional format. Chapter 1 is an introduction including the background, aims and objectives, and significance of the research. Chapter 2 briefly reviews the literature relating to long-term effects of preterm birth and the determinants of adverse birth outcomes and critically reviews previously published epidemiological literature investigating the effects of season and temperature on adverse birth outcomes including PTB and stillbirth. Low birth weight (LBW) is also included in the review as it is often caused by PTB. This chapter also discusses the methodological challenges in these studies and identifies research gaps, research needs and implications for our research. Chapter 3 provides the study design and methods, and Chapter 4 presents the results. Chapter 5 gives an overview of key findings and discusses these findings. Chapter 6 discusses the strengths and limitations of the study, the public health implications of the research findings and directions for future research.

Chapter 2: Literature Review

2.1 SEARCH STRATEGY

Because I wanted to focus on recent studies, the review was limited to English peer-reviewed journal articles from 1985 to 2011. Several searches with the keywords ‘preterm birth’, ‘birth weight’, ‘stillbirth’, ‘season’, ‘seasonality’, ‘temperature’, ‘air pollution’, ‘health effects’ and ‘determinants’ were performed using the databases PubMed, Medline, and Web of Science. References of the papers were examined manually to ensure that all relevant published papers were included. Studies on low birth weight (LBW) were included in the review as it is often caused by PTB (United Nations Children’s Fund and World Health Organization, 2004) and the two terms are interrelated. Studies of twins or triplets were not included as plurality is an important risk factor for PTB (Goldenberg, Culhane, Iams & Romero, 2008).

2.2 HEALTH EFFECTS

PTB and LBW are both major predictors of many health problems later in life and early death (Goldenberg & Culhane, 2007). Twenty-eight percent of all early neonatal deaths that are not related to congenital malformations, are due to PTB (Lawn, Wilczynska-Ketende & Cousens, 2006).

2.2.1 SOCIO-EMOTIONAL AND EDUCATIONAL PROBLEMS

Premature children experience significant shortcomings at school, university and in the job market (Hille et al., 2007). Extremely low birth weight (ELBW) children and extremely preterm children score significantly below normal birth weight children on full-scale IQ, indices of verbal comprehension, perceptual organization, freedom from distractibility, processing speed, reading, spelling, and arithmetic (Anderson & Doyle, 2003). LBW is associated with lower educational achievement at school age, and with perinatal morbidity and motor delay in early childhood (Sullivan & Margaret, 2003).

2.2.2 IMPAIRED VISION AND HEARING

Premature children are also at risk of various visual problems including refractive errors such as myopia and astigmatism (Ton, Wysenbeek & Spierer, 2004), impaired visual acuity (Spierer, Royzman & Kuint, 2004), and decreased sensitivity for contrasts (O'Connor et al., 2004). Prematurity is also the main risk factor for severe retinopathy of prematurity (ROP). Infants with a gestational age of less than 25 weeks have a 20 times greater odds of getting ROP than infants at 28 weeks or older (Darlow et al., 2005).

Premature and LBW infants are a high-risk group for impaired hearing and studies report a rate of hearing impairment requiring hearing aids for approximately 2% of VLBW children (Hack et al., 2005; Wilson-Costello, Friedman, Minich, Fanaroff & Hack, 2005). A study of 70 premature infants found that 14% of very low birth weight babies had a peripheral hearing impairment and 17% had a central impairment. Four percent had both peripheral and central impairments, giving a combined total rate for hearing impairment of 27% (Jiang, Brosi & Wilkinson, 2001).

2.2.3 REDUCED HEIGHT AND WEIGHT LATER IN LIFE

Children born at a gestational age of less than 26 weeks have shown to achieve poor growth in early childhood (Farooqi, Hagglof, Sedin, Gothefors & Serenius, 2006). A study in Canada found that very low birth weight (VLBW) children, followed-up at ages 16–19 years, were significantly shorter than the children born at term (Weiler, Yuen & Seshia, 2002). Studies have also shown that prenatal growth problems are associated with postnatal growth problems and those children born preterm have a lower height and weight at eight years of age (Casey, Whiteside-Mansell, Barrett, Bradley & Gargus, 2006). In addition to these findings, PTB and LBW children have significantly less bone mass content than normal birth weight children in adulthood (Weiler et al., 2002).

2.2.4 REDUCED COGNITIVE FUNCTION AND BEHAVIOURAL PROBLEMS

Premature children have reduced cognitive test scores and their immaturity at birth is directly proportional to the mean cognitive scores at school age (Bhutta, Cleves, Casey, Cradock & Anand, 2002). Marlow et al. (2005) also revealed particular problems in non-verbal reasoning and simultaneous information processing(Marlow et al., 2005). There is little consensus regarding the presence of internalising or externalising behaviours, but most studies show an increased risk of problems with attention and social behaviour later in life (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever & Oosterlaan, 2009). Studies have also shown a greater prevalence of psychiatric disorders and an increased risk of ADHD in premature children (Bhutta et al., 2002).

2.2.5 CEREBRAL PALSY (CP)

CP is the most well known adverse health outcome associated with PTB (Marlow, 2004). In Korea, the prevalence of CP was 12% in infants that weighed < 2,000 grams at birth, and only 0.4% in those that weighed > 2,000 g. Preterm labour, preterm rupture of membrane, severe birth asphyxia, neonatal sepsis, and respiratory distress syndrome have strong correlations with the development of CP (Han, Bang, Lim, Yoon & Kim, 2002). In Finland, the rate of CP among extremely premature infants was 14% (Mikkola et al., 2005). In Ohio, USA, the rate was 14% among extremely low birth weight children compared to none of the normal birth weight children (Hack et al., 2005).

2.2.6 ECONOMIC ISSUES

In addition to health service costs incurred during the initial hospital stay, preterm birth can result in substantial costs to the health services throughout childhood and can impose a substantial economic burden on special education and other services (Petrou, Eddama & Mangham). In Sweden, 13.2% of children born between 24 and 28 weeks of gestation, and 5.6% of children born between 29 and 32 weeks of gestation received economic assistance because of a handicap or persistent illness (Lindstrom et al., 2007). The authors estimated that this was equivalent to almost four times the risk of those born at term (RR 3.76, 95% CI 3.14, 4.49). PTB was associated with a lower chance of completing a university education and a lower net salary. The study projected that the total economic gain for the Swedish society, in terms of taxes and decreased costs for benefits, if all PTBs had have been prevented in 2002, would have been €65 million (USD 85 million).

2.3 GENETIC, SOCIO-ECONOMIC AND BEHAVIOURAL FACTORS INFLUENCING BIRTH OUTCOMES

Genetic, socio-economic, and behavioural factors can influence birth outcomes. These include maternal age, maternal stature, maternal morbidity, previous pregnancy outcomes, antenatal care, pregnancy complications, marital status, socio-economic status, maternal smoking, alcohol consumption, nutrition, physical activity, medication, drug use, and ethnicity (Friis et al., 2004; Nohr, Bech, et al., 2007; Phillips, Wise, Rich-Edwards, Stampfer & Rosenberg, 2009; Tyldum, Romundstad & Slørdahl, 2010; Ward, Lewis & Coleman, 2007). These factors can have a direct effect on birth outcomes, but most of them do not interact with season therefore they do not confound any association between temperature and birth outcomes.

2.3.1 PREGNANCY COMPLICATIONS

Hypertensive disorders complicate about 7% of all pregnancies (Hladunewich, Karumanchi & Lafayette, 2007). The literature emphasizes the increased risk of adverse birth outcomes in the presence of pre-eclampsia (PE) and pregnancy-induced hypertension (PIH) (Goldenberg et al., 2008; Gul et al., 2005). Induced delivery is always the treatment of choice for the mother as there is no other effective cure for preeclampsia (Sibai, 2006). Babies born from mothers with PE or PIH have an elevated risk of adverse birth outcomes such as PTB, LBW and stillbirth (Vigil-De Gracia, Lasso & Montufar-Rueda, 2004). Buchbinder et al. (2002) found that compared with mild PE, women who developed severe gestational hypertension had higher rates of PTB infants (RR= 2.1, 95% CI 1.2, 3.7).

2.3.2 MATERNAL AGE

Maternal age is an important risk factor for adverse birth outcomes. Young mothers (< 16 years) have substantially higher risks for adverse birth outcomes than adolescents between 16 and 19 years (Conde-Agudelo, Belizán & Lammers, 2005). Chen et al. (2009) reported that the youngest mothers had the lowest mean infant birth weight of 2,983 g compared with 3,177 g in the age group 20–24 years, and a rate of LBW of 13.2% compared with 5.2% in the older mothers in Taiwan(Chen et al., 2009). In Australia, remote and very remote areas have the highest rates of adolescent mothers, and infants of teenage mothers in very remote areas have higher rates of PTB, small for gestational age (SGA) and stillbirth than infants of older mothers (Robson, Cameron & Roberts, 2006). Younger teenagers (< 16 years of age) also had higher odds for very preterm birth (VPTB) than older teenagers (OR 1.63, 95% CI 1.06, 2.52)

An increasing number of mothers choose to delay childbearing until after the age of 35–40. In Israel, mothers between 45 and 64 years of age gave birth to babies of a mean gestational age of 37.6±2.6 weeks compared with 39.5±2.0 weeks in the general population (Simchen, Yinon, Moran, Schiff & Sivan, 2006). Studies have reported higher rates of stillbirth, LBW, PTB, and placental abruption with increasing maternal age (Cleary-Goldman et al., 2005; Hoffman et al., 2007).

2.3.3 MATERNAL WEIGHT

Low maternal weight and body mass index (BMI) at both the time of conception and the time of delivery, and poor weight gain during pregnancy are associated with LBW, PTB and fetal growth restrictions (Ehrenberg, Dierker, Milluzzi & Mercer, 2003). In addition, overweight and obese women are at higher risk of Caesarean section, PTB and PE (Driul et al., 2008). A Danish study investigating overweight mothers found that neonatal mortality increased in infants of mothers who were overweight or obese compared with infants of mothers who were a normal BMI before pregnancy (Nohr, Vaeth, et al., 2007).

2.3.4 MATERNAL MORBIDITY

The rate of pre-gestational diabetes mellitus requiring insulin is estimated to be between 0.3% and 0.9%, with increasing risk with increasing maternal age (Vangen et al., 2003). A study in Sweden found that PE was much more frequent among type 1 diabetes patients than among the control population (OR = 4.47, 95% CI 3.77–5.31) (Persson, Norman & Hanson, 2009), and the frequency of PE increased significantly with increasing severity of diabetes ($p < 0.01$) (Sibai et al., 2000). In addition, PTB, stillbirth, and birth defects are more prevalent among diabetic mothers (Hanson & Persson, 1998; Persson et al., 2009; Vangen et al., 2003).

Asthma is the most frequent respiratory disorder complicating pregnancy, affecting between 3.2% and 8.9% of pregnant women (Kwon, Belanger & Bracken, 2003). A pregnancy can affect the course of asthma, and increase the risk of asthma complications requiring intervention compared to non-pregnant women (Hanania & Belfort, 2005). In addition, studies have reported that maternal asthma significantly affects a number of adverse birth outcomes, including PTB and SGA infants, PE, PIH, and caesarean delivery (Alexander, Dodds & Armson, 1998; Liu, Wen, Demissie, Marcoux & Kramer, 2001).

2.3.5 PREVIOUS PREGNANCIES

In a large study in California covering 17 years and approximately 500,000 births, Getahun et al. (2009) found an increased risk of fetal distress, extreme prematurity, and early neonatal mortality after a previous stillbirth. Mothers who have gone through a previous abortion have a higher risk of abortion, PTB and LBW in subsequent pregnancies than women who have previously given birth to live babies (Bhattacharya, Townend, Shetty & Campbell, 2008; Kashanian, Akbarian, Baradaran & Shabandoust, 2006). Ancel et al. (2004) investigated induced abortions and found that the risk of PTB increased with the number of previous induced abortions.

2.3.6 ANTENATAL CARE

Numerous studies have evaluated the impact of antenatal care on birth outcomes, with the majority showing that greater antenatal care decreases the incidence of poor birth outcomes through the prolongation of pregnancy, and thus increased birth weight (Carabin et al., 2005). Women not receiving antenatal care are typically young, smoking, drinking alcohol, residing in rural and remote areas, less educated and drug users (Humphrey & Keating, 2004; Maupin et al., 2004). In the US, women going through pregnancy without antenatal care were shown to have higher risks of adverse birth outcomes and a significantly higher likelihood of PTB (OR 5.32, 95% CI 2.98–9.47) and LBW (OR 3.37, 95% CI 1.91–5.94) than women receiving antenatal care (Maupin et al., 2004).

2.3.7 MARITAL STATUS

From 2002 to 2007 approximately one-third (32%) of all births in Australia were delivered by unmarried mothers, twice the average rate of the 1980s (16%) (Australian Bureau of Statistics, 2009). Numerous studies have found that pregnancies of unmarried women are associated with increased risk of PTB, LBW and SGA (Holt, Danoff, Mueller & Swanson, 1997; Luo, Wilkins & Kramer, 2004;

Zeitlin, Saurel-Cubizolles & Ancel, 2002). A recent study in Finland found that unmarried women had higher rates of PTB (OR 1.15, $p < 0.01$), SGA infants (OR 1.11, $p < 0.01$), and LBW infants (OR 1.17, $p < 0.01$) (Raatikainen, Heiskanen & Heinonen, 2005). Arntzen et al. (1996) in Norway found that stillbirth, neonatal, and post-neonatal mortality rates were higher among offspring of unmarried mothers than among married mothers.

2.3.8 SOCIO-ECONOMIC STATUS

Being born into a low socio-economic status is associated with adverse birth outcomes (Fairley & Leyland, 2006; Genereux, Auger, Goneau & Daniel, 2008). Luo et al. (2004) examined birth outcomes and trends in infant mortality from 1985 to 2000 in British Colombia. Comparisons between neighbourhoods with high income and neighbourhoods with low income revealed that infant mortality rates were two-thirds higher in the latter group. Similarly, in an analysis of the Quebec birth registry from 1991 to 2000, Luo et al. (2006) found that living in the lowest income neighbourhood was associated with a 30% increased risk of stillbirth.

2.3.9 MATERNAL SMOKING

A causal relationship has been established between maternal smoking and the risk of having a LBW infant and PTB (McCowan et al., 2009; Wills & Coory, 2008). Women who smoke also have increased risks of abortion, stillbirth and neonatal death (Andres & Day, 2000; Cnattingius, 2004). Robson et al (2006) found an increased risk of stillbirth for infants of teenage mothers who smoked more than 10 cigarettes a day. Compared to non-smokers, the OR for stillbirth was 1.65 (95% CI 1.15–2.38) among smokers.

2.3.10 MEDICATIONS

In a study investigating the use of marijuana, methadone, amphetamines and heroin, Kennare et al. (2005) found that the exposed babies had an increased risk of PTB, SGA, stillbirth and neonatal death. Also antidepressants (Hendrick et al., 2003; Kallen, 2004), and cocaine (Ogunyemi & Hernandez-Loera, 2004) have been shown to adversely affect the unborn baby.

2.3.11 ALCOHOL CONSUMPTION

Several studies have shown that both excessive and moderate drinking influence the unborn child and that a dose-response relationship exists. For example, Kesmodel et al. (2010) reported that the risk of stillbirth increased with increasing alcohol intake during pregnancy (RR = 1.37 for women consuming <1 drink/week and 8 for women consuming ≥5 drinks/week) in Denmark. Also Albertsen et al. (2004) reported that the relative risks for PTB among mothers who consumed 4–7 drinks and ≥ 7 drinks/week during the pregnancy compared with those who did not drink, were 1.15 (95% CI: 0.84–1.57) and 1.77 (95% CI: 0.94–3.31), respectively.

2.3.12 ETHNICITY

A study using data from the National Collaborative Perinatal Project in the United States found that mean birth weight was significantly higher in white infants compared to Puerto Rican or black infants (van Hanswijck de Jonge, Waller & Stettler, 2003). In Australia in 2005, 13.9% of Aboriginal and Torres Strait Islander mothers had premature babies compared with 7.9% of non-Indigenous mothers and the percentage of LBW babies in Aboriginal and Torres Strait Islander mothers was 13.2%, more than double that in non-Indigenous mothers (6.1%) (Australian Institute of Health and Welfare, 2008). In addition, stillbirth rates for Indigenous women are over twice that of non-Indigenous women (Australian and New Zealand Stillbirth Alliance, 2010).

2.3.13 KNOWLEDGE GAPS IN ASSESSING MULTIFACTORAL DETERMINANTS OF BIRTH OUTCOMES

Few previous studies had sufficient information about these factors to investigate the effect of ambient temperature on birth outcomes. In the current project, I will have a large dataset with a big range of socio-demographic factors. Thus, I will get one step closer to determining the true association between ambient temperature and birth outcomes.

2.4 SEASONALITY OF BIRTH OUTCOMES

Numerous studies have found that birth outcomes vary by season (Bodnar & Simhan, 2008; Chodick, Flash, Deoitch & Shalev, 2009; Murray et al., 2000). The seasonal variation differs from country to country and peaks can occur in any season. Table 2.1 describes the studies included in this review.

Table 2.1

Characteristics of the Studies on Seasonality of Birth Outcomes

	Study	Location	Temp (°C)	Design	Sample	Exposure	Outcome	Adjusted for confounders	Results		
									Statistic	Estimate	p-value
Preterm birth											
1	Cooperstock & Wolfe 1986	12 sites in the USA	14.1	RC	Live births at 12 hospitals from 1959 to1966 (4,579)	Month of birth	Preterm birth	Yes	Chi-square for seasonal sinusoid	X^2 (2) = 25.6, amplitude ± 24%	< 0.01
2	Lee et al 2006	London, UK	10.5	RC	Live, singleton births from 1988 to 2000 in 18 maternity units in London (509,173)	Month of birth	Preterm birth	No	Odds ratio for winter compared with spring	1.10 (95% CI 1.07, 1.14)	< 0.05
									Odds ratio for summer compared with spring	1.03 (95% CI 0.99, 1.06)	> 0.05
3	Keller & Nugent 1983	Minnesota USA	6.5	RC	Singleton births from 1967 to 1973 (402,540)	Month of birth	Gestational age	No	Chi-square	X^2 (11) > 26.7	< 0.005
4	Matsuda & Kahyo 1992	Japan	15.1	RC	Live, singleton infants from 1979 to1983 (7,675,006)	Season of birth	Preterm birth	No	Autocorrelation	0.8 for males and 0.5 for females at 12 month lag	Not given
5	Matsuda & Kahyo 1998	Japan	15.1	ES	Same sample as above	Season of birth	Preterm birth	Yes	Correlation with peak in winter	–0.42	< 0.01
									Correlation with peak in summer	0.54	< 0.01
6	Bodnar & Simhan 2008	Pennsyl-vania, USA	12.8	RC	Live, singleton births from 1995 to 2005 (82,213)	Season of conception	Preterm birth	Yes	Relative risk for summer compared with spring conceptions	0.92 (95% CI 0.86, 0.98)	< 0.05
									Relative risk for autumn compared with spring conceptions	0.91 (95% CI 0.85, 0.96)	< 0.05
13	Flouris et al 2009	Greece	18.3	RC	All births from 1999 to 2003 (516,874)	Season of birth	Gestational age and preterm birth	Yes	MANOVA eta-squared	0.12	< 0.01
									Chi-square	Not given	< 0.05
7	Rayco-Solon et al 2005	West Kiang District, Gambia	26.5	RC	All live births in 3 villages from 1976 to 2003 (2,472)	Season of birth	Preterm birth	Yes	Fourier analysis	X^2 (6) = 20.1	0.0027

8	Friis et al 2004	Harare, Zimbabwe	18.6	PC	Births between 22 and 36 weeks of gestation from 1996 to 1997 (1,106)	Season of birth	Gestational age and preterm birth	Yes	Change when comparing early dry season to late rainy season	–2.3 weeks (95% CI –2.8, –1.7 weeks)	< 0.01
									Change when comparing late dry season to late rainy season	–0.6 weeks (95% CI –1.2, –0.1 weeks)	0.01
									Change when comparing early rainy season to late rainy season	–0.8 weeks (95% CI –1.3, –0.3 weeks)	0.003
									Odds Ratio of early dry season compared to late rainy season	2.9 (95% CI 1.65, 5.2)	< 0.01
									Odds Ratio of late dry season compared to late rainy season	0.94 (95% CI 0.51, 1.72)	0.83
									Odds Ratio of early rainy season compared to late rainy season	1.38 (95% CI 0.75, 2.52)	0.30
Stillbirth											
9	Torrey et al 1993	New York State, USA	9.0	RC	All stillbirths reported to the NYS Health Department from 1908 to 1959 (428,406)	Month of birth	Stillbirth	No	ANOVA	Not given	< 0.01
3	Keller & Nugent 1983	Minnesota, USA	6.5	RC	All white, singleton births from 1967 to 1973 (402,540)	Month of birth	Stillbirth	No	Chi-square	X^2 (11) > 26.7	< 0.005
10	Eriksson & Fellman 2000	Switzerland	8.6	RC	All births recorded from 1876 to 1990 (sample size not given)	Month of birth	Stillbirth	Yes		No estimate given	
11	Barnett & Dobson 2010	Queensland, Australia	20.6	RC	All births from 1998 to 2000 (60,110)	Month of birth	Stillbirth	No	Chi-square	X^2 (11) = 9.4	0.59
Low birth weight											
12	van Hanswijck de Jonge et al 2003	12 sites in the USA	14.1	RC	Live births from 12 sites from 1962 to 1965 (24,325)	Season of birth	Birth weight	Yes	t-test of autumn compared to winter	2.15	0.03
									t-test of autumn compared to spring	2.48	0.01
13	Flouris et al 2009	Greece	18.3	RC	All births from 1999 to 2003 (516,874)	Season of birth	Birth weight	Yes	MANOVA eta-squared	0.14	< 0.01
									Chi-square	No estimate given	< 0.05

14	Chodick et al 2007	Israel	17.4	RC	Singleton births from 1998 to 2004 with birth weight registered (225,545)	Month of birth	Low birth weight	Yes	Change in June compared to January	25.8 g (95% CI 15.8, 35.9 g)	
15	Matsuda et al 1993	Japan	15.1	RC	Live, singleton births from 1974 to 1983 (16,796,415)	Season of birth	Birth weight	No	Two-way ANOVA	No estimate given	< 0.01
16	Torche & Corvalan 2010	Santiago, Chile	15.0	ES	Live, singleton births of 37 to 41 weeks of gestation from 1987 to 2007 (5,000,000)	Month of birth	Birth weight	Yes	Change in March compared to January Change in July compared to January Change in November compared to January	8.10 g (95% CI 7.70, 9.50 g) –8.83 g (95% CI –10.45, –7.21 g) 7.03 g (95% CI 5.6, 8.46 g)	< 0.01 < 0.01 < 0.01
17	Murray et al 2000	Northern Ireland	9.1	RC	Live, singleton births born on term from 1971 to1986 (447,499)	Month of birth	Birth weight	Yes	Change in July compared to January	–31.6 g (95% CI –35.2, 28.0 g)	< 0.01
18	McGrath et al 2005	Four regions in Australia	12.9	RC	Singleton, term births from 1985 to 2003: Queensland (350,171), Sydney (775,521), Victoria (1,039,893) and Tasmania (59,763)	Latitude, season of birth	Birth weight	No	Annual amplitude	Queensland: 7.7 g (95% CI 4.8, 10.7 g). Sydney: 2.9 g (95% CI 0.7, 5.5 g) Victoria: 1.4 g (95% CI 0.2, 3.0 g) Tasmania: 6.4 g (95% CI 1.6, 11.8)	
19	Hort 1987	Dhaka, Bangladesh	26.1	PC	Live, singleton babies born from 1983 to 1984 (1,772)	Season of birth	Birth weight	Yes	ANOVA	No estimate given	< 0.05
7	Rayco-Solon et al 2005	West Kiang District, Gambia	26.5	RC	Live, births in 3 villages from 1976 to 2003 (2,472)	Season of birth	Small for gestational age	Yes	Fourier analysis	X^2 (6) = 24.7	0.0004
20	Rousham & Gracey 1998	Kimberley Region, Australia	26.7	RC	Aboriginal live births from 1981 to 1993 (4,508)	Season of birth	Low birth weight	No	Odds ratio of wet season compared to dry season	2.7 (95% CI 2.3, 3.7)	< 0.01

Temp (°C) = Average yearly temperature in the study area, PC = Prospective cohort, RC = Retrospective cohort, ES = Ecological study

2.4.1 SEASONALITY OF PRETERM BIRTH

Eight studies investigated the seasonality of preterm birth (Table 2.2). Cooperstock and Wolfe (1986) found an autumn peak of preterm birth in a study of 4,579 women in Missouri, USA, between 1959 and 1966, and reported a peak in September and a trough in May. The authors discovered that the seasonal pattern was more prominent in groups less predisposed to preterm birth: among mothers older than 22 years; mothers with high socio-economic status; and married mothers ($p < 0.05$). However, there was no statistically significant seasonal pattern in younger mothers, mothers with low socio-economic status and unmarried mothers (Cooperstock & Wolfe, 1986).

Lee et al. (2006), Keller and Nugent (1983), and Matsuda and Kahyo (1992) found peaks of preterm birth in winter. In London, in a cohort of almost 500,000 live singleton births covering a 12 year period, babies were more likely to be born preterm in winter than in spring (odds ratio (OR): 1.10, 95% confidence interval (CI): 1.07–1.14). There were more preterm births in January (6.8%) and less in September (5.6%) (Lee, Steer & Filippi, 2006). In addition to the winter peaks, Keller and Nugent (1983), Matsuda, and Kahyo (1992) reported peaks of preterm birth in summer, indicating a bi-modal seasonal pattern. Keller and Nugent's (1983) study of 402,540 white, singleton live births and stillbirths of more than 29 weeks of gestation in Minnesota showed a seasonal pattern of preterm births with peaks in July (summer) and December (winter). Matsuda and Kahyo (1992) found two peaks in Japan, one in summer and one in winter. The shape of the two peaks was different as judged by the skewness and kurtosis. The authors interpreted this outcome as a sign that the causes of preterm birth may differ between the two seasons. Using the same cohort, Matsuda and Kahyo (1998) examined geographical differences in the seasonality of preterm births and reported that the peaks depended on location – the winter peak was dominant among the northern areas and the summer peak was dominant among the southern areas. The increase of preterm births in winter was negatively correlated with mean temperature, whilst the increase in summer was positively correlated with mean temperature. This result indicates that both cold and hot temperatures may increase the risk of preterm birth.

Table 2.2

The Seasonal Pattern of Preterm Births Ordered by Average Yearly Ambient Temperature

Study	**Location**	**Temp (°C)**	**Winter**	**Spring**	**Summer**	**Autumn**
Keller & Nugent 1983	Minnesota, US	6.5	■		■	
Lee et al. 2006	London, UK	10.5	■			
Bodnar et al. 2008[a]	Pennsylvania, US	12.8	■	■		
Cooperstock et al. 1986	12 sites, US	14.1				■
Matsuda et al. 1998	Japan	15.1	■		■	
Flouris et al. 2009	Greece	18.3		■	■	
Friis et al. 2004	Zimbabwe	18.6	■			
Rayco-Solon et al. 2005	Gambia	26.5			■	■

Grey boxes show seasons where a peak was found.
Temp (°C): Average yearly temperature (°C).
[a] The study reported peaks in preterm birth based on date on conception, not date of birth.

Bodnar and Simhan (2008) investigated a cohort of 82,213 live singleton births in Pennsylvania and found peaks of preterm birth in pregnancies conceived in spring compared to summer and autumn, and the overall seasonal pattern was statistically significant ($p < 0.01$). A similar pattern was found for preterm birth of less than 32 weeks of gestation. The seasonal effects remained after controlling for maternal age, ethnicity, marital status, education and parity ($p < 0.01$) (Bodnar & Simhan, 2008). Flouris et al. (2009) found lower rates of preterm birth among babies born in Greece during autumn and winter than in spring and summer ($p < 0.05$).

Studies in developing countries have also reported seasonality of preterm birth. In the West Kiang District of The Gambia researchers investigated 1,916 births in three rural communities between 1976 and 2003 and found peaks of preterm births in July and October. Prematurity was dependent on season of birth ($p = 0.0027$) (Rayco-Solon et al., 2005). In Harare, Zimbabwe, births in the early dry season (June–August) had a 2.3 weeks (95% CI 1.7–2.8 weeks) shorter gestation than those born in the late rainy season (March–May) (Friis et al., 2004). Since these studies were conducted in developing countries, the results may have been due to seasonal factors other than the weather, such as hard physical work during harvest season, food availability, and seasonal malaria infections which peaked in the same months (Rayco-Solon et al., 2005).

2.4.2 SEASONALITY OF STILLBIRTH

Four studies investigated the seasonality of stillbirth (Table 2.3). In New York State, a significantly increased risk of stillbirth in winter ($p < 0.01$) was found (Torrey, Bowler, Rawlings & Terrazas, 1993). In Minnesota, peaks of fetal deaths were found in autumn and winter (Keller & Nugent, 1983). The pattern was only present for fetal deaths occurring *before* labour (antenatal death), and there was no seasonal pattern of deaths *during* labour (intranatal death). In Switzerland, between 1876 and 1990, a higher rate of stillbirth was found in winter and spring (Eriksson & Fellman, 2000). In Queensland, Australia, researchers found a peak of stillbirth in summer (Barnett & Dobson, 2010).

Table 2.3

The Seasonal Pattern of Stillbirths Ordered by Average Yearly Ambient Temperature

Study	**Location**	**Temp (°C)**	**Winter**	**Spring**	**Summer**	**Autumn**
Keller & Nugent 1983	Minnesota, USA	6.5	▨			▨
Eriksson & Fellman 2000	Switzerland	8.6	▨	▨		
Torrey et al. 1993	New York, USA	9.0	▨			
Barnett & Dobson 2010	Queensland, Australia	20.6			▨	

Grey boxes show seasons where a peak was found.
Temp (°C): Average yearly temperature (°C).

2.4.3 SEASONALITY OF BIRTH WEIGHT

Birth weight has also been found to fluctuate by season and 10 studies have examined this relationship (Table 2.4). Two studies reported autumn or spring peaks of low birth weight births. Van Hanswijck de Jonge et al. (2003) conducted a study in the US that investigated almost 25,000 live births from 12 sites between 1962 and 1965. They found that infants born in the autumn had a lower birth weight than those born in the winter ($p = 0.03$) and spring ($p = 0.01$). Similar results were found in Greece, where birth weight was found to be lowest in spring and summer ($p < 0.05$) (Flouris et al., 2009).

Chodick et al. (2007) in Israel found that the lowest mean birth weights were between December and February (winter) in six of the seven years investigated. Matsuda et al. (1993) in Japan reported a bi-modal pattern with lowest mean birth weights in both summer and winter ($p < 0.01$). Similarly, a recent study by Torche and Corvalan (2010) found a bimodal pattern with lower birth weights in summer and winter in Santiago, Chile. Murray et al. (2000) in Northern Ireland reported a peak in low birth weight births in summer with an infant born in July having a birth weight of 31.6 g (95% CI 35.2, 28.0) less than one born in January. However, the pattern disappeared almost entirely after adjustment for mean maximum temperature during the second trimester.

McGrath et al. (2005) in Australia reported fluctuations of birth weight according to season between four different regions. The authors found that birth weight varied significantly by season, and peaked in spring, but they did not report the season with the lowest mean birth weights.

Table 2.4

The Seasonal Pattern of Low Birth Weight Oredered by Average Yearly Ambient Temperature

Study	**Location**	**Temp (°C)**	**Winter**	**Spring**	**Summer**	**Autumn**
Murray et al. 2000	Northern Ireland	9.1			■	
van Hanswijck de Jonge et al. 2003	12 sites, US	14.1				■
Torche & Corvalan 2010	Santiago, Chile	15.0			■	
Matsuda et al. 1993	Japan	15.1	■		■	
Chodic et al. 2007	Israel	17.4	■			
Flouris et al. 2009	Greece	18.3		■	■	
Hort 1987	Dhaka, Bangladesh	26.1				■
Rayco-Solon 2005	Gambia	26.5	■			■
Rousham & Gracey 1998	Kimberly, Australia	26.7			■	■

Grey boxes show seasons where a peak was found.
One study was not included in the figure as it reported a peak in birth weight and not when it was lowest (McGrath et al. 2005).
Temp (°C) = Average yearly temperature (°C).

Studies in developing countries have also reported seasonality of birth weight. Hort (1987) studied 1,772 singleton babies born in 1983 and 1984 in Dhaka, Bangladesh, and found lower mean birth weights in autumn. Poor maternal nutrition in the last trimester (for mothers that delivered in autumn or winter) was the likely cause of the lower birth weights. Similar patterns were described in The Gambia where the highest incidence of small for gestational age (SGA) was in autumn and winter with the incidence of SGA being 31% in November (winter) compared with the yearly mean of 25% (Rayco-Solon et al., 2005). Seasonal factors (e.g., nutrition and seasonal agricultural work) are likely to be determinants of low birth weight in developing countries. In Australia, the Aboriginal population have significantly poorer birth outcomes than non-Aboriginals. Rousham and Gracey (1998) conducted a study in the Kimberley region of Western Australia, which covered live singleton births from 1981–1993; they found that very low birth weight babies (< 1,500 g) were more common in the wet season (January–June) compared with the dry season (July–December) (OR: 2.7, 95% CI: 2.3–3.7). Low birth weight babies (< 2,500 g), however, were not more common in the wet season. The authors argued that the lack of seasonal patterns in low birth weight excludes food shortages during wet season as a determining factor.

2.4.4 KNOWLEDGE GAPS IN EXAMINING THE ASSOCIATION BETWEEN SEASONALITY AND TEMPERATURE

Peaks of preterm birth and low birth weight were found to occur during almost any season in the studies included in this review (Figure 2.1). The inconsistent results in regard to what season of the year the peak(s) of adverse birth outcomes occurred could be caused by differences in the climate between countries. However, when I examined the seasonal pattern by average yearly ambient temperature, no apparent pattern was found (Tables 2.2, 2.3, and 2.4). Nevertheless, most of the studies reported peaks of preterm birth, stillbirth and low birth weight in winter, summer or both. This indicates that temperature extremes may be an important determinant of poor birth outcomes. In studies of temperature-related morbidity and mortality in adults, a J- or U-shaped relationship between temperature and risk has commonly been reported (Curriero et al., 2002; Diaz, Linares, Garcia-Herrera, Lopez & Trigo, 2004; Huynen, Martens, Schram, Weijenberg & Kunst, 2001). The relationship between ambient temperature and birth outcomes may also be non-linear.

Another explanation for the different findings on the seasonality of preterm birth is due to the different denominators used to calculate the rate of preterm birth. For example, some studies used a denominator of fetuses-at-risk (ongoing gestations at gestational weeks considered preterm) (Keller & Nugent, 1983) while others used a denominator of live births (Cooperstock & Wolfe, 1986; Lee et al., 2006). Given the existence of seasonal patterns of conceptions (Darrow, Strickland, et al., 2009), the results are not comparable between studies because they have used different denominators. The problems with calculating and comparing rates of preterm birth across time will be avoided in this study, as I will compare foetuses at the same gestational point in time using a survival analysis.

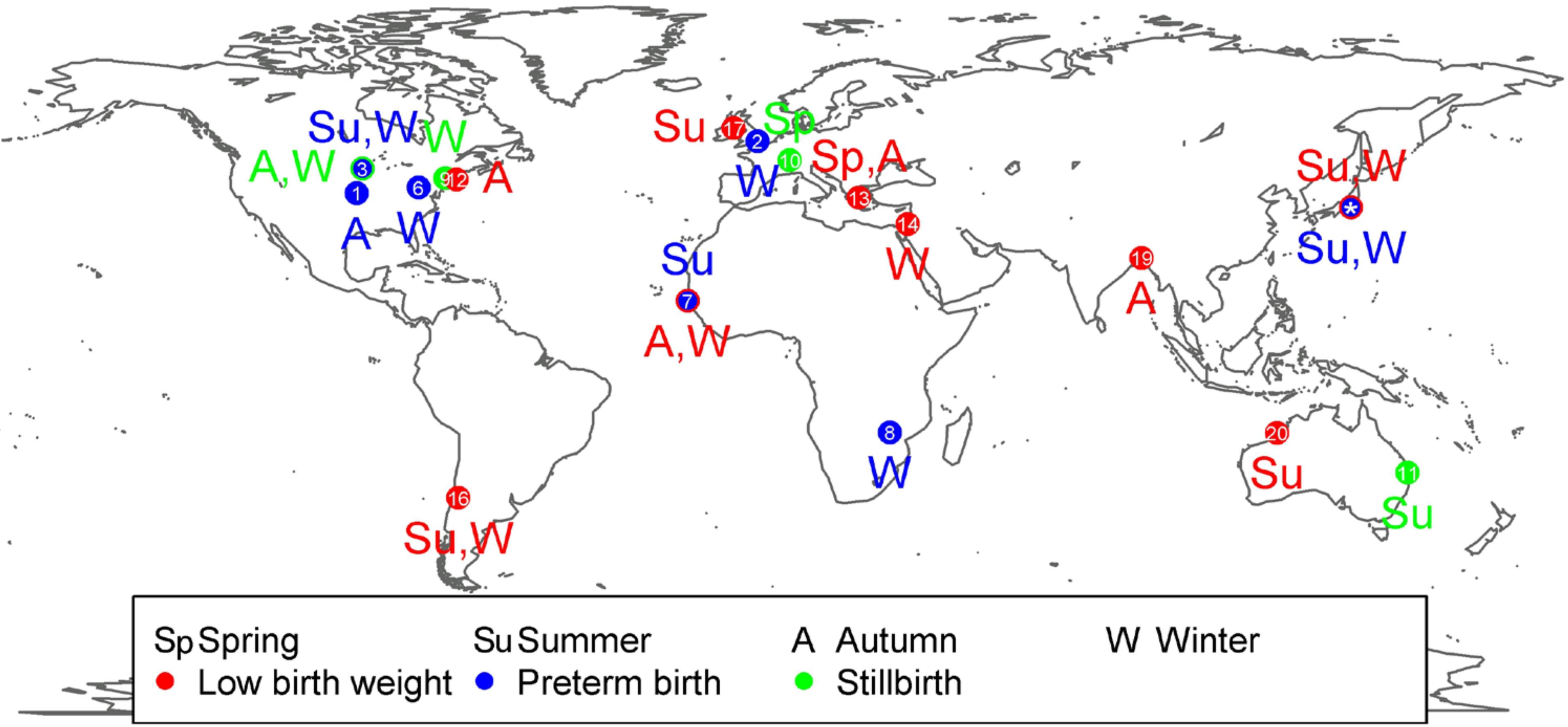


Figure 2.1. World map showing the seasonal peaks of adverse birth outcomes found by previous studies. I have numbered the studies according to Table 2.1. There were two different studies in Japan (*). One study in Australia (17) reported peaks in high birth weight and is not comparable to the studies reporting peaks in low birth weight (LBW). Thus, the study is not included in the figure.

2.5 EXPOSURE TO TEMPERATURE

Although the seasonal pattern of birth outcomes is well documented, studies have focused primarily on physiological mechanisms. Only a few studies have investigated the relationship between exposure to temperature and its effects on PTB and LBW but there are conflicting results (Table 2.5 and Figure 2.2). I was unable to identify any studies investigating the effect of temperature on stillbirth.

Table 2.5

Characteristics of the Studies on the effect of Temperature on Birth Outcomes

	Study	Location	Temp (°C)	Design	Sample	Exposure	Outcome	Adjusted for confounders	Results		
									Statistic	**Estimate**	**p-value**
Preterm birth											
1	(Lajinian et al., 1997)	Brooklyn, USA	12.2	RC	Patients receiving prenatal care from 1993 to 1994 (sample size not reported)	Mean weekly heat-humidity index in the hottest and coldest week of summer and winter	Preterm labour and preterm birth rates in each of those weeks	No	Exact test for linear trend	1.23% preterm labour rate in coldest period and 3.00% preterm labour rate in hottest period	< 0.002
									Exact test for linear trend	0.5% preterm birth rate in coldest period and 0.9% preterm birth rate in hottest period	0.29
2	(Yackerson et al., 2008)	Negev, Israel	17.4	RC	Births at the Soroka Medical Centre during 1999 (11,979 births)	Max and min temperature and humidity at time of birth	Preterm birth	No	Correlation	Not given	0.008
3	(Flouris et al., 2009)	Greece	18.3	RC	All births from 1999 to 2003 (516,874)	Mean temperature during month of birth	Gestational age	Yes	Correlation	–0.21	< 0.01
4	Basu et al 2010	California, USA	24.5	RC	All singleton births from May to September each year from 1999 to 2006 (58,681)	Apparent temperature at time of birth	Preterm birth	No	Percent change per 5.6 °C increase	8.6% (95% CI 6.0, 11.3)	
5	(Lee, Hajat, Steer & Filippi, 2008)	London, UK	10.5	RC	Live, singleton births from 1988 to 2000 (482,568)	Max and min temperature, and relative humidity at time of birth	Preterm birth	Yes	Odds ratio per 1 °C increase	1.00 (95% CI 0.99, 1.00)	
6	(Porter, Thomas & Whitman, 1999)	Chicago, Illinois, USA	10.5	RC	Singleton births during the months of June to August 1995 (11,792)	Heat-humidity index at time of birth	Gestational age	Yes	One-tailed t-test	Mean gestational age was 38.6 weeks in the coldest period (<90 °F) and 38.9 weeks in the hottest period (≥110 °F)	> 0.05

Low birth weight											
7	(Matsuda, Furuta & Kahyo, 1998)	Japan	15.1	ES	Births in 1982 (sample size not reported)	Mean temperature in each prefecture	Mean birth weight in each prefecture	Yes	Correlation	–0.63	< 0.01
8	(Wells & Cole, 2002)	Worldwide	–	ES	Births in 140 populations (5,558, median sample size)	Mean temperature and humidity	Mean birth weight	Yes	Percent change per 1 unit increase	–2.7% (95% CI –3.8, –1.6%)	< 0.01
9	(Lawlor, Leon & Smith, 2005)	Aberdeen, Scotland	7.9	RC	Live births from 1950 to 1956 (12,150)	Mean temperature for the middle ten days of each trimester and mean temperature for the 10 days around conception	Birth weight	Yes	Change per 1 °C increase in the first trimester	–5.4 g (95% CI –7.9, –2.9 g)	< 0.01
									Change per 1 °C increase in the second trimester	1.8 g (95% CI –0.7, 4.3 g)	0.35
									Change per 1 °C increase in the third trimester	1.3 g (95% CI 0.50, 2.1 g)	0.002
10	(Deschenes et al., 2009)	48 states and District of Colombia, USA	14.1	RC	Singleton births from 1972 to 1988 (37.1 million)	Mean daily max and min temperature in each trimester of the pregnancy	Birth weight	Yes	Percent change per day above 85 °F in the first trimester	Whites: 0.0003% (95% CI 0.0001, 0.0004%) Blacks: –0.0002 (95% CI –0.0003, 0.0007%)	
									Percent change per day above 85 °F in the second trimester	Whites: –0.0007% (95% CI –0.0008, –0.0006%) Blacks: –0.0016 (95% CI –0.0012, –0.0020%)	
									Percent change per day above 85 °F in the third trimester	Whites: –0.0009% (95% CI –0.0013, –0.0005%) Blacks: –0.0016 (95% CI –0.0012, –0.0.0020%)	
3	(Flouris et al., 2009)	Greece	18.3	RC	All births from 1999 to 2003 (516,874)	Mean temperature during month of birth	Birth weight	Yes	Correlation	–0.22	< 0.01
11	(Elter, Ay, Uyar & Kavak, 2004)	Marmara, Turkey	14.1	RC	Live, singleton births after 36 weeks of gestation from 1992 to 2003 (3,333)	Mean daily temperature, and humidity for each trimester	Birth weight	Yes	t-test for second trimester	2.37	0.018

12	(Murray et al., 2000)	Northern Ireland	9.1	RC	Live, singleton births after 36 weeks of gestation from 1970 to1986 (447,499)	Mean daily max and min temperature for each trimester	Birth weight	Yes	Change per 1 °C increase for females	3.50 g (95% CI 1.78, 5.22 g)	< 0.01
									Change per 1 °C increase for males	1.02 g (95% CI 0.14, 1.90 g)	0.25
13	(Tustin et al., 2004)	Dunedin, New Zealand	9.7	RC	Births after 38 weeks of gestation from 1999 to 2003 (8,516)	Mean temperature in second trimester	Birth weight	No	ANOVA F-statistic	0.31	> 0.05

Temp (°C) = Average yearly temperature, RC = Retrospective cohort, ES = Ecological study

2.5.1 TEMPERATURE AND PRETERM BIRTH

Lajinian et al. (1997) were the first to report a relationship between ambient temperature and preterm birth. The authors examined births from March 1993 to March 1994 at a municipal hospital in Brooklyn, USA. They divided the year into four periods and reported an increase in the rate of preterm *labour* from 1.2% in the period with lowest heat-humidity index to 3.0% in the period with the highest heat-humidity index. A statistically significant association between the heat-humidity index and preterm labour was found ($p < 0.002$). The pattern was similar for preterm birth, but the increase was not statistically significant.

Yackerson et al. (2008) investigated 11,979 births in Negev, Israel, and found that the occurrence of preterm birth was correlated with maximum temperature ($p = 0.008$) at the time of birth. A large study of more than a million babies in Greece also reported that mean ambient temperature during the month of birth was negatively correlated with gestational age ($r = -0.210$, $p < 0.01$) (Flouris et al., 2009). Basu et al. (2010) in California covering 60,000 births from 1999 to 2006 found that a 10 °F (5.6 °C) increase in temperature was associated with a 8.6% (95% CI 6.0, 11.3%) increase in preterm birth.

Lee et al. (2008) studying a large cohort of almost 500,000 births in London found no relationship between exposure to meteorological factors (ambient temperature and air pollution) and preterm birth. Porter et al. (1999) in Chicago investigated the effects of an infamous heatwave in 1995 by dividing ambient temperature into four categories during the year of 1995, but also found no relationship between ambient temperature and gestational age.

Studies by Flouris et al. (2009), Lajinian et al. (1997) and Yackerson et al. (2008) reported a significant relationship between preterm birth and ambient temperature, but Lee et al. (2008) and Porter et al. (1999) did not detect any link. However, the two latter studies only investigated exposure from the time of birth up to six days before birth. Ambient temperature may have had more adverse or different effects on preterm birth if exposure was estimated at different times (e.g., first trimester) or using longer 'exposure windows' of the pregnancy (e.g., 30 days prior to birth).

2.5.2 TEMPERATURE AND BIRTH WEIGHT

Eight studies examined the relationship between ambient temperature and birth weight. All these studies adjusted for gestational age either by excluding preterm infants or by controlling for it in the model. Matsuda and colleagues (1998) investigated Bergman's rule of larger body size in animals in colder climates (Blackburn, Gaston & Loder, 1999). They used an ecological study design, and were the first to report an association between ambient temperatures and birth weight. They compared 47 prefectures in Japan and found that mean birth weight was negatively correlated with mean temperature ($r = –0.63$, $p < 0.01$). Another ecological study by Wells and Cole (2002) examined 140 populations worldwide and the authors reported a significant negative correlation ($r = –0.59$, $p < 0.01$) between heat index and birth weight, and found that a one unit increase in heat index was associated with a 2.7% (95% CI 1.6–3.8%) decrease in birth weight.

The effect of high ambient temperatures may depend on the stage of gestation, with a possibly greater impact of temperature early in the pregnancy. Lawlor et al. (2005) investigated the association between prenatal exposure to temperature and birth weight in a cohort of 12,150 infants in Aberdeen, Scotland, and found that a 1 °C increase in mean temperature during the *first* trimester was associated with a 5.4 g (95% CI: 2.9–7.9 g) decrease on birth weight. In the *third* trimester, however, a 1 °C increase in mean temperature was associated with 1.3 g (95% CI 0.5–2.1 g) *increase* in birth weight.

Deschenes et al. (2009) conducted a large study in the United States, which examined extreme temperatures and birth weight in 37 million singleton births. There was a strong negative relationship between birth weight and temperature in white mothers, particularly when the mother was exposed to hot days (temperature higher than 85 °F) in the second and third trimester (0.0007% and 0.0009% decline in birth weight per hot day, respectively). For African-American mothers, exposure to hot days in all three trimesters was associated with a statistically significant decrease in birth weight, ranging from 0.0002% to 0.0016% per hot day.

Flouris and colleagues (2009) examined more than a million births in Greece between 1999 and 2003, and found a negative correlation between mean ambient temperatures during the month of birth and birth weight ($r = -0.22$, $p < 0.01$).

Elter et al. (2004) and Murray et al. (2000) found a relationship between cold ambient temperatures and low birth weight. In Marmaris, Turkey, cold temperatures were associated with low birth weights and that the temperature to which the mother was exposed in the second trimester was an independent determinant of birth weight (Elter et al., 2004). This study had a sample size of only 3,333 singleton births, which may have meant it would have been unable to detect small effects due to hot temperatures. In Northern Ireland, in a larger cohort (n = 418,817), an increase in mean birth weight of 3.5 g per 1 °C increase in mean daily maximum temperature during the second trimester was found (Murray et al., 2000). The authors stated that the effect from cold temperatures on birth weight may have been caused by processes that affect fetal growth in winter, such as exposure to infectious agents, decreased physical activity, increased exposure to environmental smoke, or increased pregnancy-induced hypertension.

Tustin et al. (2004) examined a cohort of 7,039 term infants between January 1999 and December 2003 in Dunedin, New Zealand. They found that the average birth weight did not differ as a function of maternal exposure to high or low temperatures ($p > 0.05$).

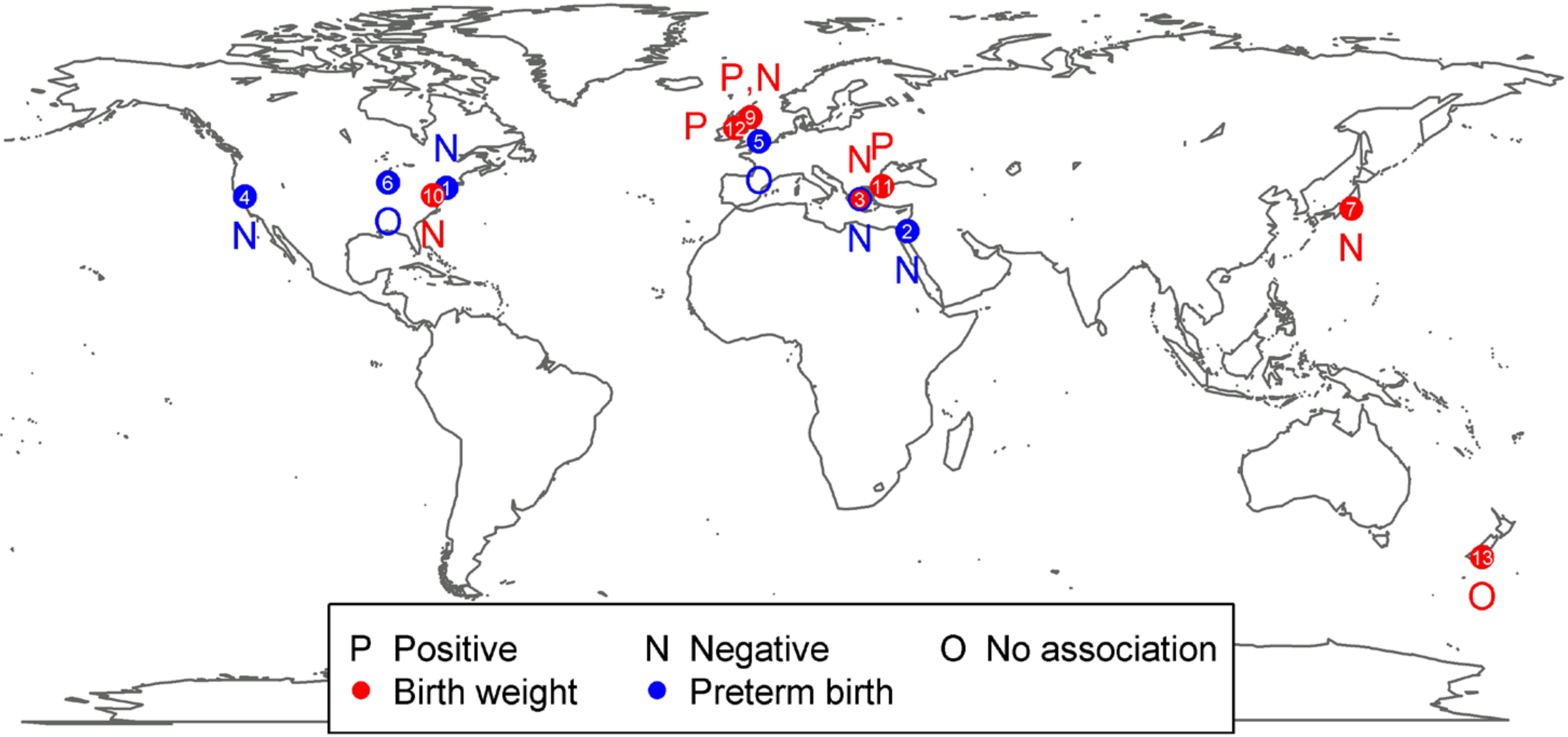


Figure 2.2. World map showing the associations between temperature and adverse birth outcomes found by previous studies. The studies are numbered according to Table 2.5. The study in Scotland found a negative association in first trimester and a positive association in third trimester. One worldwide study was conducted that found a negative relationship between temperature and birth weight (8).

2.6 OTHER ENVIRONMENTRAL FACTORS

In addition to temperature, other factors might help explain the seasonality of birth outcomes. These include humidity, sunlight, barometric pressure and air pollution.

2.6.1 HUMIDITY

At high temperatures, alternative means of heat loss such as convection and radiation cease to operate and sweating is the only way of losing heat. However in humid environments the effectiveness of sweating can be compromised (Dubois, 1938). Most studies investigating temperature and its influence on birth outcomes have included humidity in their analyses. Some have adjusted for humidity in their models (Bergstrom, Povey, Songane & Ching, 1992; Driscoll & Merker, 1984; Elter et al., 2004; Lee et al., 2008; Yackerson, Piura & Friger, 2007; Yackerson et al., 2008), and others have calculated a heat-humidity index (Lajinian et al., 1997; Porter et al., 1999; Tam, Sahota, Lau, Li & Fung, 2008; Wells & Cole, 2002).

2.6.2 SUNLIGHT

Studies have examined the relationship between exposure to sunlight and the effects on birth weight. In New Zealand, birth weight was significantly higher when mothers were exposed to peak, as opposed to trough, periods of sunshine during their first trimester of gestation ($F = 4.61$, $p < 0.05$) (Tustin et al., 2004). One study reported that the peak in birth weight lagged the month of peak sunshine hours by 6–9 months indicating that sunlight has the most effect on birth weight in early pregnancy (Waldie, Poulton, Kirk & Silva, 2000). Sunlight is necessary for making Vitamin D and is suggested to explain the positive effect on birth weight (McGrath, Burne & Eyles, 2005). A study conducted at 12 sites in the United States during

1959 to1965 found a significant association between season of birth by ethnicity, and birth weight (van Hanswijck de Jonge et al., 2003). The interaction was strongest among white mothers and no association was found among African Americans. As blacks produce less vitamin D than whites in response to sun exposure (Dawson-Hughes, 2004), this supports the notion about a relationship between exposure to sunlight and birth weight.

2.6.3 BAROMETRIC PRESSURE

Researchers in Mozambique covering one year of birth data, undertook linear regression analysis of monthly mean atmospheric pressure and monthly PE/delivery ratios and reported a significant relationship ($p < 0.01$) (Bergstrom et al., 1992). In Japan, researchers reported an increased number of ruptured membranes, deliveries at barometric pressures lower than 1010.7 hPa. This relationship was found in both women with spontaneous rupture of membrane and women with premature rupture of membrane ($p < 0.01$), suggesting that low barometric pressure induces rupture of the fetal membranes and preterm delivery (Akutagawa, Nishi & Isaka, 2007).

2.6.4 AIR POLLUTION

Air pollution is highly seasonal and has been found to adversely affect birth outcomes (Glinianaia, Rankin, Bell, Pless-Mulloli & Howel, 2004). Most combustive pollutants, such as nitrogen dioxide (NO_2) and particular matter (PM), peak in winter due to the increased demand for heating while low-level ozone peaks in summer because it is formed by the reaction between combustive pollutants and sunlight (Queensland Department of Environment and Resource Management, 2010). Air pollution has been associated with adverse birth outcomes such as LBW and PTB in most trimesters and exposure windows (Bell, Ebisu & Belanger, 2007;

Hansen, Barnett & Pritchard, 2008; Nascimento & Moreira, 2009). Only a few studies have investigated the effect on stillbirth (Pearce, Glinianaia, Rankin & Pless-Mulloli, 2008; Pope et al., 2010) and the results are contradictory. Thus, air pollution is an important potential confounder of the effect of temperature on birth outcomes.

2.7 BIOLOGICAL MECHANISMS

High environmental temperatures can cause hyperthermia. Physical exertion on hot days can generate heat beyond a healthy body's ability to cool itself, because the heat and humidity of the environment reduces the efficiency of the normal cooling mechanisms of the body (Cheuvront, Kenefick, Montain & Sawka, 2010). During periods of hot weather, the physiological changes experienced during pregnancy that are likely to intensify maternal heat stress include (Prentice, Goldberg, Davies, Murgatroyd & Scott, 1989; Wells & Cole, 2002):

- increased fat deposition leading to higher core body temperature
- change in body weight and shape that decreases the ratio of surface area to body mass, reducing the capacity of the body to lose heat by sweating
- weight gain and fetal growth that increases basal heat production
- interactions between the increased body mass and physical activity that may further aggravate production of heat
- the fetus adding to the maternal heat stress through its body composition and metabolic rate.

Maternal hyperthermia has been reported to be associated with abortions and stillbirths with lags of days to several weeks (Edwards, 2006). Li et al. (2003) investigating hot tub and Jacuzzi use during the pregnancy and its effect on abortions found that pregnant women using a hot tub or Jacuzzi were twice as likely to have an abortion than women who did not (HR = 2.0, 95% CI 1.3, 3.1). They also found that the risk of abortion may increase with increasing water temperature, increasing frequency of use, and with use at very early gestational ages.

Maternal factors including increased uterine activity could also contribute to the PTB or death of the fetus. Khamis and colleagues (1983) found that application of heat to the abdominal wall of women in labour increased uterine activity. Dehydration caused by heat stress and sweating may also be harmful to the fetus. Insufficient fluids in the mother can decrease the amount of blood available to the fetus and lead to increased risk of preterm contractions (Stan, Boulvain, Pfister & Hirsbrunner-Almagbaly, 2002).

Hyperthermia has also been shown to cause birth defects in numerous animal and human studies and some of the suspected mechanisms are cell death, disturbance of cell migration, disruption of gene expression and damage to cell membranes (Edwards, Saunders & Shiota, 2003; Moretti, Bar-Oz, Fried & Koren, 2005). Neural tube defects and other birth defects caused by damage to the nervous system are the most common birth defects and these types of birth defects may be a direct cause of stillbirth (Hernán, Hernández-Díaz, Werler & Mitchell, 2002).

2.8 METHODOLOGICAL CHALLENGES

Several epidemiological study designs and statistical methods have been applied to assess the effects of ambient temperature on birth outcomes. Early studies investigating season and ambient temperature were mainly descriptive, while recent investigations have used regression models to estimate odds ratios measuring the risk of low birth weight and preterm birth per unit increase in temperature or by season of birth (Tables 1 and 5). Expected rates of birth outcomes in extreme temperatures have been calculated using a variety of measures, including averages from similar time periods in previous years, moving averages, and regression models (Chodick et al., 2007; Elter et al., 2004; Friis et al., 2004; Lawlor et al., 2005; Murray et al., 2000). The great variety of methods and outcomes used makes it difficult to compare the effect estimates of these studies formally, using meta-analysis.

2.8.1 CONFUSING DEFINITIONS

The great variation in the definitions of birth outcomes makes it difficult to compare results from different studies. For example, there is a variety of definitions for stillbirth and cut-offs at different gestational ages ranging from 20 to 28 weeks or birth weights ranging from 350 to 1,000 grams (Kramer et al., 2002; Morrison & Rennie, 1995). For example, in the United Kingdom, the Still-Birth (Definition) Act (1992) states: “any ‘child’ expelled or issued forth from its mother after the 24th week of pregnancy that did not breathe or show any other signs of life should be registered as a stillbirth” (Office of Public Sector Information, 1992). In Australia any birth where the baby is dead at birth weighing more than 400 grams, or more than 20 weeks in gestation, is defined as stillbirth (Australian Institute of Health and Welfare, 2008). "Miscarriage" tends to be used if the death occurs earlier in development. In contrast, others use the term "stillbirth" regardless of the stage of fetal development (Kowaleski, 1997). Also perinatal mortality, neonatal mortality, and fetal mortality have different definitions making the comparison of studies difficult (Morrison & Rennie, 1995).

Not all LBW babies are preterm and not all preterm babies are LBW. It is important to distinguish between LBW caused by PTB and LBW caused by intrauterine growth restriction. One way of taking gestational age into account when assessing LBW is to use the term SGA, which excludes babies with normal birth weight relative to their age and includes only the lightest 10% in each gestational age stratum (Wilcox, 2001).

2.8.2 LINEARITY

Most studies found an association between high temperatures and LBW (Deschenes et al., 2009; Flouris et al., 2009; Lawlor et al., 2005; Matsuda et al., 1998; Wells & Cole, 2002), but the results are inconsistent. Two studies found a relationship between cold temperatures and LBW (Elter et al., 2004; Murray et al., 2000), and one found no relationship (Tustin et al., 2004). Other health outcomes (such as adult mortality and morbidity) have been shown to have a J- or U-shaped association with ambient temperature, with elevated risks at temperature extremes (Curriero et al., 2002; Huynen et al., 2001). A non-linear association between temperature and birth outcomes could be the cause of the contradictory results among the studies, which all assumed a linear association. To use a linear association when the effect is actually U-shaped would mean that either: no effect was found (if the increases in risk at low and high temperatures were roughly equal); a linear increased risk at low temperatures was found (if the risk at low temperatures was strongest); or a linear increased risk at high temperatures was found (if the risk at high temperatures was strongest). However, any increased risks observed would likely be an underestimate of the true association, as the slope would be ‘pulled’ towards zero by the opposing risk (biased towards the null).

2.8.3 LAST MENSTRUAL PERIOD (LMP)

Studies investigating gestational age often did not use last menstrual period (LMP) due to lack of data and the gestational age was often derived from ultra-sound screening in the first trimester of the pregnancy and from assessment at birth as reported on the birth certificate (Basu et al., 2010; Bodnar & Simhan, 2008; Flouris et al., 2009; Keller & Nugent, 1983; Lee et al., 2006; Lee et al., 2008). If temperature affected fetal growth prior to the ultra-sound or the clinical assessment, then the effects of temperature would be underestimated (Skalkidou et al., 2010b; Slama, Darrow, et al., 2008).

2.8.4 EXPOSURE WINDOWS

A methodological challenge for all studies in this area is to identify whether there are particular periods of susceptibility during pregnancy. Previous studies have been inconsistent in their exposure windows for temperature. Most studies have focused on exposure during the last week or days before birth (King, Fleschler & Cohen, 1997; Lajinian et al., 1997; Lee et al., 2008; Yackerson et al., 2007). Another approach is to focus on exposure at conception (Tam et al., 2008). Some have assessed exposure to ambient temperature by trimester (Deschenes et al., 2009; Elter et al., 2004; Murray et al., 2000). In these studies a difficulty arises when dealing with PTB, because when the pregnancy is shorter than 37 weeks it does not have three full trimesters (Woodruff et al., 2009). When there are no strong *a priori* biologic hypotheses concerning which period is more vulnerable, investigating smaller time scales (e.g., months or weeks) might be a more useful and appropriate approach.

2.8.5 CONFOUNDERS

Many studies investigating season or temperature's influence on birth outcomes have not included any or very limited confounders in their analysis (Flouris et al., 2009; Lajinian et al., 1997; Lee et al., 2008; Tustin et al., 2004; Yackerson et al., 2007; Yackerson et al., 2008). Confounders and possible effect modifiers such as air pollution, humidity, maternal age, marital status, ethnicity, socio-economic status, smoking, previous pregnancies, antenatal visits, and pregnancy complications, should be included when examining determinants of birth outcomes. Only one of the studies identified in the literature review controlled for maternal smoking (Bodnar & Simhan, 2008). This may have influenced the results as smoking is a very strong determinant of both LBW and PTB (Andres & Day, 2000). A study in the US found that the sale of tobacco was seasonal (Chandra & Chaloupka, 2003), therefore, it could be a confounder for the temperature effect on birth outcomes. Nutrition and physical activity are also highly seasonal and may have similar confounding effects (Mercer, 1998).

Adaptive behaviours such as use of air conditioning will affect the association between ambient temperatures and indoor temperatures and increase variation in heat exposure among mothers at a particular ambient temperature. Thus, the ambient temperature of an area may not accurately represent the actual temperature exposure of each individual in that area. As all the reviewed studies were population-based observational studies, none of them was able to control for individual level indoor temperature, heating or cooling.

Another type of confounding in birth outcome studies is created by underlying seasonal patterns in conception rates between population groups. Darrow and colleagues showed how a seasonal difference in the number of births between ethnic groups, with one group at a much higher risk of PTB, could create a seasonal pattern in PTB (Darrow, Strickland, et al., 2009). This seasonal pattern might then wrongly be associated with a seasonal exposure such as temperature or air pollution. For example, Australian Indigenous women they have significantly shorter pregnancies than non-Indigenous women (Australian Institute of Health and Welfare, 2006). If more Indigenous women gave birth in January, then the average gestational age in January would appear lower than average. A reduced average gestational age could then be wrongly associated with the higher summer temperatures in January. This reiterates the importance of adjusting for important factors such as ethnicity.

Darrow and colleagues have shown a potential for confounding by gestational age created by aggregating fetuses at risk across different gestational ages, which ignores the fact that the risk of birth increases exponentially with higher gestational ages (Darrow, Strickland, et al., 2009). Platt and colleagues (2004) further explain this concept: “Gestational ages are not exchangeable; that is, an infant born at 40 weeks was at risk of being born at 30 weeks, but an infant born at 30 weeks of gestation is not at risk of being born at 40 weeks. Thus, gestational age should be considered a time axis rather than an independent variable in the model”. New methods of analysis that account for gestation age are recommended. A time-dependent analysis would eliminate the confounding by only comparing foetuses of the same gestational age (Meister & Schaefer, 2008).

A recent study investigating the effect of apparent temperatures on PTB, effectively eliminated the confounders between pregnancies by applying a case-crossover design, where each case acts as its own control (Basu et al., 2010).

However, the study design did not control for the confounding factors of conception rates or gestational age and could still present a bias (Darrow, 2010).

Future studies should aim to include all major confounders. This may be difficult for studies that rely on routinely collected data sources (such as birth registers) that have no control over the variables collected. However, an advantage of these data sources is that they offer a large study sample and therefore well powered to detect relatively small associations between temperature and birth outcomes. Additionally, they are representative of the target population.

2.9 KNOWLEDGE GAPS AND FUTURE RESEARCH NEEDS

Only a few studies have examined the relationship between temperature and birth outcomes (Basu et al., 2010; Deschenes et al., 2009; Tam et al., 2008; Wells & Cole, 2002). These studies have rarely included important confounders such as humidity, air pollution, smoking, ethnicity, and previous birth outcomes. There are also substantial differences among these studies concerning research design, exposure windows, confounders, and exposure and outcomes measures. Consequently, there are still many knowledge gaps in this area of health.

Future research is required to clarify the effect of temperature on birth outcomes. New studies should use more sophisticated study designs such as population-based cohort studies using individual fetal outcome and high-quality exposure data. Because it is not known whether there are critical time windows of exposure during fetal development, exposure windows should be defined according to previous published studies and if possible, made narrower (e.g., by examining months or weeks of the pregnancy instead of trimesters) to achieve a more accurate picture of vulnerable periods.

A few studies have calculated a heat-humidity index reflecting the actual feeling of heat stress that individuals may experience at different temperature and humidity levels. Future studies should consider this approach as it might result in a more accurate picture of heat stress that pregnant mothers experience. However, Barnett et al. (2010) examined whether one temperature measure was better than the others and found that was no one temperature measure that was superior to the others. Future studies should also consider a non-linear relationship between temperature and birth outcomes.

Potential confounding seasonal factors such as humidity and air pollution must be included to get a closer measure of the influence temperature may have on birth outcomes. In addition, future studies should control for known sources of variance (e.g. ethnicity, smoking and previous pregnancy outcomes). Given the potential confounding from aggregating fetuses of different gestational ages and other sources of confounding, future research needs to consider new methods of analysis which acuate these challenges. Research methods that only compare fetuses of the same gestational age would effectively eliminate this bias.

2.10 SUMMARY AND IMPLICATIONS

Our climate is changing, and in Brisbane, the temperature is projected to increase in the coming decades. Vulnerable groups will be most at risk of adverse health outcomes from these increased temperatures. One vulnerable group is pregnant mothers, and it is important to protect them and their unborn babies from potential adverse health effects and disease later in life.

A number of studies have shown a relationship between season, birth outcomes and more specifically, an association between exposure to temperature and LBW, PTB, and stillbirth. This literature review has identified many methodological challenges and knowledge gaps, including research design, different exposure windows, and definition of birth outcomes. Further well-designed studies using carefully considered methods are clearly needed.

This study covered a large cohort (n = 101,870) over 4.5 years in the Brisbane statistical division. It used individual level data with a range of potential confounding factors and sources of variance. The variables included maternal smoking, which has been unavailable in most previous studies. Given the substantial influence of smoking on adverse birth outcomes, this is an important improvement from previous research. Also a range of other variables were included such as relative humidity, air-pollution and maternal characteristics including maternal age, ethnicity and pregnancy complications. I used splines to account for a possible non-linear effect of temperature on birth outcomes.

I further refined the study's exposure windows to investigate vulnerable gestational periods and weeks. To remove the potential confounding arising from aggregating fetuses at different gestational ages despite of increasing risk of PTB at higher gestational ages (Darrow, Strickland, et al., 2009), I used a Cox proportional hazard model. Although this method has been applied in previous studies investigating the influence of smoking (Platt et al., 2004), urinary tract infection

(O'Neill, Hertz-Picciotto, Pastore & Weatherley, 2003),and air pollution (Suh et al., 2009) on birth outcomes, it has, to our knowledge, not been applied when investigating the effects of temperature on birth outcomes.

Chapter 3: Research design and methods

3.1 STUDY DESIGN

The study used a retrospective cohort study design to explore seasonal patterns in birth outcomes and their association with temperature. The main independent variables were season (month during the pregnancy) and mean temperature. The dependent variables were gestational age and stillbirth. I chose not to examine LBW, as it is often caused by low gestational age (United Nations Children's Fund and World Health Organization, 2004).

The research null-hypotheses are:

- H_0: There is no seasonal pattern in gestational age or stillbirth
- H_0: High temperatures do not influence gestational age or risk of stillbirth
- H_0: The risk of shortened gestational age or stillbirth posed by temperature does not differ by gestational period

3.2 STUDY AREA

I collected birth certificates from Brisbane Statistical Division (Figure 3.1), the capital of Queensland, Australia.

Figure 3.1. Brisbane Statistical Division. (Australian Bureau of Statistics, 2007a)

Brisbane is the country's third largest city and has the highest population density in Queensland with a population size of 1,763,135 at the census in 2006 (Australian Bureau of Statistics, 2007a). It is located at the latitude 27°29'S and longitude 153°8'E and has a subtropical climate. The city often experiences long periods of hot temperatures. As per the rest of Australia, an increased intensity and frequency of heatwaves have been predicted because of climate change (Woodruff et al., 2006).

3.3 CONCEPTUAL FRAMEWORK

As described in Chapter 2, biological, socio-economic and behavioural variables adversely influence birth outcomes. In the analysis, I looked at seasonal factors to examine whether they influence birth outcomes as suggested by previous studies. Figure 3.2 illustrates the conceptual framework for the analysis, which includes key independent and dependent variables and a range of confounding factors.

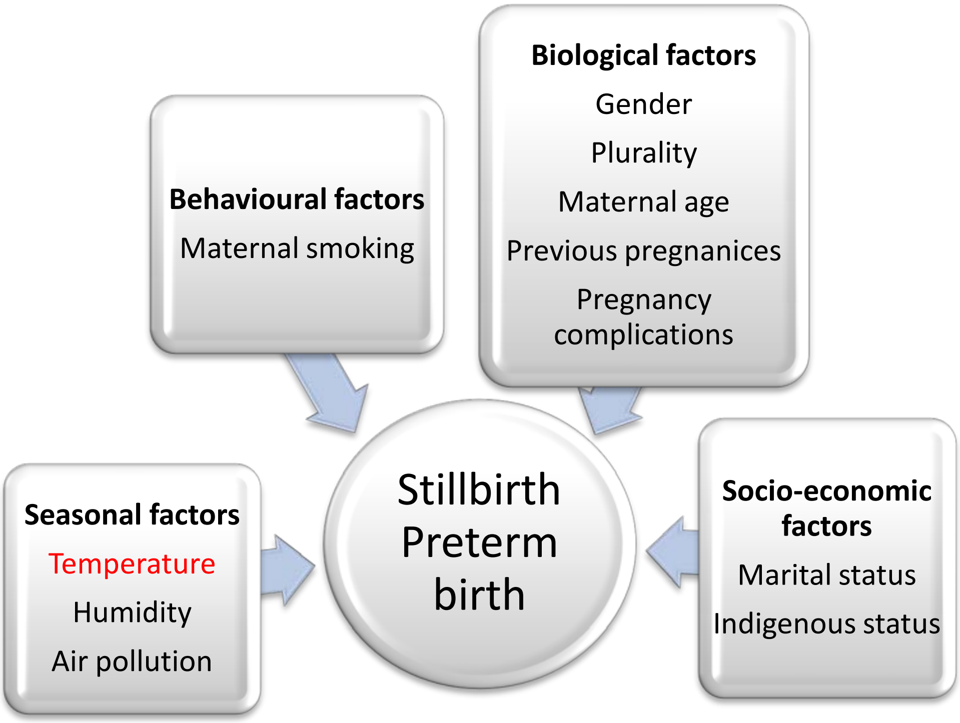


Figure 3.2. The conceptual framework for the analysis.

3.4 OUTCOME ASSESSMENT

3.4.1 BIRTH CERTIFICATE DATA

I obtained birth outcome data covering all singleton births between 1 July 2005 and 30 June 2009 in Brisbane Statistical District (*n* = 114,932) from the Queensland Health Perinatal Data Collection Unit. I chose these dates because the Queensland Health Perinatal Data Collection Unit started collecting data on smoking from July 2005, and June 2009 was the most recent data available. Because twins and triplets often are born with lower birth weight and are more likely to be born preterm

(Bortolus et al., 1999), I only collected singleton births. As described in the literature review, biological and socio-economic factors are important potential confounders in birth outcome studies and I requested information about a range of socio-demographic and biological factors. Variables requested were:

Details on the mother:

- age
- Indigenous status
- marital status (never married, married/de facto, or 'other')
- number of previous pregnancies (including live births, abortions and stillbirths)

Details on the pregnancy:

- date of last menstrual period (LMP)
- pregnancy complications (pre-eclampsia and pregnancy-induced hypertension)
- smoking during the pregnancy
- number of antenatal visits

Details on the child:

- date of birth
- birth weight (grams)
- gestational age (weeks)
- sex
- birth outcome (live birth/stillbirth)

Because the addresses or postcodes of the mothers could be used to re-identify the birth files, I was not allowed access to these data.

3.4.2 ASSESSMENT AND CODING OF GESTATIONAL AGE

I assessed gestational age based on clinical evaluation at time of birth as reported on the birth certificate. This method may underestimate the effect of temperature on the growth of the fetus as the clinical evaluation is partly based on birth weight and size, thus growth restrictions happening before the evaluation is missed (Slama, Khoshnood & Kaminski, 2008). Another method of assessing gestational age is to calculate the difference between the first day of the last menstrual period and the date of birth. However, estimation of gestational age based on LMPs can be subject to recall bias (Ayas et al., 2003; Skalkidou et al., 2010a). In addition to the questionable accuracy, LMP dates are often incomplete (Berkowitz & Papiernik, 1993). This was also the case in this cohort (29% of the LMP dates were missing) making the clinical assessment of gestational age a better measure in my study. Gestational age was reported on the birth certificate in completed weeks of gestation.

I treated gestational age as a continuous outcome variable. Most previous studies have categorised gestational age into preterm birth (PTB) and term birth. Whilst this has some clinical significance, it may cause a loss of statistical power (Greenland, 1995). However, I did also divide the pregnancy into gestational periods to investigate the risk of extreme PTB (< 28 completed weeks of gestation), PTB (28–36 completed weeks of gestation), and term birth (≥ 37 completed weeks of gestation) when exposed to temperature and to make my results more comparable to other studies (Section 3.8.7).

3.4.3 ASSESSMENT AND CODING OF STILLBIRTH

I assessed stillbirth based on the Australian definition: “the loss of a fetus that shows no signs of life at birth and is at least 20 weeks in gestation or 400 grams in birth weight”. Fetal death before week 20 of gestation is considered an abortion in Australia and is not included in the birth certificates. I coded stillbirth as a dichotomous variable (live born/stillborn).

3.4.4 FIXED COHORT BIAS

An exploratory analysis of the data revealed an interesting problem. Figure 3.3 shows a scatter plot of the gestational ages of this cohort by date of conception (date of birth minus gestational age).

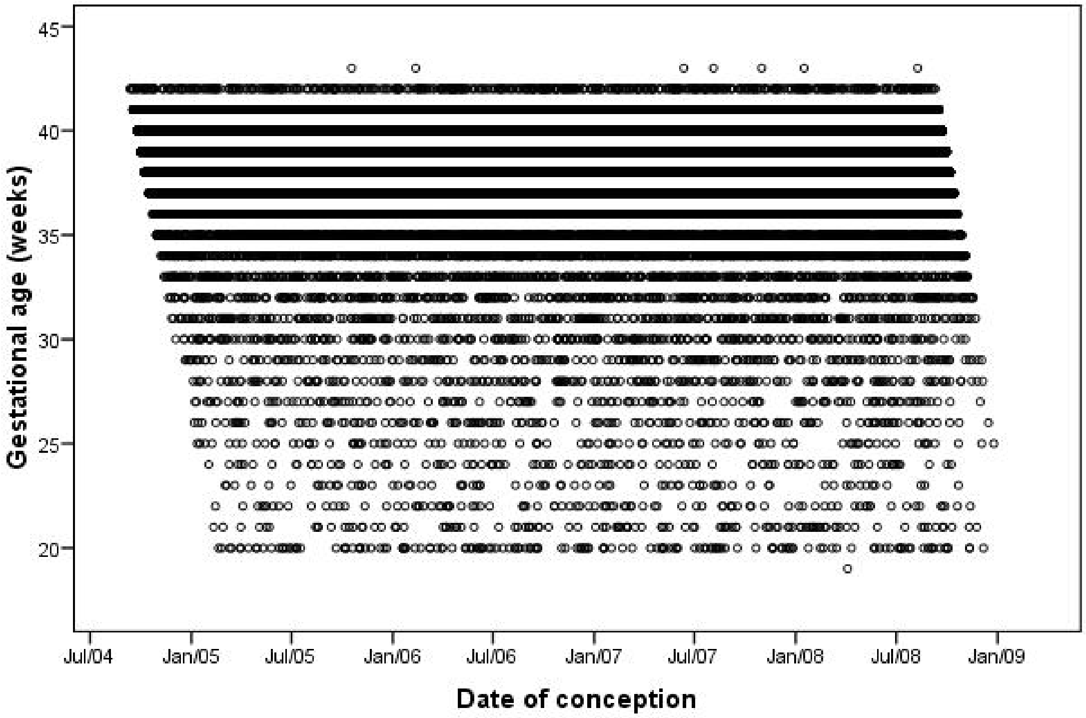


Figure 3.3. Scatter plot of gestational ages (weeks) by month of conception for the cohort. The first birth was 1 July 2005. Of these births, the first conception happened in September 2004. The last birth was 30 June 2009 and the last conception was in December 2008.

It reveals that gestation times are longer at the start of the study period and shorter at the end of the study period (based on date of conception). The reason is that the majority of the women that conceived in September 2004 gave birth before the study started. Therefore, only the long pregnancies were included at the start of the study period. Similarly, at the end of the study period, the women with long pregnancies gave birth after the study period ended, with the results that only the shorter pregnancies were included in the cohort. Figure 3.4 illustrates the concept.

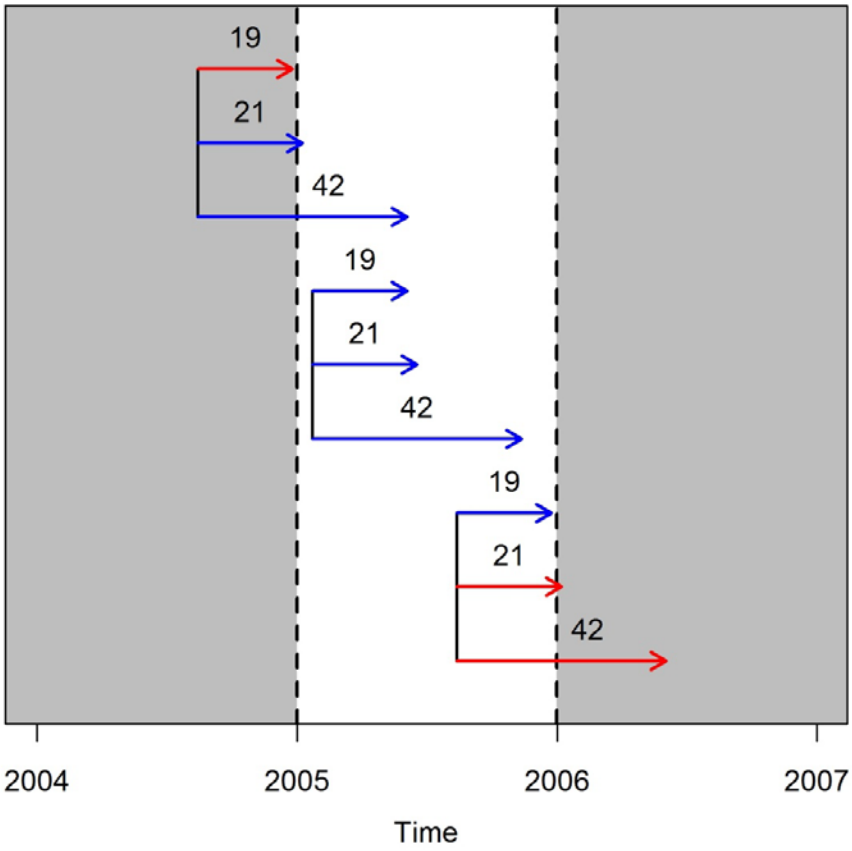


Figure 3.4. The population at risk according to birth date using a birth cohort based on all births in 2005. Blue arrows show births included in a cohort of all births in 2005 and red arrows show births that were missed. The number above each arrow shows the gestation time in weeks. The plot shows three groups of three births, and each group represents one conception date.

The observed pattern in gestation length would only occur when plotting gestation against *date of conception*, not date of birth as the cohort captures all women giving birth at the start and end of the study period. Thus, this pattern is a problem in studies investigating exposure calculated from the date of conception (e.g. month of conception or first trimester), but not for studies investigating exposure calculated from the date of birth (e.g. week of birth or last trimester).

It is a bias caused by subjects who were completely missed from the cohort, not because of subjects who were partially observed. This pattern could bias any estimates of the effects of temperature on gestational age when calculating exposure based on the date of conception. For example if September 2004 was unusually hot, then I could wrongly conclude that hot temperatures were associated with longer gestations (Figure 3.3). Conversely, if November 2008 was unusually hot then I could wrongly conclude that hot temperatures were associated with shorter gestations. I investigated how this bias can influence the results of a study in an article published in BMC Medical Research Methodology (Appendix A).

I avoided this bias by removing some pregnancies from the cohort. The adjusted cohort is created by limiting the included pregnancies to those with conception dates:

i. 19 weeks before the cohort started, and
ii. 43 weeks before the cohort ended.

We used 19 and 43 weeks as cut-offs since 19 weeks was the shortest pregnancy resulting in live birth in the cohort (a stillbirth would be considered an abortion) and 43 weeks was the longest pregnancy regardless of birth outcome. This means that only the pregnancies that had conception dates after 25 February 2005 and before 2 September 2008 were included in the final analysis (*n* = 101,870, 88.6% of the total number of births). This ensured that the long pregnancies at the beginning of the cohort, and the short pregnancies at the end of the cohort (Figure 3.3), were excluded. The exclusions ensured that all comparable pregnancies were included and helped ensure that the estimation of the temperature effect on gestational age was unbiased.

3.5 EXPOSURE ASSESSMENT

3.5.1 WEATHER DATA

I obtained weather data including hourly temperature and relative humidity from the Queensland Department of Environment and Resource Management for the period 25 February 2005 to 30 June 2009. The data requested were from the five weather stations: Pinkenba, South Brisbane, Woolloongabba, Rocklea, and Springwood. Figure 3.5 shows the locations of these weather stations.

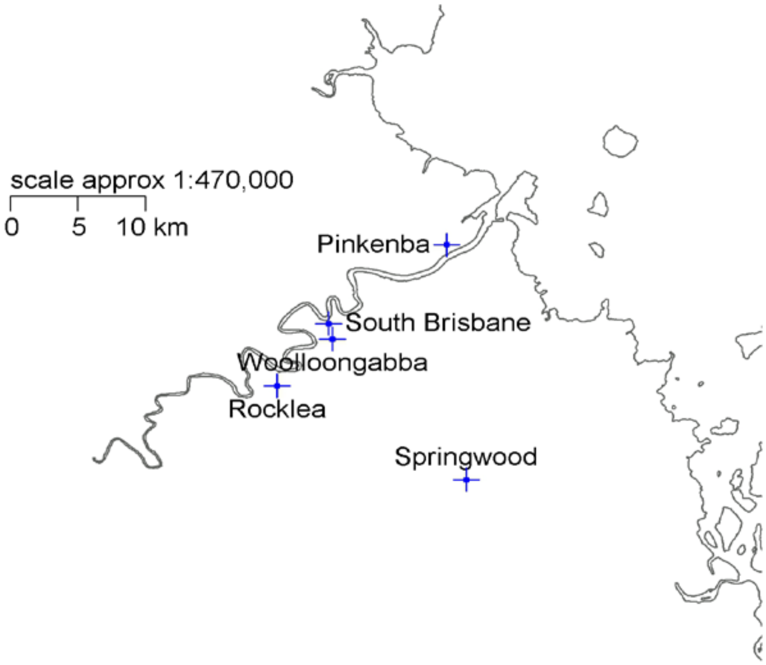


Figure 3.5. The weather/pollution stations in Brisbane.

Mean daily temperature and relative humidity were derived from the hourly values. I chose to use mean temperature as a recent study in the United States found that there was little difference between humidex, minimum, mean and maximum temperatures when examining temperature-related health effects (Barnett et al., 2010). It has also been a common measure in previous studies on the effect of ambient temperature on birth outcomes (Flouris et al., 2009; Lajinian et al., 1997; Lawlor et al., 2005). Average temperature and humidity for each week of each pregnancy were calculated based on the daily averages.

3.5.2 AIR POLLUTION

The Queensland Department of Environment and Resource Management provided data on air pollution including particulate matter with a diameter of less than 10 μm (PM_{10}), particulate matter with a diameter of less than 2.5 μm ($PM_{2.5}$) nitrogen dioxide (NO_2), carbon monoxide (CO), sulphur dioxide (SO_2) and ozone

(O_3). The data comprised hourly concentrations of the pollutants between 25 February 2005 and 30 June 2009. As I did not have information on postcodes for the mothers, the concentrations were averaged across the five monitoring sites in Figure 3.5. However, many previous studies (in Australia and worldwide) have shown significant health effects using only the temporal variation in pollution. The data were then averaged to mean weekly concentrations.

I scaled the air pollutants by dividing the variables with their own interquartile range (IQR). In line with previous studies (Bobak, 2000; Hansen et al., 2006), I assumed that the air pollutants had a linear effect on birth outcomes.

3.6 DATA MANAGEMENT

3.6.1 MERGING THE DATASETS

The data on birth outcomes, weather, and air pollution were merged so that the mean temperature and humidity, and mean air pollution concentrations, corresponded with each date of birth. I also created a temperature variable that corresponded with date of conception. The descriptive and bivariate analyses were made using this dataset.

3.6.2 MISSING DATA

There were few missing values in the birth files with the exception of last menstrual period where 29.1% of the records (29,644) were missing (Table 3.1). The small amount of missing data shows the high quality of this dataset. ‘Gestational age’ or ‘birth outcome’ did not have any data missing. I randomly imputed the small number of other missing values in the birth data. This imputation was based on the marginal distribution for each variable. For example, 17.2% of women smoked during the pregnancy. So missing smoking data were randomly imputed as “Yes” with probability 0.172.

Table 3.1

The Missing Values in the Birth Certificates

	Missing	**%**
Birth outcome	0	0
Gestational age	0	0
Sex	0	0
Pregnancy complications	0	0
Smoking status	763	0.7
Antenatal visits	50	<0.1
Last menstrual period	29,644	29.1
Marital status	31	<0.1
Previous pregnancies	0	0
Maternal age	0	0
Indigenous status	76	0.1

Table 3.2 displays the missing data on the weather and air pollution variables for each of the five monitoring stations. I imputed missing values from individual monitoring stations based on a regression model that fitted a trend, a cosinor for season, the stations average reading, and a correlation matrix between the stations. This correlation matrix means that imputed values for individual stations were strongly dependent on the observed values from other stations on the same day. After imputing any missing values from single monitoring stations, I calculated the daily averages across all stations. I calculated the average after imputing any missing values to avoid possible biases created by particular stations being missing. For

example, if data from the “dirtiest” station were missing on a particular day then averaging over the other stations would make that day look artificially “clean”.

Table 3.2

Missing Values in the daily Weather and Air Pollution Datasets for each station

	Rocklea		**Pinkenba**		**Woolloon-gabba**		**South Brisbane**		**Springwood**	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Temp	3	0.2	1	0.1	433	27.3	15	0.9	37	2.3
Hum	7	0.4	1	0.1	▨	▨	▨	▨	▨	▨
PM_{10}	10	0.6	4	0.3	435	27.4	8	0.5	28	1.8
$PM_{2.5}$	14	0.9	▨	▨	▨	▨	▨	▨	40	2.5
NO_2	73	4.6	143	9	▨	▨	20	1.3	94	5.9
SO_2	▨	▨	21	1.3	▨	▨	▨	▨	111	7.0
O_3	80	5.0	64	4.0	▨	▨	▨	▨	158	10.0
CO	▨	▨	96	6.0	427	26.9	42	2.6	▨	▨

3.7 DESCRIPTIVE ANALYSES

I conducted descriptive analyses on the weather variables and birth outcomes as outlined below:

- I generated a survival curve for live birth and stillbirth to examine the most common gestational ages for live born and stillborn babies.
- I examined the distribution of each variable.
- Descriptive statistics were made for each variable.

- I plotted the temporal distribution of each variable including gestational age, temperature, relative humidity, and air-pollution. I used these plots to assess seasonal patterns.
- I created scatter plots and Spearman's rank correlations between the weather and air pollution variables to check for multicollinearity. The scatter plots helped identify non-linear associations or outliers. I used Spearman's correlation rather than Pearson's because the variables were not normally distributed.
- To crudely examine the seasonal pattern of the variables, and to get a picture of which period of the pregnancy (month of conception or month of birth) is more important in terms of temperature exposure, I plotted mean gestational age and mean stillbirth rate together with mean temperature against month of birth and month of conception.
- I used chi-square tests to assess the bivariate association between the socio-demographic variables and the categorical variable stillbirth. I used Mann-Whitney and Kruskal-Wallis tests for the bivariate relationship between the socio-demographic variables and the continuous variable gestational age. I used non-parametric tests, as the gestational age was not normally distributed.

3.8 MULTIVARIABLE ANALYSES

3.8.1 SURVIVAL ANALYSIS

I analysed the effect of temperature on birth outcomes using a Cox proportional hazard model because it accounted for the increasing risk of birth caused by increasing gestational age (see section 2.8.5). A problem for studies investigating gestational age as an outcome is that pregnancies ending in preterm delivery have a shorter time during which exposure can occur than longer pregnancies (O'Neill et al., 2003). Since I compared only fetuses at the same gestational age using a Cox model, this was not a problem in the study.

All analyses were made using the R software (version 2.11.1).

Competing risk

I fitted live birth and stillbirth as competing risks (Allignol, Schumacher & Beyersmann, 2010). At any time after 19 weeks of pregnancy (the gestation of the shortest live birth included in the Brisbane birth register) a woman could stay pregnant, or give birth to either a live baby or a stillborn baby. A live birth is therefore a competing risk for a stillbirth, and vice versa. Many previous analyses have only examined specific outcomes (e.g., all live births or all stillbirths), and hence removed the other births from the at-risk population. However, the method of competing risks is able to model the effects of temperature on stillbirth and live birth simultaneously. This gave the results a broader perspective of the overall effects of temperature, and I avoided any possible biases from excluding data. Figure 3.6 illustrates the competing risks survival model.

In survival models, risks are expressed using a Hazard Ratio (HR). A HR above 1 for stillbirth means an increased risk of stillbirth, and a HR below 1 means a decreased risk of stillbirth. However, for live birth a HR above 1 means a shorter gestational age (increased “risk of live birth”), and a HR below 1 means a longer gestational age (reduced “risk” of live birth).

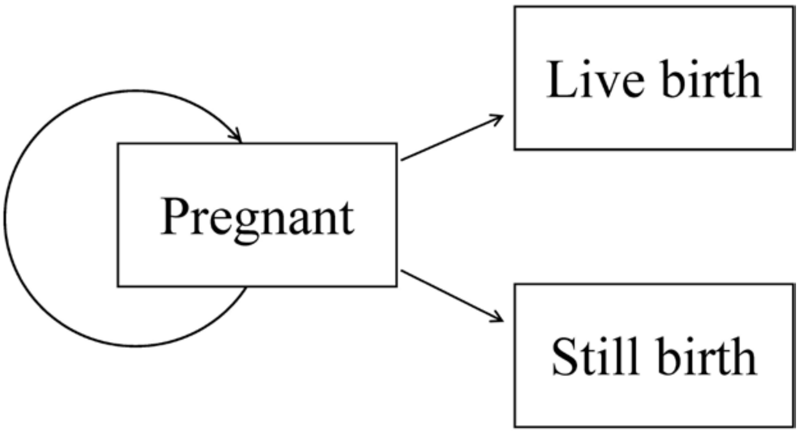


Figure 3.6. Competing risks survival model with cause-specific hazards.

Time-dependence

In a pregnancy covering up to nine months, important independent variables will change over time. A full pregnancy covers almost three seasons and a woman will be exposed to a great range of seasonal factors. I fitted mean temperature, humidity and air pollution as time-dependent variables to allow them to change over the course of the pregnancy (Meister & Schaefer, 2008). To examine the seasonal pattern and to control for confounding by season I therefore fitted *month of the year* as a time-dependent variable.

3.8.2 EXPOSURE WINDOWS

As mentioned in Section 2.8.4, a methodological challenge in all studies investigating the effect of temperature on birth outcomes has been to identify particularly vulnerable periods in the pregnancy where exposure to high or low temperatures is especially harmful. Due to potential confounding from season when examining long exposure windows (e.g., a trimester), I chose to examine only the acute effect of temperature on gestational age and stillbirth. The time period of interest in this study is the last four weeks before birth from 19 weeks of gestation to 43 weeks of gestation (if the pregnancy lasted that long). That way, I avoided the potential confounding by season, but still extended the exposure window previous studies have used. Figure 3.7 illustrates the concept. At week 19 of the pregnancy, I examined the temperature exposure in weeks 16–19. At week 38, I examined temperature exposure from weeks 35 to 38.

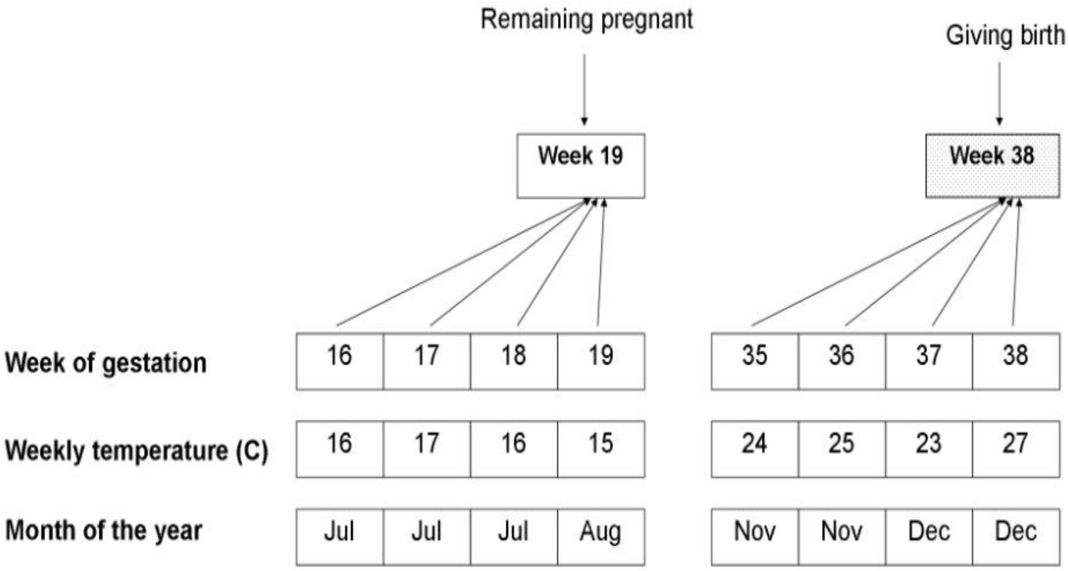


Figure 3.7. Illustration showing how the model examines the time-dependent variables of temperature and month in the last four weeks at each week of gestation. The figure illustrates one pregnancy at 19 and 38 weeks.

3.8.3 DATASET FORMATION

I fitted the weather and air pollution variables as time-dependent variables by calculating mean weekly temperature, humidity and air pollution concentrations for each week from week 16 (four lag weeks before the shortest gestational age in the cohort) of the pregnancy until birth (Figure 3.7). This means that the dataset has between four (the one born in week 19) and 28 (those born on week 43) rows of data for each pregnancy.

An example of the dataset is given in

Table 3.3. The table shows the data for two cases only and just for a selection of the variables. The start and stop times are the gestational age in weeks (“startd” and “stopd”). The earliest survival time is from 18 to 19 weeks. This is because the first live birth in the cohort had a gestational age of 19 weeks. Stillbirths were only included if the fetus was 20 gestational weeks or older. Any stillbirths before this time were not registered. Using this data arrangement allowed me to incorporate time-dependent variables, mean temperature and air pollution, by calculating a mean weekly value for each of the rows in the dataset (Putter, Fiocco & Geskus, 2007).

This data arrangement also allowed me to examine competing risks. Each birth has one set of rows for the outcomes live birth (“live”) and one set of rows for the outcomes stillbirth (“still”). The “status” variable indicates the outcome with ‘0’ meaning censored and ‘1’ meaning birth (live or stillbirth). This first baby was born alive at 39 weeks, as status is ‘1’ in the final row of the “live” set of rows. The second baby in the example dataset was born alive at 38 weeks, as status again is ‘1’ in the final row of the “live” set of rows. In the example in

Table 3.3, I use the variable “Sex_S” to examine the effect of the baby’s sex on the risk of stillbirth and “Sex_L” to examine its effect on live birth.

Table 3.3

Extract of the Survival Analysis Dataset for two Subjects

id	startd	stopd	status	date	endpoint	Sex_S	Sex_L
1	18	19	0	21/07/2005	still	F	99
1	19	20	0	28/07/2005	still	F	99
…	…	…	…	…	…	…	…
1	38	39	0	08/12/2005	still	F	99
1	18	19	0	21/07/2005	live	99	F

1	19	20	0	28/07/2005	live	99	F
…	…	…	…	…	…	…	…
1	38	39	1	08/12/2005	live	99	F
2	18	19	0	11/07/2005	still	M	99
2	19	20	0	18/07/2005	still	M	99
…	…	…	…	…	…	…	…
2	37	38	0	18/07/2005	still	M	99
2	18	19	0	11/07/2005	live	99	M
2	19	20	0	18/07/2005	live	99	M
…	…	…	…	…	…	…	…
2	37	38	1	18/07/2005	live	99	M

Because of all these additional rows of data per pregnancy, the dataset was very big and a standard computer did not have enough memory to handle the data or the analyses. Therefore, the High Performance Computer and Research Support Unit of the Queensland University of Technology managed the data analyses.

3.8.4 THE SEASONAL PATTERN

I plotted the HR and 95% CI for each of the months in the model to examine the seasonal pattern in the risk of live birth and stillbirth. I interpreted a higher risk of live birth as shorter gestations. First, I ran the model without temperature to get an estimate of the overall seasonal pattern. I then ran the model after adjusting for temperature, to examine how much the seasonal pattern changed. If the seasonal pattern changed after the adjustment, I interpreted this as a sign that temperature contributed to the seasonal pattern of birth outcomes.

3.8.5 THE NON-LINEAR EFFECT OF TEMPERATURE

As identified in Section 2.8.2, temperature may have a U- or J-shaped relationship with birth outcomes. I therefore used polynomial splines for temperature in the models. The number of degrees of freedom controls the degree of smoothness of the estimated temperature-birth outcome curve of HRs. A linear function has one degree of freedom for its one slope, and a quadratic spline has two degrees of freedom for its slope and curve. To allow for further non-linear shapes, I used three degrees of freedom to describe the association between mean temperature and the birth outcomes. I defined the mean temperature in Brisbane (21 °C) as the reference temperature (i.e., HR = 1). The splines were created using the 'dlnm' package in the R software package (Gasparrini, Armstrong & Kenward, 2010).

3.8.6 THE DELAYED EFFECT

I first examined the overall effect of temperature on the risk of live birth and stillbirth over the last four weeks before birth. I then examined the lagged effect over the four lag weeks. Because of the short period, I assumed that the delayed effect was likely to be linear, and for the lagged effect of temperature, I used a linear term. Also for the delayed effect of air pollution, I used a linear spline with one degree of freedom.

3.8.7 THE EFFECT AT DIFFERENT GESTATIONAL AGES

To identify at which gestational age acute exposure to temperature has the most adverse effect on the risk of birth (live birth or stillbirth), I divided the pregnancy into periods representing the periods of gestational age as defined by the World Health Organization (2007). The three categories were; extreme PTB (< 28 completed gestational weeks), PTB (28–36 completed weeks), and term birth (37+

completed weeks). I further examined each weeks of the pregnancy. Since very few births had a gestational age of 19 and 43 weeks, I refined the analysis to include each gestational week from 20 to 42 weeks.

3.8.8 INTERACTIONS

Ren et al. (2006) have shown that PM_{10} and temperature have interactive effects on mortality and morbidity. In this study however, I was investigating rare outcomes and if I was to stratify the data by level of PM_{10}, I would substantially lose statistical power. Thus, interactions between temperature and air pollutants were beyond the scope of this study, but could be a subject for future analyses.

3.9 POTENTIAL CONFOUNDING FACTORS AND EFFECT MODIFIERS

Factors that could confound and/or modify the association between temperature and birth outcomes were identified in the literature review (Section 2.3) as: maternal age, maternal stature, maternal morbidity, previous pregnancies, antenatal care, pregnancy complications, marital status, socio-economic status, smoking, medications, alcohol consumption and ethnicity. Birth certificates in Queensland only contained parts of this information, and the analyses were conducted using the available variables.

Other potential cofounding variables identified in the literature review were season, sunshine, barometric pressure, and air pollution. I chose to only include humidity and air pollution as the relationship between these variables and birth outcomes have been more thoroughly investigated previously (Bobak, 2000; Lajinian et al., 1997; Suh et al., 2009).

3.9.1 MATERNAL AGE

Previous research has suggested that maternal age has a U- or J-shaped relationship with birth outcomes (Conde-Agudelo et al., 2005; Simchen et al., 2006). To account for this, I used a spline with three degrees of freedom to model the impact of maternal age on birth outcomes.

3.9.2 PREVIOUS PREGNANCIES

I originally collected this variable as a continuous measure. The number of previous pregnancies ranged from 0 to 27 however, and I therefore divided it into the four groups: 0, 1–2, 3–4, and 5+ pregnancies to remove the influence of outliers. Previous pregnancies included previous live birth, stillbirths and abortions.

3.9.3 ANTENATAL CARE

The variable ‘antenatal visits’ (a count of the total number of visits for each woman) was divided into less or more than average at each gestational age in order to control for the correlation between gestation age and antenatal visits, - the women with long pregnancies are likely to have more antenatal visits than those with short pregnancies (Figure 3.8).

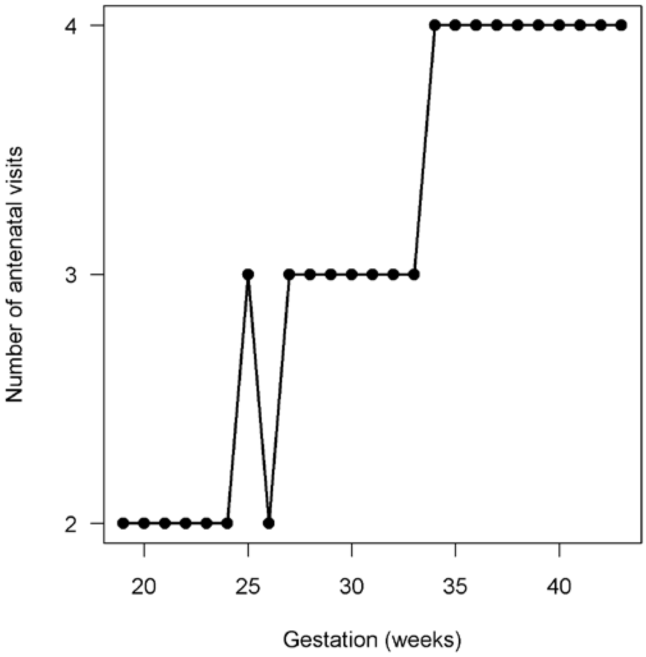


Figure 3.8. The median number of antenatal visits by week of gestation

The number of antenatal visits would therefore be a strong, but false, predictor of gestation length. I then compared each woman to the median number of visits for her gestation length and created a variable that categorised her number of visits as being below, equal to, or above the median. However, this new variable still almost perfectly predicted birth for some pregnancies, so I decided not to adjust for this variable. The estimated effects of temperature changed little when this variable was dropped.

3.9.4 PREGNANCY COMPLICATIONS

The pregnancy complications collected included pregnancy-induced hypertension (PIH) and pre-eclampsia (PE). For simplicity, I collapsed these complications in one category (yes/no). Temperature has been shown to be associated with PE (Bergstrom et al., 1992) which is also a risk factor for stillbirth and preterm birth. Thus PE is likely to be on the causal pathway between temperature and birth outcomes. I therefore ran the model without this variable. This did not influence the results, and I chose to keep the variable in the model for the prudent reason.

3.9.5 MARITAL STATUS

The original grouping of this variable was married, divorced, widowed, separated, and never married. In this cohort, very few mothers were divorced or widowed (525 and 106 respectively). To remove these small categories, I combined these mothers with the separated women. The total number of women in the 'separated' group was then 1,602.

3.9.6 MATERNAL SMOKING

I adjusted for maternal smoking in the model. I did not have information about the amount smoked or if the smoking occurred only in parts of the pregnancy or the whole pregnancy, so I could not assess a dose-response relationship. I defined smoking status as either 'yes' or 'no'.

3.9.7 ETHNICITY

Indigenous status was dichotomous with the two categories: Indigenous and non-indigenous. I did not have data on other ethnical groups (e.g. Asian, Hispanic, and African)

3.9.8 SEX OF THE CHILD

Sex has been suggested as an effect modifier of the relationship between a range of factors and birth outcomes (Ghosh, Rankin, Pless-Mulloli & Glinianaia, 2007). I included it in my model as a covariate, but because of the rare event of stillbirth and the large cohort size needed in order to detect the relationship between temperature and stillbirth, I chose to focus on the overall relationship and did not stratify by sex.

3.9.9 TRENDS IN BIRTH OUTCOMES

There were significant secular trends in both live and stillbirth in the dataset (stillbirths decreased over the study period). The trend did not affect the estimates of temperature. I did however include a spline for trend with two degrees of freedom to model these slow changes. I chose two degrees of freedom because we would expect any trend over 4 years to be smooth. I would not expect any sudden bumps or dips in risk.

3.9.10 SEASON

I only investigated the effect of temperature exposure on gestation length and stillbirth during the last four weeks of the pregnancy. It has been shown that 28 day periods are short enough to avoid confounding by season in studies assessing temperature effects (Barnett & Dobson, 2010). I also included a term for season in the model as I included the time-dependent variable *month of the year* (Section 3.8.1).

3.9.11 HUMIDITY

I averaged the relative humidity over the week, and adjusted for relative humidity in the Cox model.

3.10 SENSITIVITY ANALYSIS

3.10.1 AIR POLLUTION

Several studies have shown that PM_{10}, $PM_{2.5}$, O_3, NO_2, CO and SO_2 have adverse effects on pregnancy (Bell et al., 2007; Bobak, 2000; Hansen et al., 2006). I looked at different combinations of temperature, humidity and air pollutants to investigate if the temperature effect changed. I ran the analysis with each air pollutant (one at a time) because of the strong correlations between pollutants.

3.10.2 SPLINES

I fitted several splines with various degrees of freedom to try and get a good picture of the relationship between temperature and birth outcomes. I fitted natural splines, and polynomial splines. Due to some odd looking 3D plots showing the results for the four lag weeks when I used smooth splines (Figure 4.16) I fitted a double threshold parameterisation spline to allow for two independent linear relationships at cold and hot thresholds. The thresholds were chosen by visually assessing the smooth natural and polynomial splines.

3.10.3 THE FIXED COHORT BIAS

To evaluate the effect of removing the pregnancies at the beginning and end of the cohort (Section 3.4.4), I ran the exact same model on the original cohort (n = 114,932). I compared the difference between these two models.

3.11 ETHICS

The study analysed potentially identifiable data such as date of birth and birth weight. A Human Research Ethics Committee (HREC) application was submitted to Queensland University of Technology Human Research Ethics Committee. The project was exempt from review of the committee (Appendix B). A Public Health Act application was submitted to the Queensland Health, before the data were disclosed. Their approval is attached in Appendix C.

The data were securely stored (and still are) on QUT password protected computers. There has not been (and will not be) any attempts to identify the participants and the data will only be used for the epidemiological analyses. No person not directly involved in the project has had (or will have) access to the data.

Chapter 4: Results

4.1 INTRODUCTION

In this chapter, I describe the characteristics of the cohort using counts, percentages, means, and standards deviations for each variable. For the weather and air pollution variables, I report the mean, minimum and maximum value for each month of the year (25 February 2005 – 30 June 2009). Associations between temperature and birth outcomes are described in terms of Hazard Ratios (HR). An increased HR for live birth means increased risk of live birth (decreased gestation length), while an increased HR for stillbirth means increased risk of stillbirth. I present the temperature splines with 95% confidence interval (CI) in the figures. The HRs for the covariates are presented with 95% CI and p-values.

4.2 DESCRIPTIVE STATISTICS

4.2.1 BIRTH OUTCOMES

To investigate the risk of live birth and stillbirth throughout the pregnancy, I plotted a survival curve of the birth outcomes (using the Kaplan-Meier method). The stillbirth rate was highest early in the pregnancy with about 20% of the stillbirths happening in week 20 with another 10% in week 21. After week 23 of gestation, the number of stillbirths in each week remained stable. The probability of giving birth to a live baby, however, increased exponentially with increased gestation, with most live births happening after week 35. Figure 4.1 displays the survival curve for live birth and stillbirth.

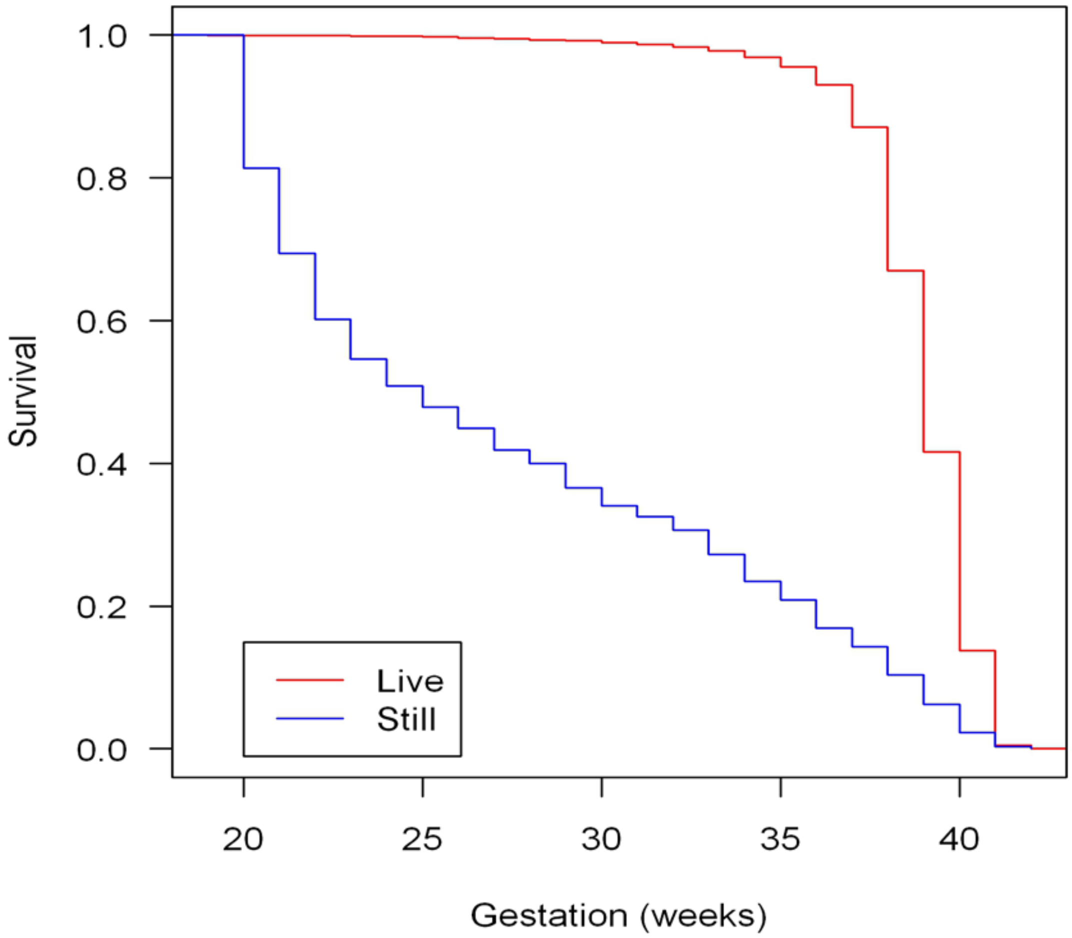


Figure 4.1. Survival times for live birth and stillbirth.

Gestational age ranged from 19 to 43 weeks with a mean of 38.8 weeks. Because of an increased birth rate with increasing gestation (Figure 4.1), the distribution was strongly skewed to the left (Figure 4.2) suggesting that nonparametric methods should be used in this study. Only 0.6% (n = 653) of the total births in this cohort were stillbirths. As seen in Figure 1.2, the early stillbirths are largely explained by spontaneous preterm birth as infants born that early, rarely survive (Field, Dorling, Manktelow & Draper, 2008). The increased stillbirth rate in weeks 20–22 may also be due to the human intervention factor (i.e., deliberate termination of pregnancy). However, these terminations were unlikely to be associated with temperature and should therefore not confound the results.

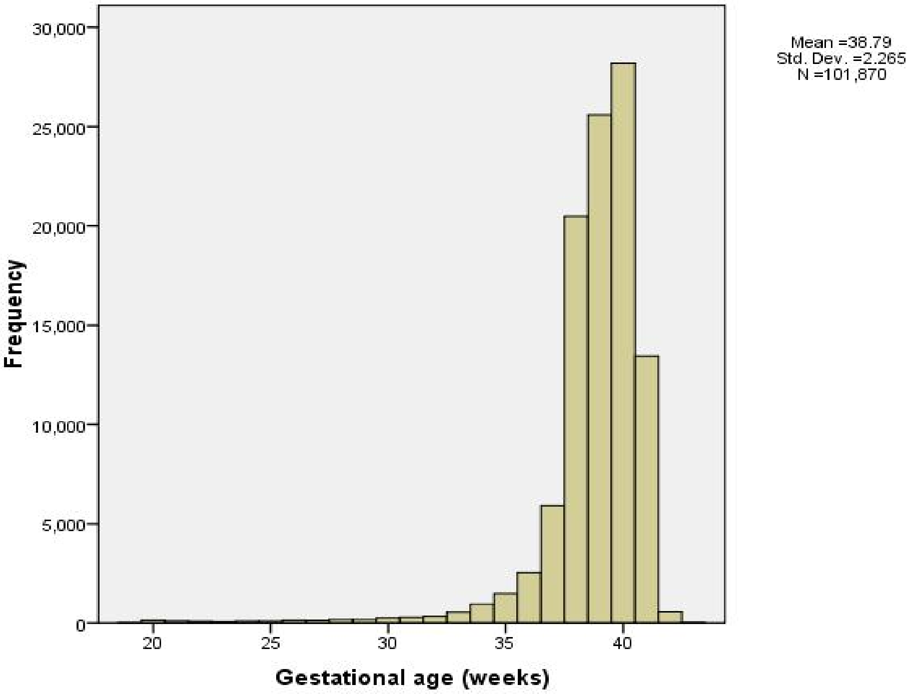


Figure 4.2. Bar chart of gestational ages

4.2.2 SOCIO-DEMOGRAPHIC CHARACTERISTICS

Just over half the cohort (51.7%; 52,647/101,870) was male. The majority of the children were of non-Indigenous background (97.8%; 99,531/101,870) with 2,263 children having Indigenous mothers (2.2%). The mother's age ranged from 12 to 58 years with a median age of 30 years. More than 86% of the mothers were married or in a de facto relationship (87,439/101,870).

Almost 18,000 (17.2%) mothers smoked during the pregnancy. Approximately 5% of the cohort had pregnancy complications (PE or PIH) during the pregnancy. The number of previous pregnancies ranged from zero to 27 with a median of 1. Thus, I categorised the variable to eliminate the outliers, and 30.4% had no previous pregnancies, 48.5% had 1–2, 15.2% had 3–4 and 6.1% had 5 or more. The demographics are described in Table 4.1.

Table 4.1

Characteristics of the Cohort

	Births	
	n	%
Total births	101,870	100
Birth outcomes		
Stillbirth	653	0.6
Live birth	101,217	99.4
Sex		
Male	52,647	51.7
Female	49,223	48.3
Marital status		
Married/De facto	87,439	86.3
Never married	12,791	12.6
Separated/Divorced	1,609	1.6
Not stated	31	< 0.1
Indigenous status		
Indigenous	2,263	2.2
Non-indigenous	99,531	97.8
Not stated	76	0.1
Smoking		
Non-smoker	83,548	82.0
Smoker	17,559	17.2
Not stated	763	0.7
Pre-eclampsia		
No	96,606	94.8
Yes	5,264	5.2
Previous pregnancies		
0	30,918	30.4
1–2	49,224	48.3
3–4	15,469	15.2
5+	6,259	6.1
Mother’s age, mean (SD)	29.6 (5.77)	
Gestational age, mean (SD)	38.8 (2.27)	

4.2.3 WEATHER AND AIR POLLUTION DATA

I examined the distribution of each weather and air pollution variable. The distribution curves are displayed in Appendix D. The minimum, maximum and mean value of each meteorological variable is listed in

Table 4.2. As the data ranged from 25 February 2005 to 30 June 2009, it covered five years of March, April, May and June, and four years of the remaining months. Therefore, the data are presented by month to avoid the bias towards the values in March, April, May, and June when averaging over the year.

Table 4.2

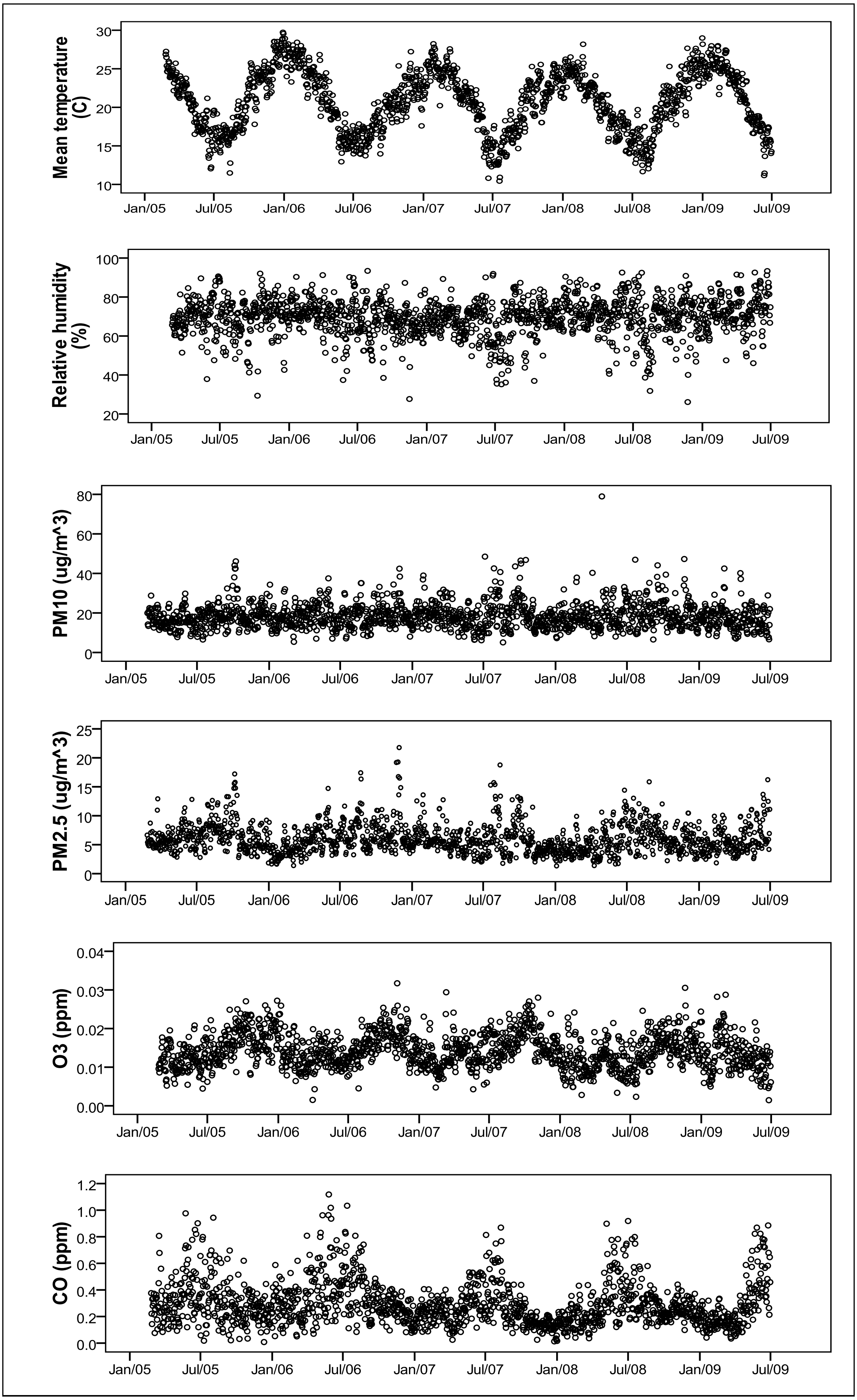
Monthly Mean Temperature, Humidity, and Air Pollutants, Brisbane, Australia, 2005–2009

	January	**February**	**March**	**April**	**May**	**June**	**July**	**August**	**September**	**October**	**November**	**December**
Temp (°C)	25.4	25.0	23.7	21.6	18.5	16.2	15.4	16.3	19.1	21.6	22.8	24.7
Hum (%)	71.9	72.7	70.2	69.6	69.9	72.7	66.4	64.9	69.5	68.2	70.2	68.5
PM_{10} (ug/m^3)	17.3	18.7	18.8	17.6	18.3	15.8	18.7	20.2	20.1	21.7	18.4	18.2
$PM_{2.5}$ (ug/m^3)	4.8	5.1	5.4	5.1	6.1	6.4	7.0	8.0	7.0	6.9	5.9	5.4
NO_2 (ppb)	5.6	7.6	8.4	10.3	14.3	14.6	15.3	15.2	12.2	10.0	8.3	6.9
O_3 (ppb)	12.5	12.9	12.5	12.8	12.6	11.7	13.0	15.7	18.3	19.1	17.1	15.7
SO_2 (ppb)	0.92	0.98	1.15	1.05	1.12	1.12	1.07	1.25	1.02	1.05	0.93	0.78
CO (ppm)	0.20	0.23	0.23	0.25	0.41	0.43	0.42	0.37	0.28	0.23	0.24	0.01

Hum = humidity; Temp = temperature; ppb = parts per billion; ppm = parts per million; µg/m^3 = micrograms per cubic meter of air

4.2.4 THE TEMPORAL DISTRIBUTION OF THE VARIABLES

Figure 4.3 presents the time series of the weather and air pollution variables. Mean temperature, O_3 had a yearly peak in spring, and NO_2 and CO had a yearly peak in winter. PM_{10}, $PM_{2.5}$, SO_2 and relative humidity had a less pronounced seasonal pattern. PM_{10} had an outlier in April 2008, which was probably due to a dust storm in Brisbane on 28 April 2008. There is a declining trend in SO_2 over time, which may be due to increased use of low sulphur diesel (Australian Government, 2005).


Mean temperature (C)
10
15
20
25
30
Relative humidity (%)
20
40
60
80
100
PM10 (ug/m^3)
0
20
40
60
80
PM2.5 (ug/m^3)
0
5
10
15
20
25
O3 (ppm)
0.00
0.01
0.02
0.03
0.04
CO (ppm)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Jan/05
Jul/05
Jan/06
Jul/06
Jan/07
Jul/07
Jan/08
Jul/08
Jan/09
Jul/09

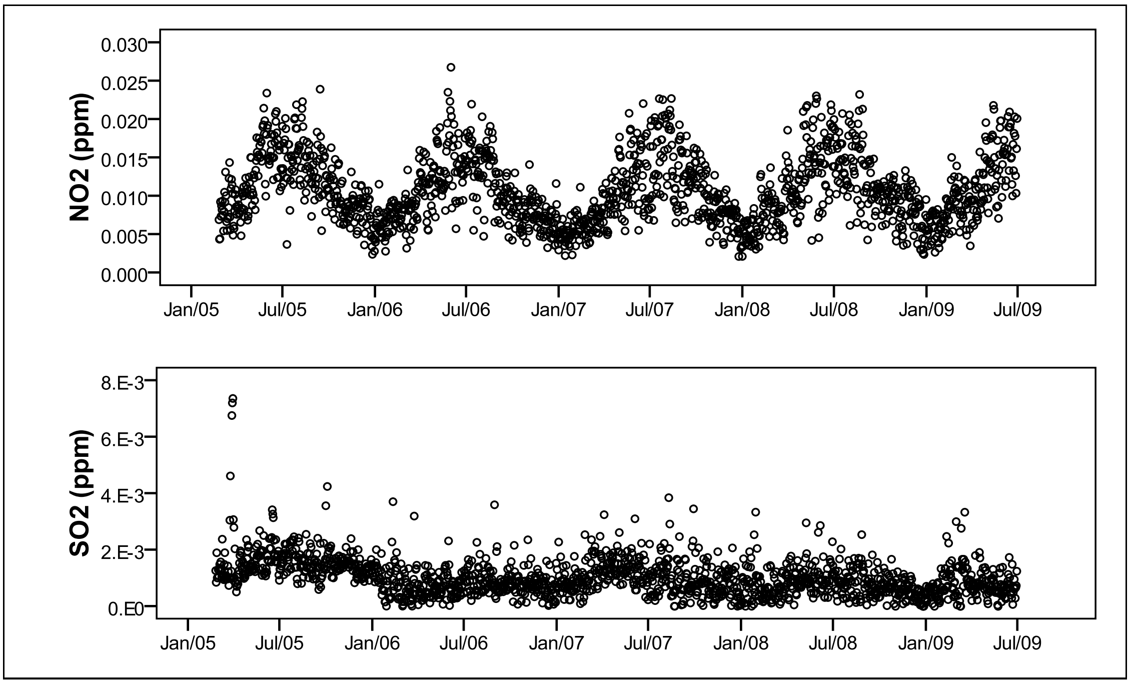


Figure 4.3. Time series of the meteorological and pollution variables (25 Feb 2005 – 30 Jun 2009).

4.2.5 MULTICOLLINEARITY

Scatter plots (Figure 4.4) and Spearman’s correlations (Table 4.3) were used to check for possible multicollinearity.

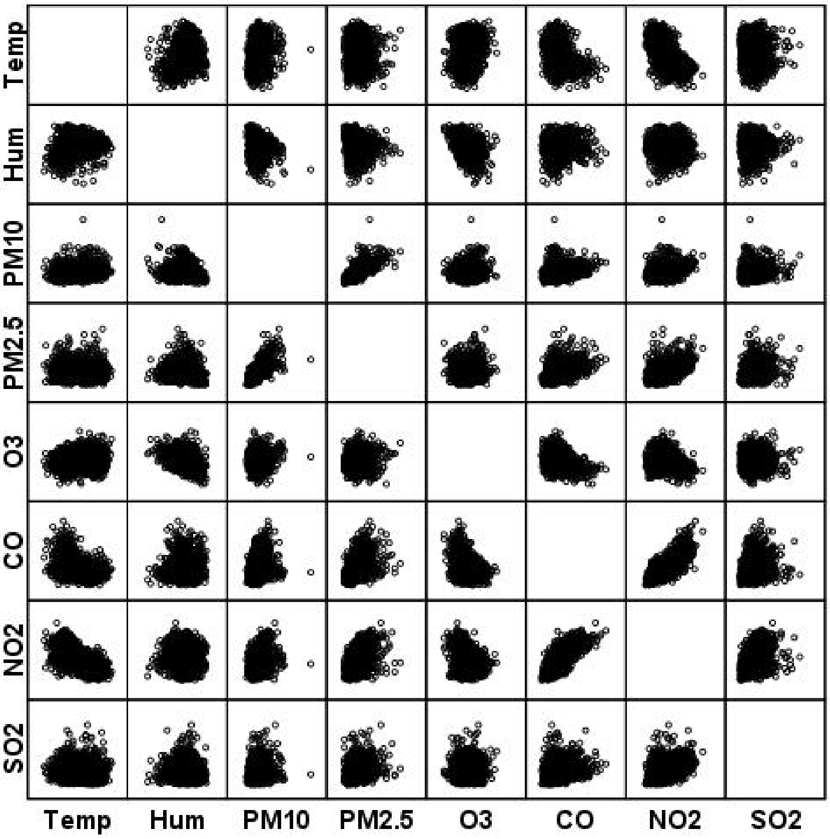


Figure 4.4. Scatter plots between the daily meteorological and air pollution variables (25 February 2005 – 30 June 2009). Plots are arranged so that adjacent plots share a common axis. All plots in a row share a common Y-axis, and all plots in a column share a common X-axis.

All the air pollutants were significantly correlated with temperature. In particular NO_2 and CO were both correlated with temperature (–0.683 and –0.403 respectively, $p < 0.01$) and with each other (0.682, $p < 0.01$). I was therefore cautious about fitting these pollutants with temperature, and the possibility of multicollinearity should be considered when interpreting the results.

Table 4.3

Spearman's Correlations between the Meteorological and Air Pollution Variables (25 February 2005 – 30 June 2009)

	Temp	**Hum**	**PM_{10}**	**$PM_{2.5}$**	**O_3**	**CO**	**NO_2**
Hum	.132**						
PM_{10}	.092**	-.214**					
$PM_{2.5}$	-.162**	-.114**	.727**				
O_3	.076**	-.332**	.080**	.099**			
CO	-.403**	.112**	.262**	.424**	-.304**		
NO_2	-.683**	.002	.262**	.460**	-.179**	.682**	
SO_2	-.083**	-.015	.160**	.279**	-.025	.231**	.332**

** Correlation is significant at the 0.01 level (2-tailed)

4.3 THE SEASONAL PATTERN OF BIRTH OUTCOMES

I plotted the seasonal pattern of the variables, first according to month of birth, then according to month of conception. This allowed us to get a crude picture of whether exposure to high or low temperatures was most dangerous at the time of birth or at the time of conception. As expected, temperature was lowest in June and July (winter) and highest in December and January (summer). Gestational age also appeared to have a seasonal pattern with the mean gestational age being lowest when the baby was born in December and highest in May (Figure 4.5). When plotting gestational age against month of conception the seasonal pattern was less pronounced, but I observed a possible peak in gestational age for conceptions in July (Figure 4.6).

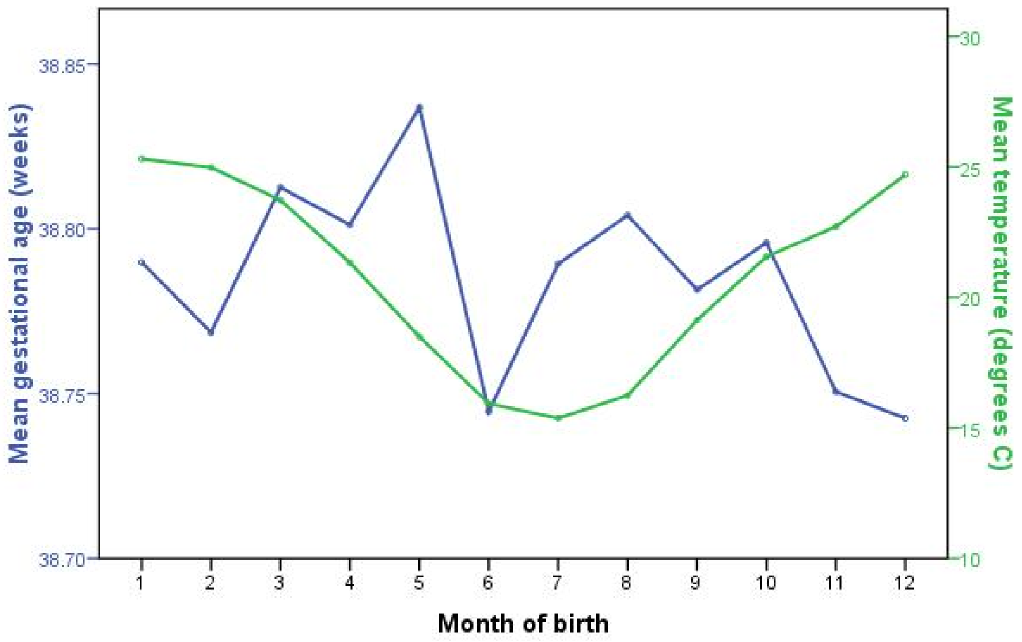


Figure 4.5. Monthly summaries of mean temperature and mean gestational age by month of birth.

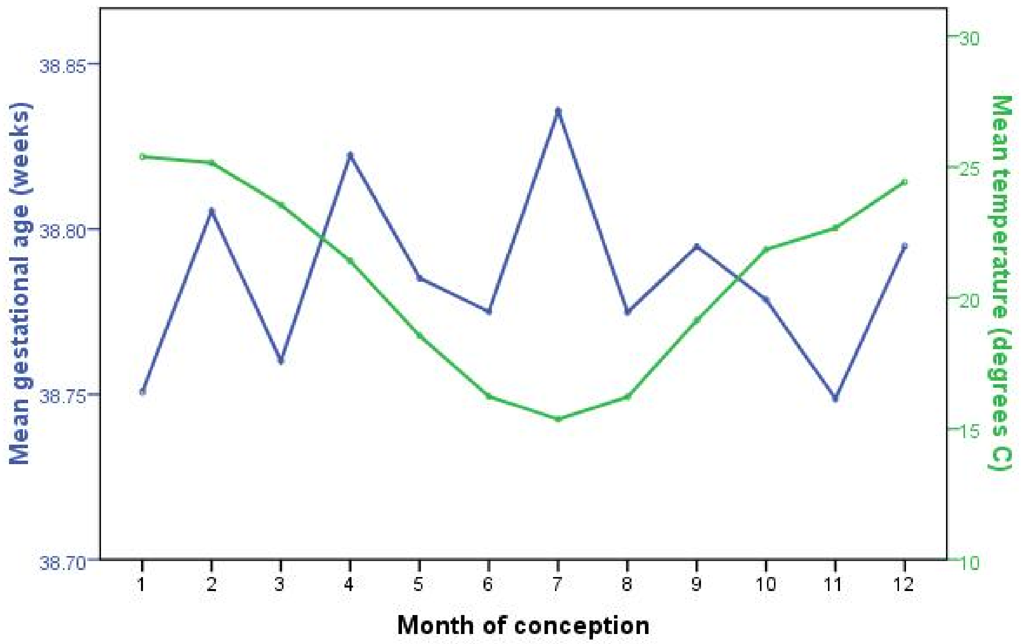


Figure 4.6. Monthly summaries of mean temperature and mean gestational age by month of conception.

For stillbirth rate (per 1000 births) plotted by month of birth, I observed a peak in January and a trough in March before it gradually increased month by month until the peak in January (Figure 4.7). Again, when I plotted the stillbirth rate against month of conception, I could not identify any crude seasonal pattern in stillbirth rate in the cohort (Figure 4.8).

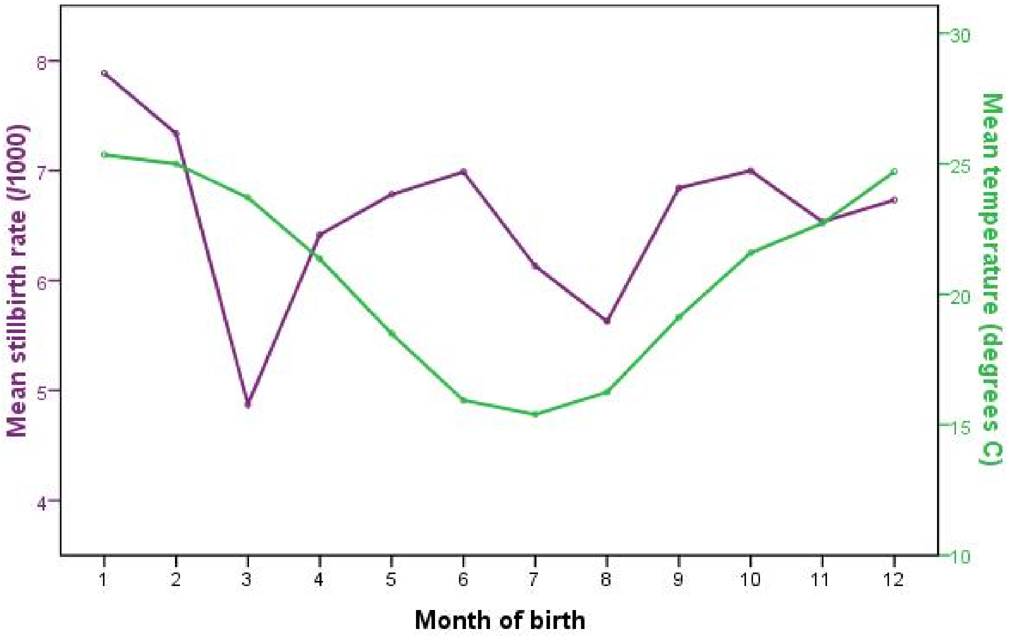


Figure 4.7. Monthly summaries of mean temperature and rate of stillbirths by month of birth.

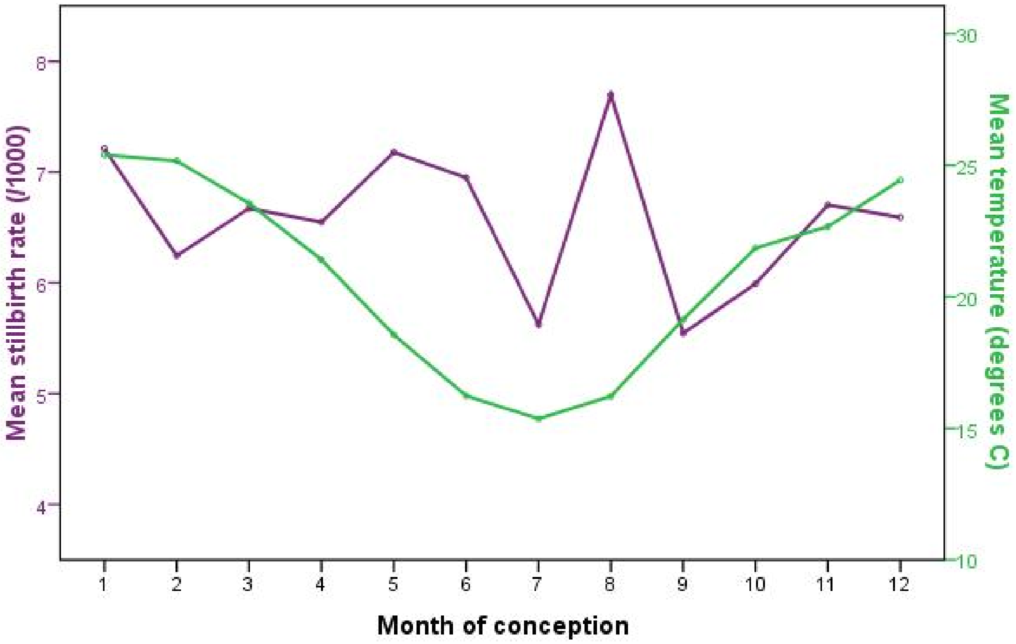


Figure 4.8. Monthly summaries of mean temperature and rate of stillbirths by month of conception.

4.4 BIVARIATE ANALYSIS

I assessed the bivariate relationship between the covariates and the birth outcomes. For gestational age, a Non-Parametric Mann-Whitney U test and Kruskal-Wallis test showed that all covariates were significantly associated with gestational age. Chi-square tests indictaed that all covariates were significantly associated with stillbirth except for sex of the child, and pregnancy complications (Appendix E). Because of the significant bivariate relationship between the covariates and the birth outcomes, I included them all in the multivariable model.

4.5 SURVIVAL ANALYSIS OF THE SEASONAL PATTERN OF BIRTH OUTCOMES

4.5.1 LIVE BIRTH

Figure 4.9 and Figure 4.10 illustrate the seasonal pattern of risk of live birth (gestation length) before and after adjusting for temperature. I observed a bimodal pattern when I did not adjust for temperature. Compared to January there was a significantly higher risk of live birth (shorter gestations) in February, March, and August to December. A trough (although not statistically significant) appeared in June.

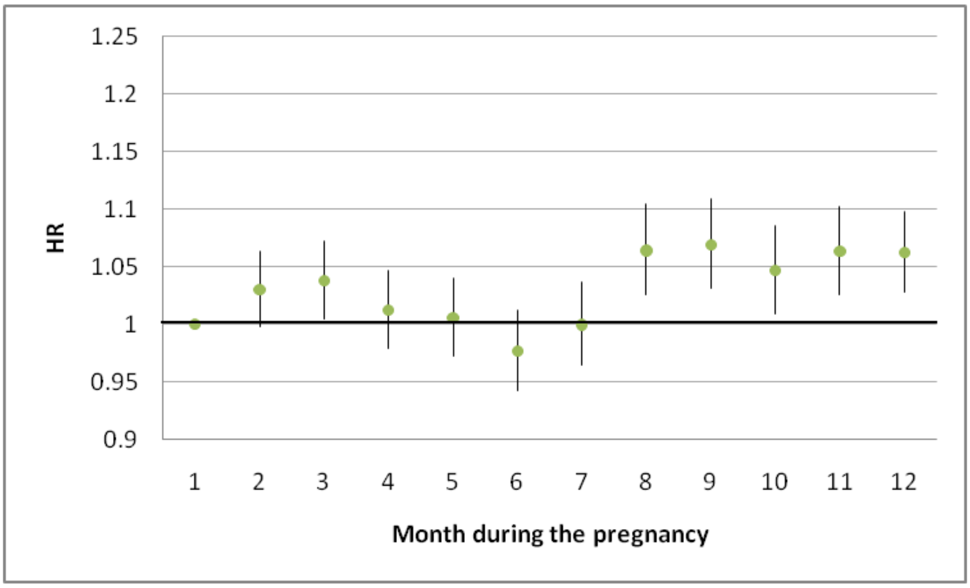


Figure 4.9. The seasonal pattern of live birth risk by month, unadjusted for temperature (January is the reference month).

After adjusting for temperature, the pattern changed dramatically. All months appeared to have a significantly higher risk of live birth compared to January with a peak in August (winter). I found the lowest risk of live birth (longest gestations) in January and February (summer). The pattern was only unimodal (one seasonal peak) compared with the previous bimodal pattern. This might be because the high summer temperatures caused the shorter gestations in February and March in the unadjusted model.

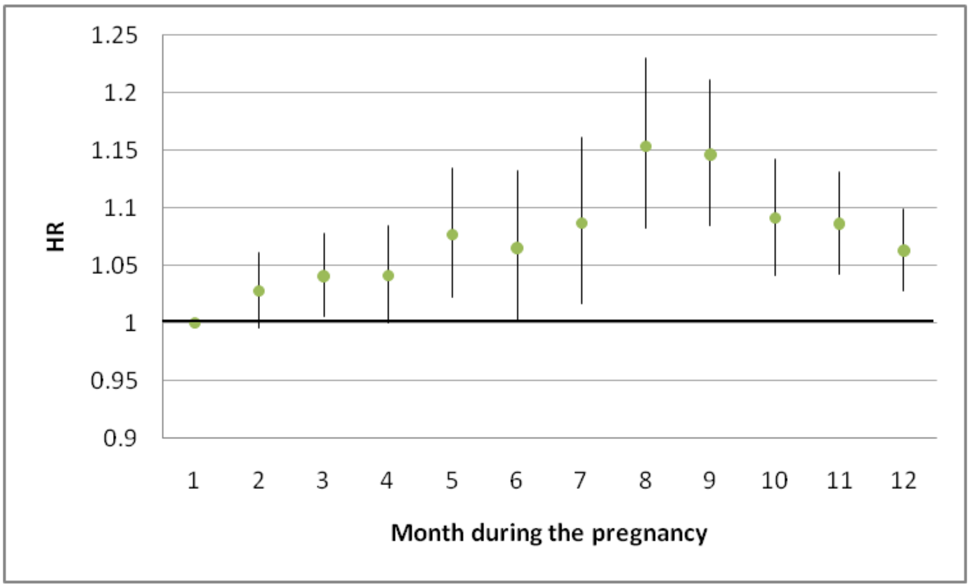


Figure 4.10. The seasonal pattern of live birth risk by month, adjusted for temperature (January is the reference month).

4.5.2 STILLBIRTH

Figure 4.11 and Figure 4.12 illustrate the seasonal pattern in stillbirth risk before and after adjusting for temperature. There was little seasonal pattern before adjusting for temperature. I found a significant lower risk of stillbirth in March (HR = 0.61, 95% CI 0.41–0.90) compared to January.

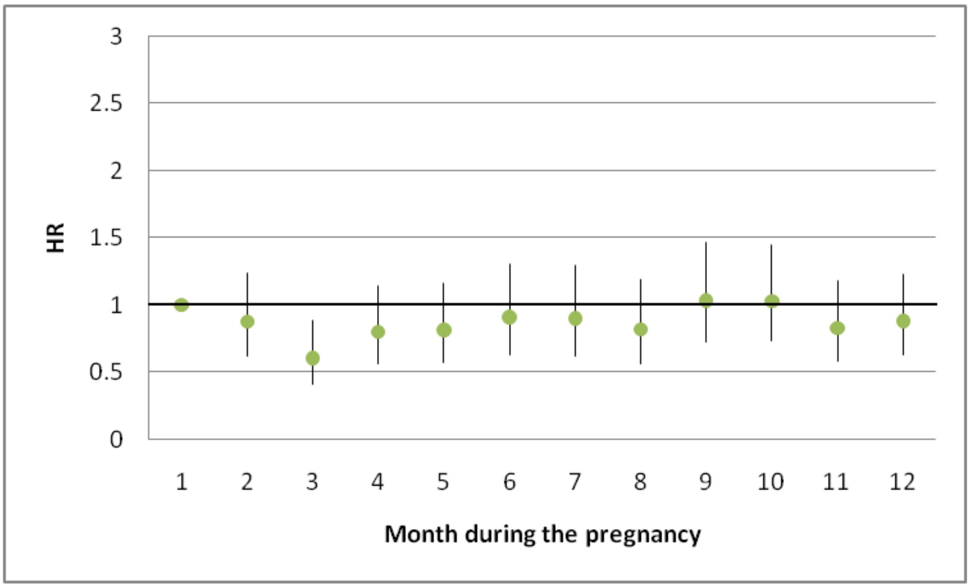


Figure 4.11. The seasonal pattern of stillbirth risk by month, unadjusted for temperature (January is the reference month).

After adjusting for temperature, the trough in March was still significant (HR = 0.57, 95% CI 0.38–0.86). A more distinct seasonal pattern seemed to appear after the adjustment for temperature, with increased stillbirth risk in winter (although this was not statistically significant). The winter increase in stillbirth risk after adjusting for temperature might have occurred because the cold winter temperatures had a protective effect on the risk of stillbirth thus lowering the risk in winter in the unadjusted model.

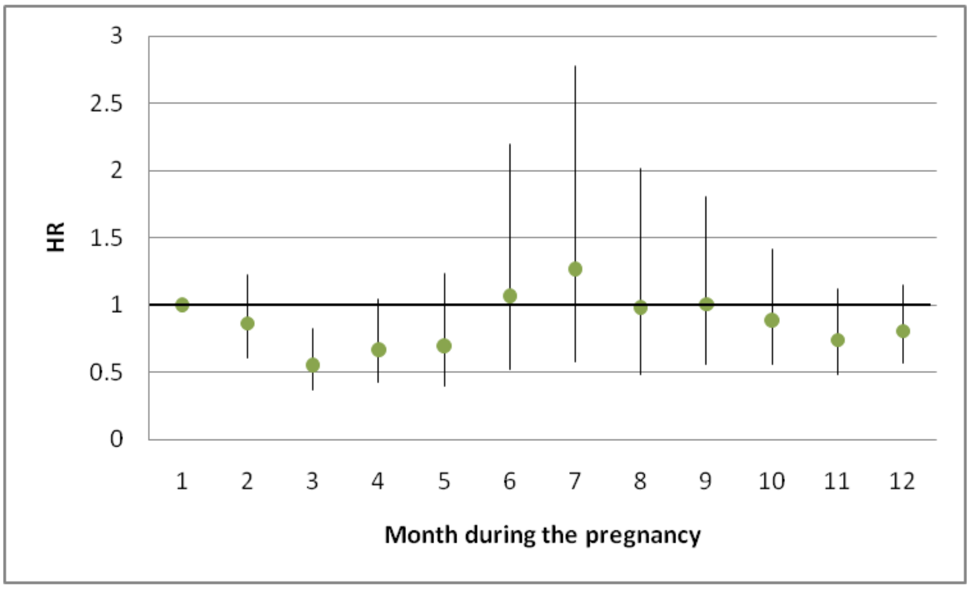


Figure 4.12. The seasonal pattern of stillbirth risk by month, adjusted for temperature (January is the reference month).

4.5.3 SUMMARY

I found a significant seasonal pattern of both gestational age and stillbirth risk in Brisbane. After adjusting for temperature, the pattern changed from being bimodal to a single peak in winter. I found a statistically significant seasonal pattern in the risk of stillbirth with a significantly lower risk in March compared to January. After adjusting for temperature, the March trough was still statistically significant and a peak, although not significant, was observed in winter.

4.6 THE EFFECT OF TEMPERATURE

4.6.1 LIVE BIRTH

I examined temperature effects after adjustment for humidity and covariates on all live births (with stillbirth as a competing risk) over the last four weeks of the pregnancy from week 19 of gestation (the shortest pregnancy in the cohort) to week 43 (the longest pregnancy in the cohort).

Table 4.4 lists the HRs, 95% CIs, and p-values for the covariates. All covariates were significantly associated with the risk of live birth (length of gestation) with the surprising exceptions of sex and smoking status.

The estimates for the splines (temperature, humidity, maternal age and trend) are difficult to interpret on their own. The only way to examine the effect of the splines is to plot the estimates against temperature and/or lag.

Table 4.4

Hazard Ratios for Live Birth

	HR	**Lower 95%**	**Upper 95%**	**P-value**
Previous pregnancies [a]				
1-2	1.237	1.215	1.259	< 0.01*
3-4	1.273	1.240	1.307	< 0.01*
5+	1.258	1.207	1.311	< 0.01*
Sex [b]	0.997	0.981	1.013	0.712
Smoking status [d]	1.021	0.999	1.045	0.067
Marital status [e]				
Never married	0.925	0.902	0.949	< 0.01*
Separated/divorced	0.920	0.857	0.988	0.022*
Indigenous status [f]	1.142	1.074	1.215	< 0.01*
Pre-eclampsia [g]	1.659	1.590	1.732	< 0.01*
Temperature splines				
temp.v1.l1	1.003	0.996	1.010	0.417
temp.v2.l1	1.000	0.999	1.000	0.478
temp.v3.l1	1.000	1.000	1.000	0.385
temp.v1.l2	1.000	0.997	1.003	0.995
temp.v2.l2	1.000	1.000	1.000	0.550
temp.v3.l2	1.000	1.000	1.000	0.153
Humidity splines				
hum.v1.l1	1.000	0.999	1.000	0.311
hum.v1.l2	1.000	1.000	1.001	0.304
Mother' s age splines				
mage.v1.l1	1.279	1.215	1.347	< 0.01*
mage.v2.l1	1.413	1.113	1.794	0.005*
mage.v3.l1	1.799	1.366	2.369	< 0.01*
Trend splines				
time.v1.l1	0.772	0.663	0.900	< 0.01*
time.v2.l1	0.923	0.895	0.951	< 0.01*

[a] Reference category = 0, [b] Reference category = Female, [c] Reference category = Median, [d] Reference category = No, [e] Reference category = Married, [f] Reference category = Non-Indigenous, [g] Reference category = No, * = significant at the 0.05 level

The overall risk of live birth in the cohort increased by approximately 10% (HR from 0.95 to 1.05) when the mean temperature increased from 15 °C to 25 °C during the last four weeks of the pregnancy (Figure 4.13). As the temperature decreased below 15 °C and increased above 25 °C, the relationship was not significant (i.e., the confidence intervals include 1) and it was uncertain what happened to gestation length. An explanation may be that there were too few weeks with a mean temperature below 15 °C and above 25°C in the dataset, which may result in wide confidence intervals and uncertainty.

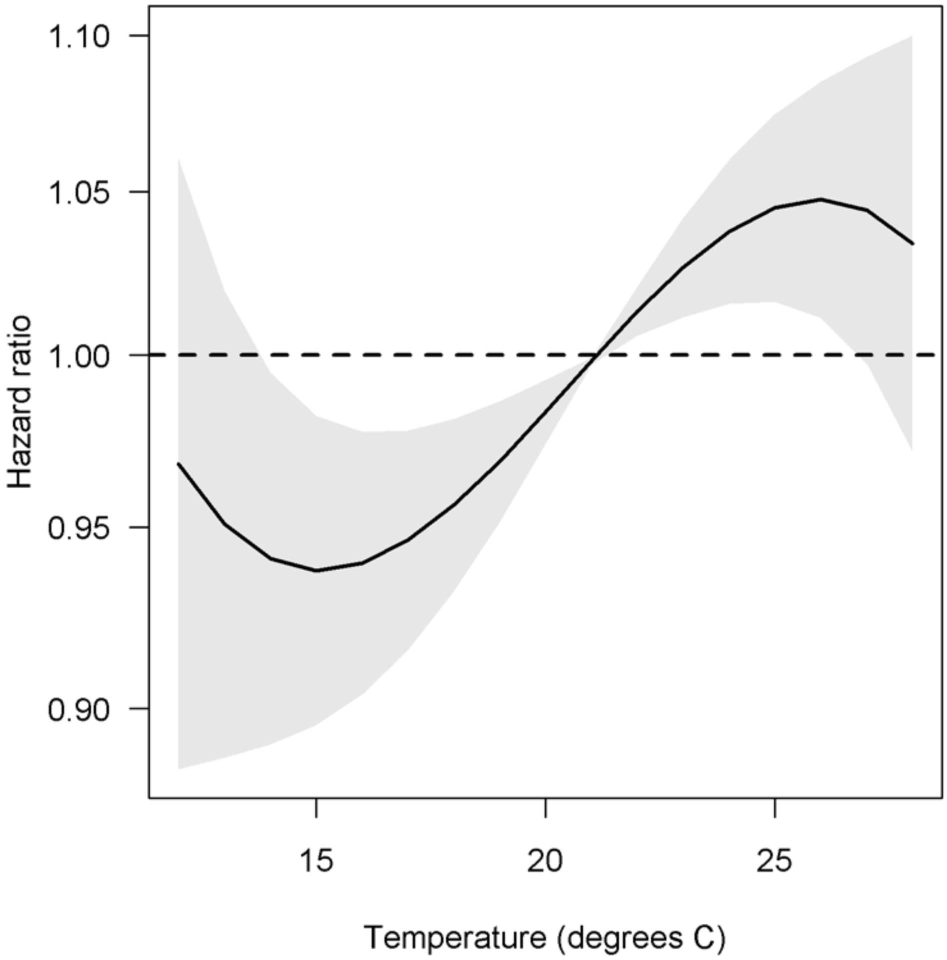


Figure 4.13. The effect of temperature on the risk of live birth. The solid line shows the mean HR and the grey area the 95% confidence limits. The dotted horizontal line at 1 represents no change in risk. The reference temperature is 21 degrees Celsius.

When I examined each of the four lag weeks before birth (Figure 4.14), exposure to high temperatures was more dangerous in the last and the second last week before birth, with approximately 10% increase in risk from 15 °C to 25 °C, similar to the overall effect (Figure 4.13). In weeks three and four before birth however, the direction changed and cold temperatures appeared to increase the risk of live birth (shorten gestation) when moving from 25 °C to 15 °C.

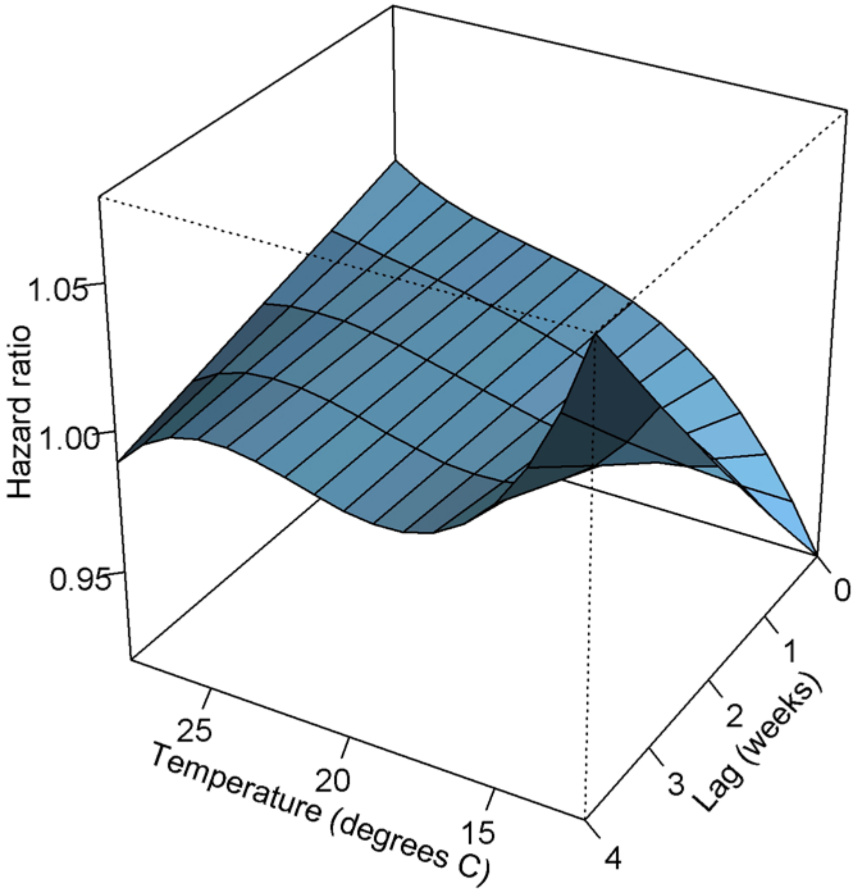


Figure 4.14. The mean effect of temperature on the risk of live birth over the last four weeks before birth.

4.6.2 STILLBIRTH

I also examined the effect of temperature on risk of stillbirth (with live birth as a competing risk) from week 19 of gestation to week 43. Previous pregnancies and pregnancy complications were significantly associated with stillbirth. Table 4.5 lists the HRs, 95% CIs, and p-values for the covariates.

Again, the estimates for the splines (temperature, humidity, mother's age and trend) are difficult to interpret on their own. The only way to examine the effect of the splines is to plot the estimates against temperature and/or lag.

Table 4.5

Hazard Ratios for Covariates for Stillbirth

	HR	**Lower 95%**	**Upper 95%**	**P-value**
Previous pregnancies [a]				
1–2	0.987	0.815	1.196	0.897
3–4	1.306	1.021	1.669	0.033*
5+	1.699	1.242	2.325	< 0.01*
Sex [b]	1.003	0.860	1.170	0.970
Smoking status [d]	1.149	0.940	1.3405	0.175
Marital status [e]				
Never married	1.234	0.971	1.568	0.085
Separated/divorced	1.457	0.880	2.413	0.144
Indigenous status [f]	1.3479	0.987	2.217	0.058
Pre-eclampsia [g]	1.440	1.047	1.980	0.025*
Temperature splines				
temp.v1.l1	0.912	0.835	0.9956	0.040*
temp.v2.l1	0.999	0.989	1.009	0.878
temp.v3.l1	1.001	0.999	1.003	0.227
temp.v1.l2	1.047	1.003	1.092	0.034*
temp.v2.l2	0.999	0.994	1.004	0.814
temp.v3.l2	1.000	0.999	1.000	0.288
Humidity splines				
hum.v1.l1	1.000	0.987	1.013	0.962
hum.v1.l2	0.999	0.993	1.005	0.797
Mother’s age splines				
mage.v1.l1	0.651	0.384	1.103	0.111
mage.v2.l1	0.195	0.022	1.727	0.142
mage.v3.l1	0.640	0.056	7.366	0.719
Trend splines				
time.v1.l1	0.404	0.101	1.616	0.200
time.v2.l1	0.764	0.573	1.017	0.065

[a] Reference category = 0, [b] Reference category = Female, [c] Reference category = Median, [d] Reference category = No, [e] Reference category = Married, [f] Reference category = Non-Indigenous, [g] Reference category = No, * = significant at the 0.05 level

The overall risk of stillbirth decreased by approximately 70% as the temperature decreased from 21 °C (the reference temperature) to 10 °C in the last four weeks of the pregnancy (Figure 4.15). Although I can be confident that there is a decreased risk of stillbirth with decreasing temperatures as the confidence interval is very wide. For temperatures higher than approximately 16 °C, the confidence interval includes 1 and the effect on stillbirth risk is flat.

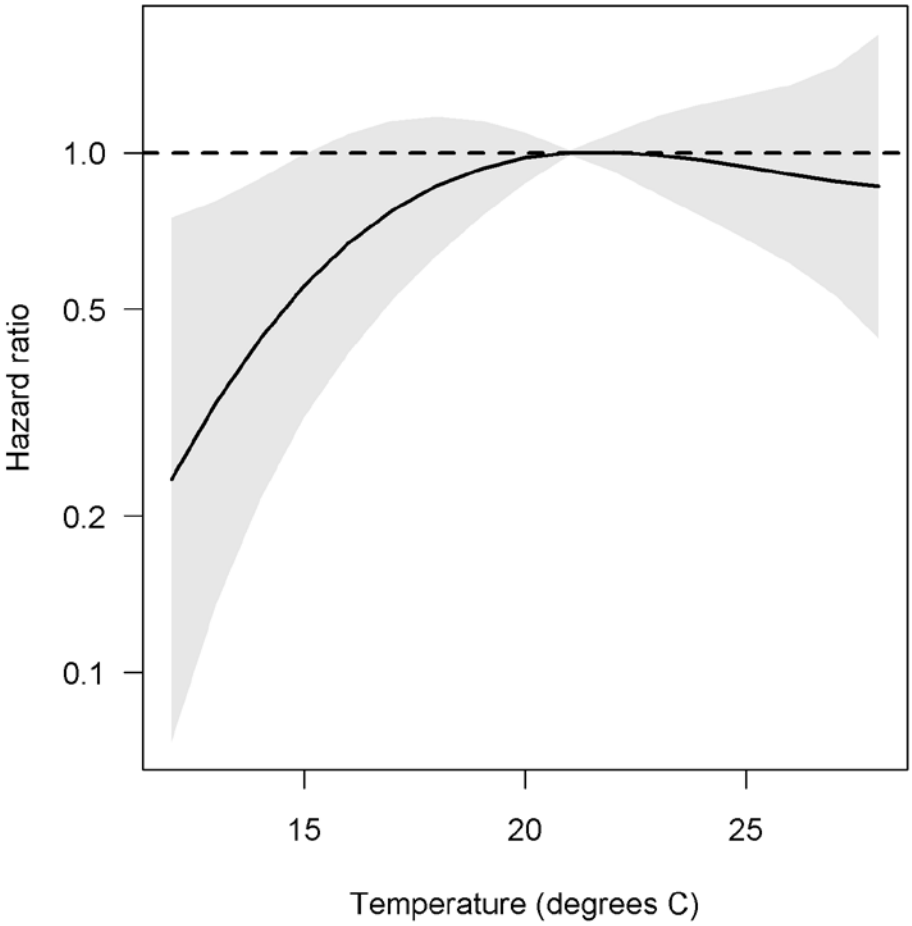


Figure 4.15. The effect of temperature on the risk of stillbirth. The solid line shows the mean HR and the grey area the 95% confidence interval. The dotted horizontal line at 1 represents no change in risk. The reference temperature is 21 degrees Celsius.

When we examined each of the four lag weeks before a stillbirth, the picture looked different. Four weeks before birth the risk of stillbirth decreased when temperatures decreased. However, the closer to the week of birth, the more the relationship changes direction. In the last week before birth, cold temperatures appeared to increase the risk of stillbirth (Figure 4.16).

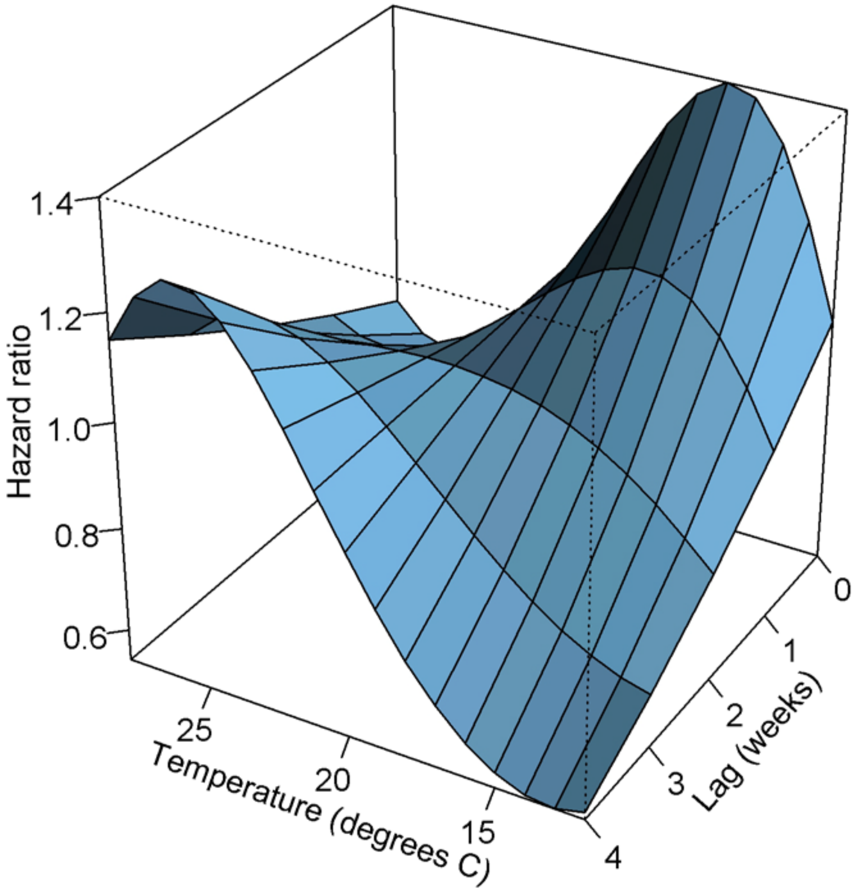


Figure 4.16. The mean effect of temperature on the risk of stillbirth over the four last weeks before birth.

4.6.3 SUMMARY

I found an acute effect of temperature on both live birth and stillbirth with an increased risk for higher temperature over the last four weeks before birth. When examining the lagged effect of temperature on live birth, the closer to the week of birth, the stronger effect temperature had on the risk of birth. I also found an increased risk of stillbirth with increasing temperatures. When examining the lagged effect, exposure to high temperatures was most dangerous during three and four weeks before birth and cold temperatures was more dangerous in the last week before birth. However, when I fitted a double threshold parameterization spline, I found a consistent increased risk with increasing temperatures across all lag weeks.

4.7 THE EFFECT AT DIFFERENT GESTATIONAL PERIODS

4.7.1 LIVE BIRTH

When I stratified the cohort by the different periods of gestation as defined by the World Health Organization, I found that increasing temperatures had a significant effect on the risk of PTB (from 28–36 completed weeks of gestation) as temperature increased above 21°C. For shorter gestations (extreme PTB), the confidence intervals were wide, and I did not observe a significantly increased or decreased risk. The risk of term birth (≥ 37 weeks of gestation) increased as the temperature increased (Figure 4.17). This relationship however, is not clinically important, as being born after week 37 of gestation is not harmful to the fetus.

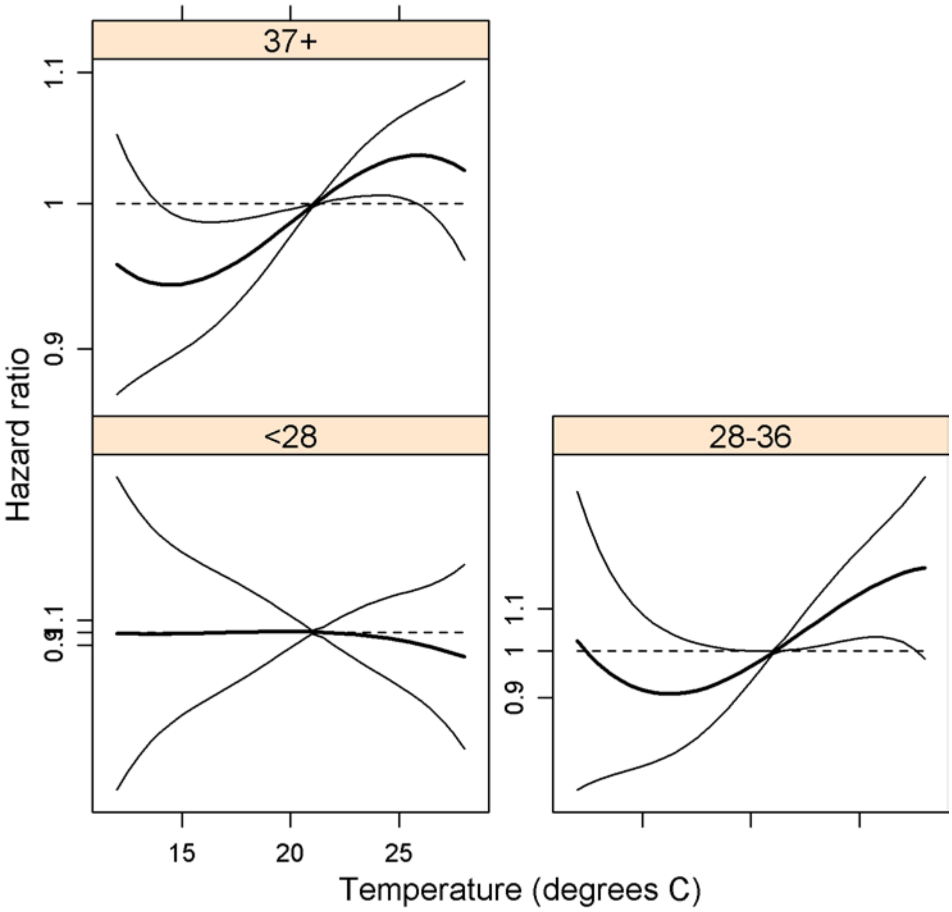


Figure 4.17. The effect of temperature on the risk of live birth in each gestational period. The thick black lines show the mean HR and the lighter black lines the 95% confidence interval. The dotted horizontal line at 1 represents no change in risk. The reference temperature is 21 degrees Celsius.

I further investigated the risk of temperature on birth outcomes in each week of the pregnancy from week 20 of gestation. An exploratory analysis was used to verify whether there were particular periods with high risks. The advantage of this approach is that I can examine whether there are vulnerable periods without pre-specifying particular gestation periods. The disadvantage is that the data were spread very thin, and some noise should be expected in the results.

Figure 4.18 plots the risk of live birth for each week of the pregnancy after week 20 of gestation. The effect on the fetuses with lower gestational ages had wider confidence intervals because the number of births in individual weeks was low. For increasing gestation time, the confidence intervals became narrower.

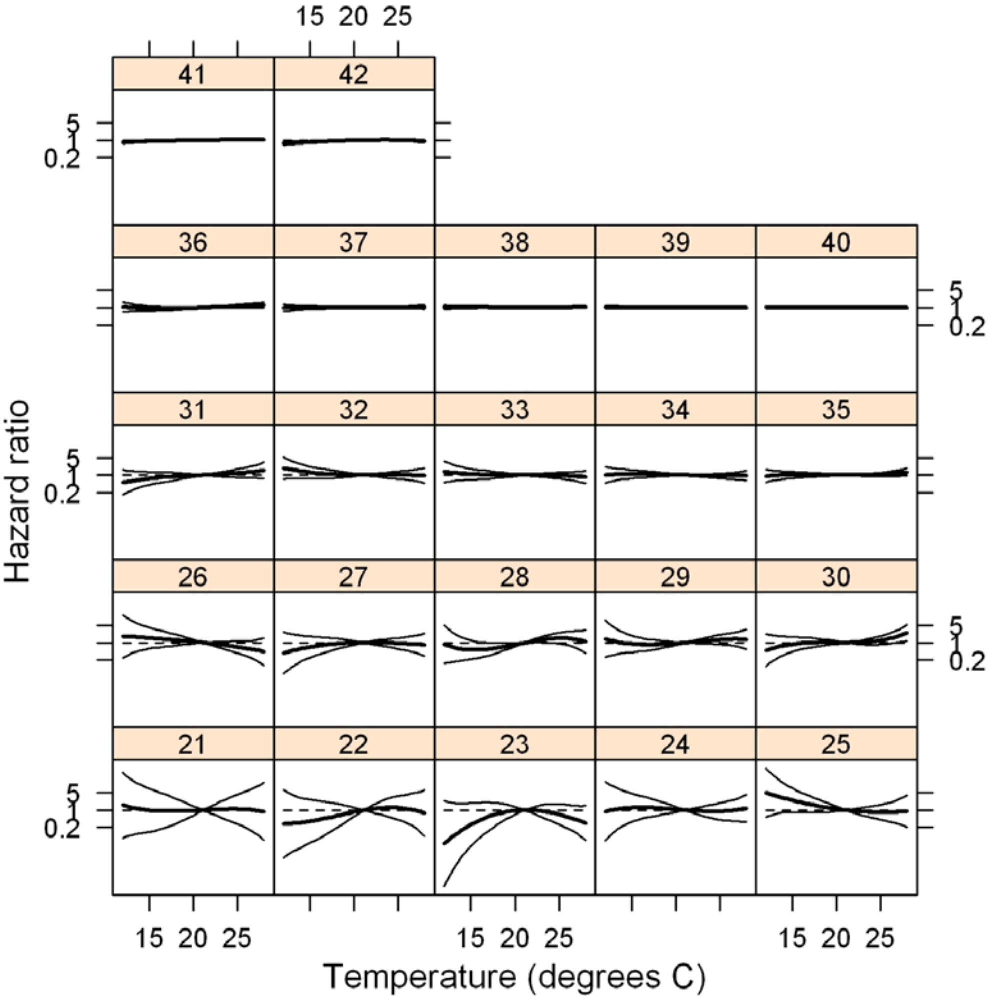


Figure 4.18. The effect of temperature on the risk of live birth in each gestational week. The thick black lines show the mean HR and the lighter black lines the 95% confidence interval. The dotted horizontal line at 1 represents no change in risk. The reference temperature is 21 degrees Celsius.

Since the confidence intervals were very wide in the early weeks, making the later weeks look very narrow and hard to read, I plotted the risk in each week from week 33 (Figure 4.19). In week 30 and week 36 of gestation, there was a significant relationship between temperatures and the risk of live birth. Also during weeks 41 and 42 of gestation the relationship was significant for temperatures below the reference value (21 °C).

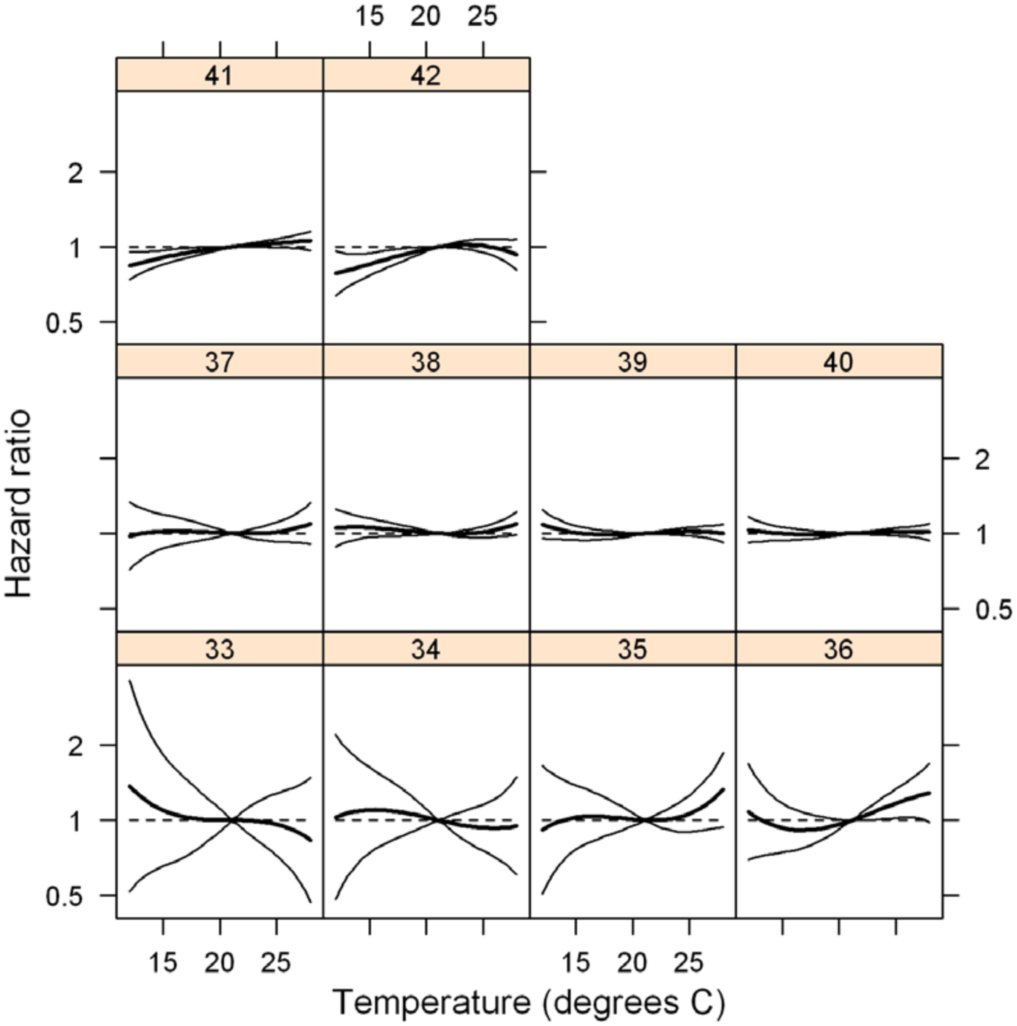


Figure 4.19. The effect of temperature on the risk of live birth in each gestational week from week 33 to week 42. The thick black lines show the mean HR and the lighter black lines the 95% confidence interval. The dotted horizontal line at 1 represents no change in risk. The reference temperature is 21 degrees Celsius.

4.7.2 STILLBIRTH

When I examined the same gestational periods and the effect of temperatures on stillbirth risk, I found that high temperature increased the risk of stillbirth mostly at lower gestational ages (Figure 4.20). The lower risk of stillbirth at colder temperatures was statistically significant for fetuses of less than 28 weeks of gestation and marginally significant for fetuses of 28 to 36 completed weeks of gestation. For older fetuses of 37 completed weeks or above, I found no apparent effect of temperature exposure.

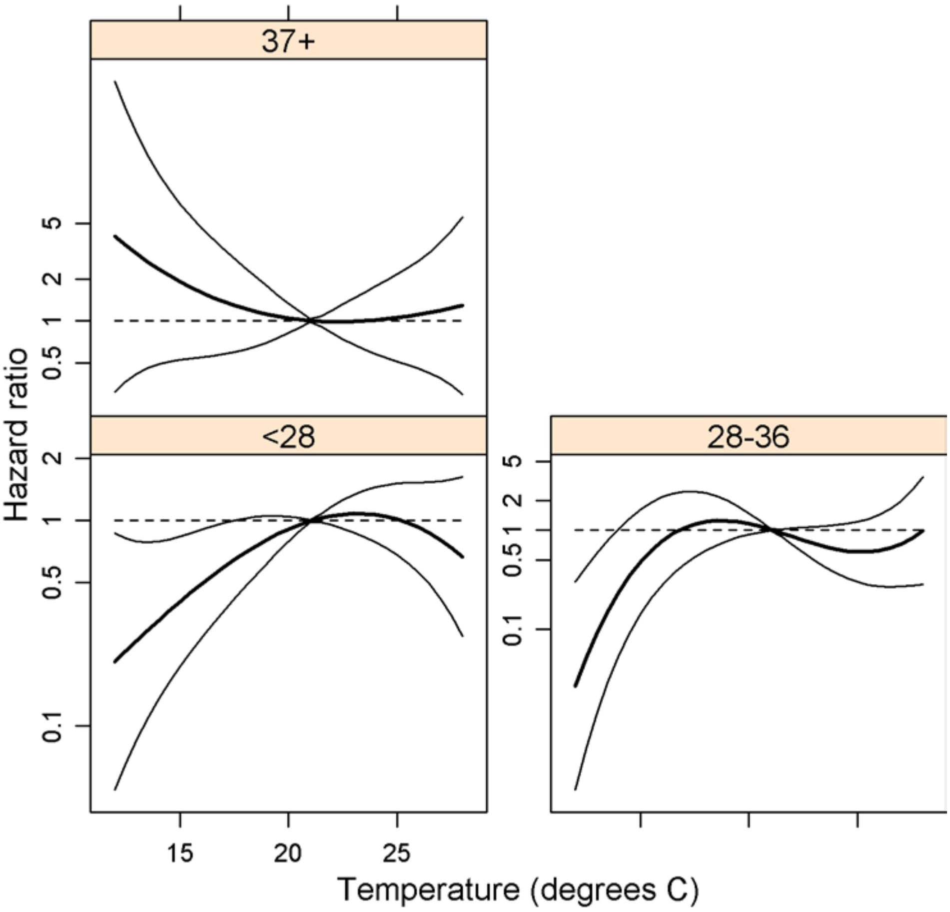


Figure 4.20. The effect of temperature on the risk of stillbirth in each gestational period. The thick black lines show the mean HR and the lighter black lines the 95% confidence interval. The dotted horizontal line at 1 represents no change in risk. The reference temperature is 21 degrees Celsius.

There was a significant effect of temperature on stillbirth in weeks 21, 28, 29, 30 and 33 of gestation (Figure 4.21). Again, temperature did not influence the risk of stillbirth at older gestational ages.

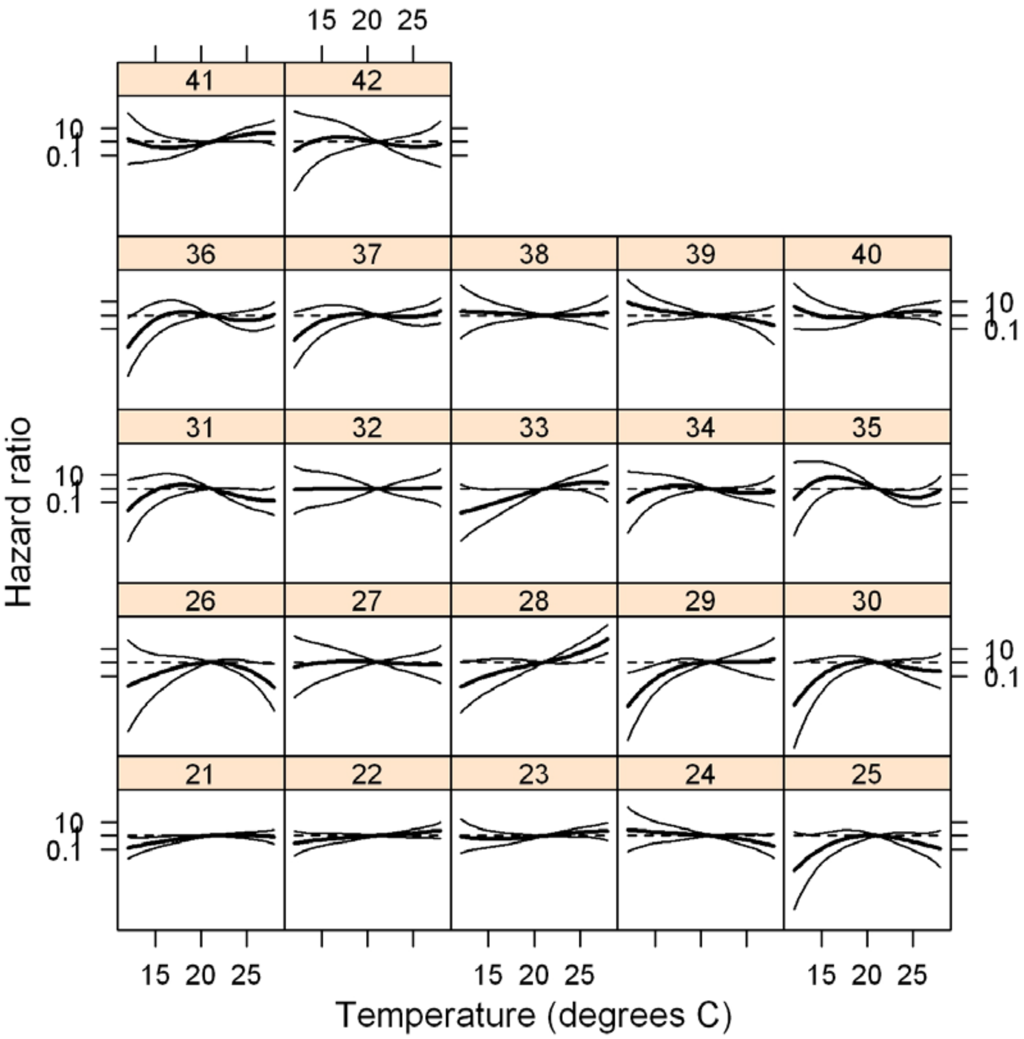


Figure 4.21. The effect of temperature on the risk of stillbirth in each gestational week. The thick black lines show the mean HR and the lighter black lines the 95% confidence interval. The dotted horizontal line at 1 represents no change in risk. The reference temperature is 21 degrees Celsius.

4.7.3 SUMMARY

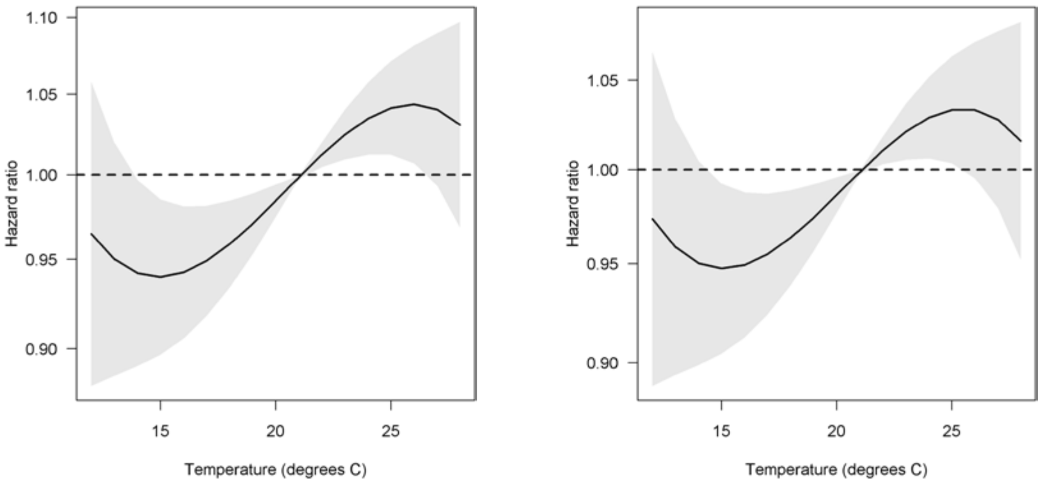
In terms of gestational age, I found a statistically significant risk from higher temperature for preterm infants and at post-term gestational ages. For stillbirth, the period before 28 completed weeks of gestation was most vulnerable to high temperatures.

4.8 SENSITIVITY ANALYSES

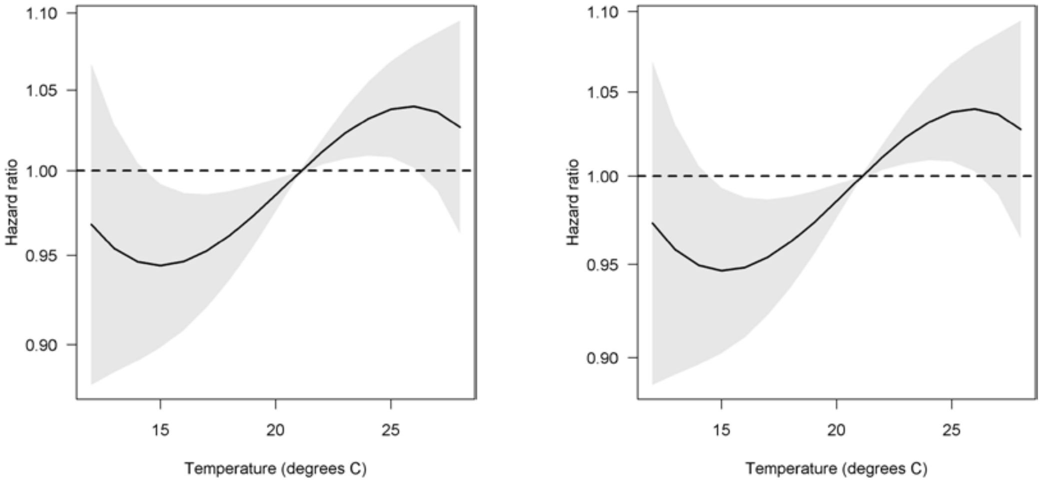
4.8.1 AIR POLLUTANTS

To examine whether air pollutants confounded the association between temperatures and the birth outcomes, I adjusted for one air pollutant at a time over the same gestational period as temperature and humidity in different models. For live birth risk (gestation length), the picture changed minimally after the adjustments (Figure 4.22). The risk of stillbirth associated with temperature exposure did not change much either, after adjustment for each air pollutant (Figure 4.23). The only exception is SO_2, which marginally decreased the effect of temperature on the risk of live birth. However, the shape of the relationship between temperature and live birth was similar.

Adjusted for NO_2 *Adjusted for O_3*



Adjusted for PM_{10} *Adjusted for $PM_{2.5}$*



Adjusted for CO *Adjusted for SO_2*

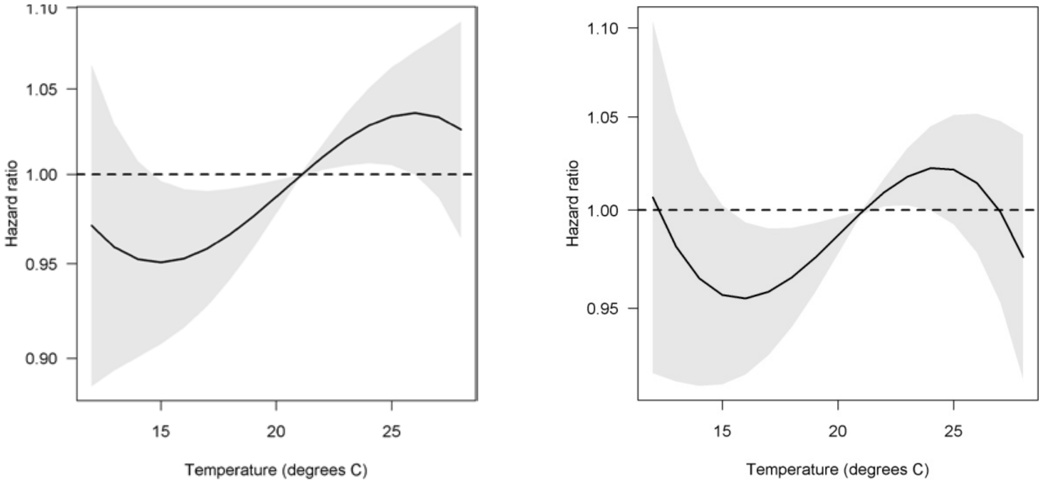
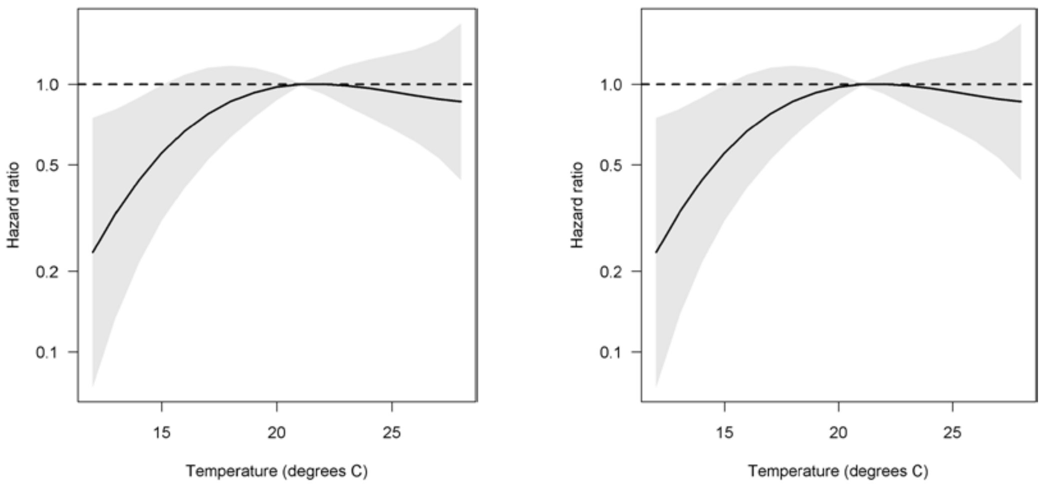
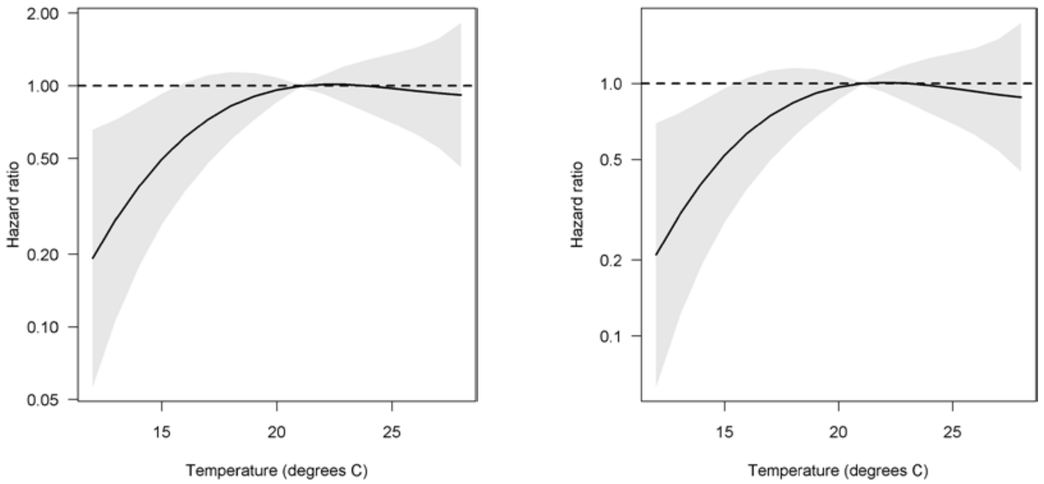


Figure 4.22. The effect of temperature on the risk of live birth after adjusting for individual air pollutants. The solid line shows the mean HR and the grey area the 95% confidence interval. The dotted horizontal line at 1 represents no change in risk. The reference temperature is 21 degrees Celsius.

Adjusted for NO_2 *Adjusted for* O_3



Adjusted for PM_{10} *Adjusted for* $PM_{2.5}$



Adjusted for CO *Adjusted for*SO_2

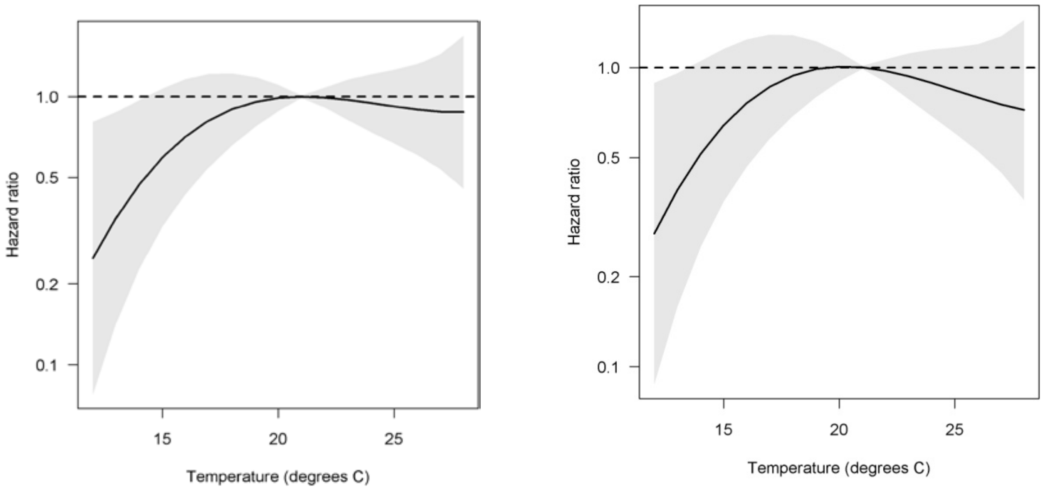


Figure 4.23. The effect of temperature on the risk of stillbirth after adjusting for individual air pollutants. The solid line shows the mean HR and the grey area the 95% confidence interval. The

dotted horizontal line at 1 represents no change in risk. The reference temperature is 21 degrees Celsius.

4.8.2 SPLINES

Due to the odd shape of the 3D plot of stillbirth risk over the four lag weeks (Figure 4.16), I fitted a double threshold spline that allowed for two independent linear relationships above the second and below the first threshold, and was flat between them. I used thresholds of 16 °C and 24 °C as they seemed to be the turning points on the smooth spline of stillbirth risk (Figure 4.15).

The smooth plot displayed a flattening risk as the temperature increased above approximately 16 °C, and the new plot displays a similar relationship below and above the thresholds. Below 16 °C, there was a statistically significant decreased risk of stillbirth with decreasing temperatures. Above 24 °C, the relationship was not statistically significant (Figure 4.24).

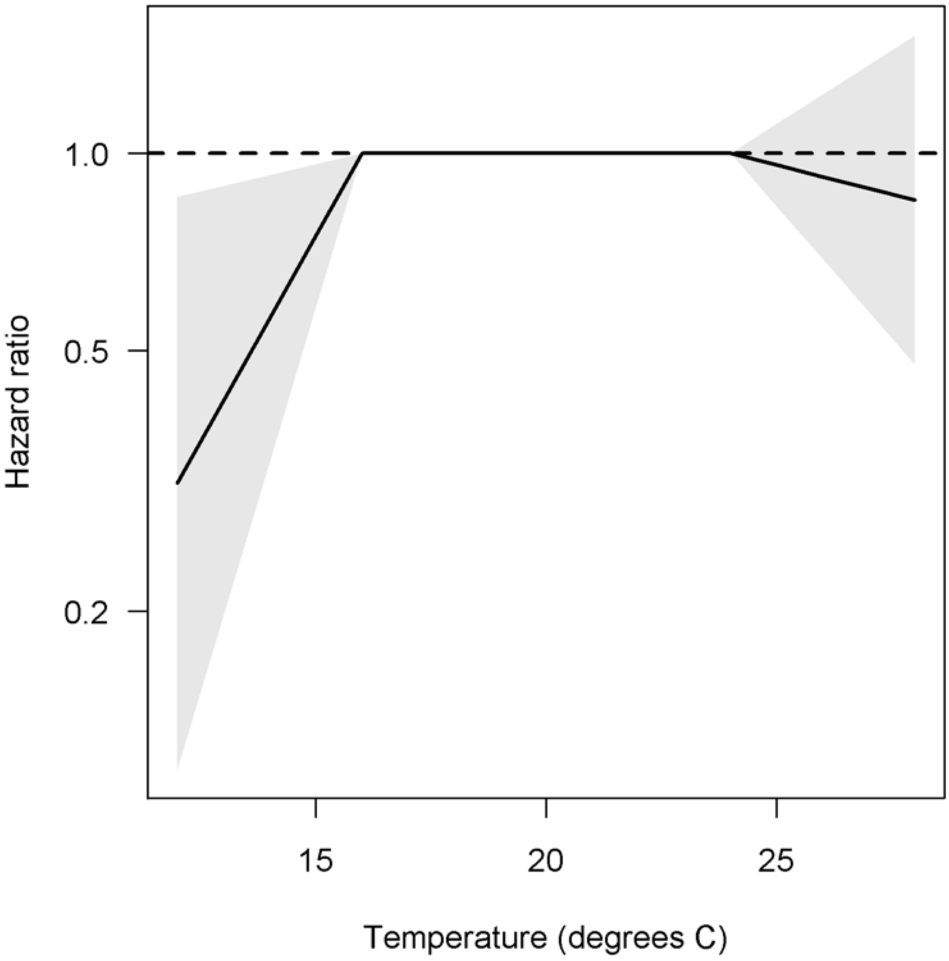


Figure 4.24. The effect of temperature on the risk of stillbirth using a double threshold spline. The solid line shows the mean HR and the grey area the 95% confidence interval. The dotted horizontal line at 1 represents no change in risk. The cold threshold is 16 degrees Celsius and the hot threshold is 24 degrees Celsius.

Using this type of spline gave a clearer 3D plot (Figure 4.25) and eliminated the odd-looking pattern that I found when using the smooth polynomial spline, and the peculiar increased risk with decreasing temperatures over the last week before birth (Figure 4.16) is no longer present.

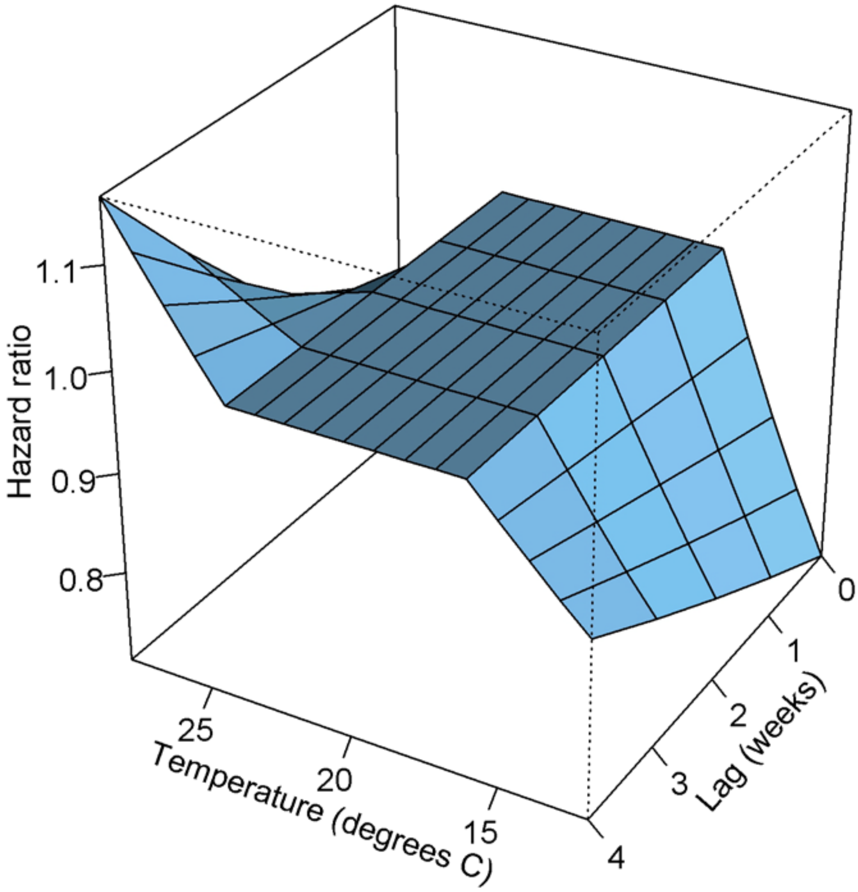


Figure 4.25. The mean effect of temperature on the risk of stillbirth over the four lag weeks using the double threshold spline. The cold threshold is 16 degrees Celsius and the hot threshold is 24 degrees Celsius.

Chapter 5: Discussion and Conclusions

5.1 THE SEASONALITY OF BIRTH OUTCOMES

5.1.1 SUMMARY OF THE FINDINGS

I found a clear seasonal pattern of birth outcomes in Brisbane. A bimodal pattern was evident in gestation length with a significant increased risk of live birth (shortened gestation), in February-March (autumn), and August-December (spring) compared to January (reference month) (Figure 4.9). However, after adjusting for temperature, the bimodal pattern changed to unimodal, and only the spring peak was present (Figure 4.10). For stillbirth, I found a significantly lower risk in March when compared to January (Figure 4.11). None of the remaining months were significantly different from January. After adjusting for temperature, the trough in March was still statistically significant suggesting that temperature in the preceding four weeks has little to do with the decreased risk of stillbirth in March. A peak (not statistically significant) was observed in July (winter) after adjustment for temperature (Figure 4.12).

5.1.2 PREVIOUS STUDIES

Previous studies have found peaks and troughs of PTB and stillbirth at different times of the year (Figure 2.1). Two studies reported a similar seasonal pattern of PTB to mine. Matsuda et al. (1992) in Japan, and Keller et al. (1983) in the USA, both found bimodal patterns of PTB. Studies of the seasonal pattern of stillbirth have found conflicting results with one study reporting an increased risk in spring (Eriksson & Fellman, 2000), one in winter (Torrey et al., 1993), and one in summer (Barnett & Dobson, 2010).

Friis et al. (2004) and Rayco-Solon et al. (2005) have reported seasonality of birth outcomes in developing courtiers. These results however, are more likely to be caused by seasonal factors such as workload, malaria and nutritional factors (Rayco-Solon et al., 2005), and may not be comparable to the socio-environmental conditions in Brisbane.

5.1.3 TEMPERATURE

As the seasonal patterns of gestational age and the risk of stillbirth changed considerably after adjusting for temperature, a likely explanation is that temperature contributed to some of the seasonal variation of birth outcomes in the cohort. Previous studies have been conducted in different populations, countries and climates, and environmental exposures that may influence gestational length vary considerably between these countries. In London, Lee and colleagues (2006) found that PTB peaked in winter. The authors argued that the temperature range experienced by English pregnant mothers is narrower than the temperature range experienced by Japanese or American pregnant women, which might be the reason for the single peak of PTB found in their study as compared with the bimodal pattern found in Japan and USA. Brisbane’s temperature variation is closer to Japan than to England, which might be the reason why the seasonal patterns in this study were more similar to the pattern found in Japan (bimodal) (Matsuda & Kahyo, 1992).

Interestingly, some studies have suggested that the seasonal pattern of birth outcomes differs by latitude. For example, in Australia, the strength of the seasonal pattern of birth weight diminished with increasing distance from the equator

(McGrath, Barnett, et al., 2005). Matsuda and colleagues (1995) found a spring peak in birth weight that increased its amplitude closer to the equator. This suggests that factors associated with warm, subtropical or tropical climates have greater influence on birth weight compared with temperate climates.

Matsuda and colleagues (1998) investigated the relationship between temperature and PTB in Japan and found that temperature was negatively correlated with the peak in winter ($r = -0.42$, $p < 0.01$) and positively correlated with the peak in summer ($r = 0.54$, $p < 0.01$). This indicates that temperature is the underlying reason for the seasonal pattern of gestational age and that the relationship is J-, or U-shaped. Elter et al. (2004) found that temperature in the second trimester was the meteorological variable that contributed most to the seasonality of mean birth weight. In my study however, adjusting for temperature only eliminated one of the seasonal peaks in the risk of live birth. For the winter peak, the risk increased from approximately 7% to 15% compared with January (Figure 4.9 and Figure 4.10). It is plausible that different underlying mechanisms caused the two peaks, and that seasonal factors other than temperature (e.g., Vitamin D) caused the peak in August.

I found one trough of stillbirth risk in March (Figure 4.11), which is difficult to explain in terms of temperature exposure. The presence of the trough after adjustment for temperature (Figure 4.12) suggests that temperature has little to do with the decreased risk of stillbirth in March. Although not statistically significant, the seasonal pattern changed after adjustment for temperature, and a peak in July (winter) appeared. A protective effect of low winter temperatures may have masked the July peak in the unadjusted pattern.

5.1.4 CONCLUSION

Seasonal patterns of adverse birth outcomes vary between populations and there are likely to be several underlying mechanisms. My intention was to provide insights into possible exposures that may influence the seasonality of adverse birth outcomes. From the seasonal pattern found in this study, and by previous studies (Lee et al., 2006; Matsuda & Kahyo, 1992), a likely explanation is that environmental factors contribute considerably to the seasonal pattern of birth outcomes. The fact that the seasonal patterns changed considerably after adjusting for temperature, suggest that temperature is an important contributing factor to birth outcomes. Many studies have found peaks of adverse birth outcomes in summer (indicating that warm temperatures are harmful), winter (indicating that cold temperatures are also harmful), or both summer and winter (indicating a U- or J-shaped relationship between temperature and adverse birth outcomes). The significant trough in stillbirth risk found in March however, is not easily explained by environmental factors. Future studies should investigate other possible explanations such as maternal physical activity level and nutrition.

5.2 THE EFFECT OF TEMPERATURE ON BIRTH OUTCOMES

5.2.1 SUMMARY OF THE FINDINGS

I found an acute effect of temperature on gestational age (Figure 4.13) with an increased risk with increasing temperatures over the last four weeks before birth. When examining each lag week for gestational age, exposure to high temperatures were more dangerous in the last and second last week before birth (Figure 4.14). In weeks three and four before birth however, the direction changed and cold temperatures appeared to increase the risk of live birth.

I found an increasing risk of stillbirth with increasing temperatures over the last four weeks before birth. When the temperature increased above approximately 16 °C however, the risk levelled out (Figure 4.15). Four weeks before birth the risk of stillbirth decreased when temperatures decreased (Figure 4.16). However, the closer to the week of birth, the more the direction changed in the relationship. In the last week before birth, cold temperatures appeared to increase the risk of stillbirth. When I fitted a double threshold spline for stillbirth (Figure 4.25), this increased risk from cold temperatures in the last week before birth disappeared. This may have been due to the polynomial spline being too restricted and a more believable surface may have been realised if I had increased the degrees of freedom beyond three.

5.2.2 PREVIOUS STUDIES

Previous studies have focused on shorter exposure windows around the time of birth. Yackerson and colleagues investigated the day of birth and found that PTB was correlated with maximum temperature (2008) while others investigating six lag days have found no relationship between temperature and PTB (Lee et al., 2008). The results show that exposure to high temperatures has an acute effect on live birth, but that it may have a slightly more delayed effect on stillbirth. Previous studies were unable to capture this relationship because of their narrow exposure windows. The results are consistent with a previous study, which found that exposure to high temperatures in the week of birth increased the rate of preterm labour (Lajinian et al., 1997), and another study which reported that increasing temperatures in the month of birth were negatively correlated with gestational age (Flouris et al., 2009). It is also possible that exposure to temperature prior to the last four weeks of the pregnancy is harmful to the fetus. No previous studies have investigated this possibility.

5.2.3 THE LAG EFFECT

The fact that the effect of temperature on live birth was greatest in the last week before birth and a more delayed effect was observed for stillbirth may be because different mechanisms underpin the two outcomes. The immediate effect on gestational age may be caused by increased uterine activity or preeclampsia due to exposure to high temperatures. Both possible reasons will result in immediate birth resulting in shortened gestational age.

While the risk of live birth was immediate, the stillbirth risk appeared to be delayed with the highest risk of hotter temperatures four weeks before birth. It is difficult to conclude at which stage the temperature is likely to cause the fetus to die. I also do not know whether the stillbirth was due to low gestational age and happened during birth (antepartum stillbirth), or if the fetus was already dead when the birth started (intrapartum stillbirth). Worldwide, it is estimated that 15–40% of all stillbirths are intrapartum (Lawn et al., 2009). An unknown factor in this type of stillbirth is how long it takes from when the fetus dies until the body starts the birth spontaneously or the birth was induced. Rough estimates however, suggest that it takes from a few days up to about six weeks and Genest (1992) found that 29% of the stillbirths happened less than six hours before birth, but as much as 18% happened more than seven days before birth. This delay may contribute to the lagged effect of temperatures on stillbirth.

The increased risk of stillbirth from cold temperatures over the week before birth is harder to explain. When I fitted the double threshold spline however, this increased risk of stillbirth with colder temperatures disappeared and the effect seemed equal across all four lags.

5.2.4 EXPOSURE WINDOWS

Exposure to high temperatures may cause PTB or stillbirth in a couple of different ways. The first possibility is that it causes PTB or stillbirth within a short time period after exposure. While it has not been established which period is more harmful, it has been suggested that the harmful effects of environmental exposures are larger during the second trimester, when the fetus is in fast development (Colvin, McGuire & Fowlie, 2004). The second possibility is that it has a delayed or cumulative effect. A paradox is that some studies have found different directions for the temperature-birth outcome relationship with exposure in different trimesters. For example, in the UK, a negative relationship between temperature and birth weight was found in the first trimester while a positive relationship was found in the third trimester (Lawlor et al., 2005). In Turkey, increased temperatures in the second trimester were associated with decreased birth weights (Elter et al., 2004), while in Northern Ireland, increased temperatures in the second trimester were associated with increased birth weight (Murray et al., 2000). In this study, I only looked at the temperature effects in the four weeks before birth and I did not investigate the possibility of a chronic or cumulative effect.

5.2.5 CONCLUSION

I found a temperature effect during the last four weeks before birth on both live birth and stillbirth. The results are consistent with some previous studies. I found an acute effect of hot temperatures on gestational age with the last two weeks before birth having the most significant impact. For stillbirth, I found a more delayed adverse effect of hot temperatures, with the third and fourth week before birth being the most dangerous. However, the mechanism causing the live birth or stillbirth is unclear, and no study has yet investigated the underlying mechanisms of this relationship.

5.3 THE EFFECT AT DIFFERENT GESTATIONAL PERIODS

5.3.1 SUMMARY OF THE FINDINGS

To get a picture of particular vulnerable periods of the pregnancy, I divided the pregnancy into three periods by definition: Extreme PTB (< 28 weeks of gestation), PTB (28–36 weeks of gestation), and term birth (≥ 37 weeks of gestation). I found an effect of high temperatures (above 21 °C) on PTB. I also found an effect of temperature on the risk of term birth although in this period of gestation the risk appeared to increase at lower temperatures (i.e., 15 °C) (Figure 4.17). When looking at each individual week of gestation, I found that temperature exposure increased the risk of live birth in weeks 30, 36, and after week 41 of gestation (Figure 4.18 and Figure 4.19). The small sample size in each gestational week resulted in a low statistical power, which caused the wide confidence intervals and hence great uncertainty.

For stillbirth, I found that the lowest gestational period (< 28 weeks) and the period from 28–36 weeks of gestation were vulnerable to temperature exposure (Figure 4.20). When I divided the pregnancy into weeks of gestation, I found that certain weeks were more vulnerable to temperature. Week 21 and the period between 28 and 33 weeks of completed gestation were the most vulnerable (Figure 4.21).

However, the interpretation of these findings should be done with caution as there is more births in the term birth group for live birth and in the extreme preterm birth group for stillbirth (Figure 4.1). Thus, in the analysis of preterm birth, there is more power to detect effects at larger gestational ages and in the analysis of stillbirth, there is more power to detect the association at lower gestational ages.

5.3.2 PREVIOUS STUDIES

I am aware of only one study investigating vulnerable weeks of gestation to high temperatures. Basu and colleagues (2010) reported the strongest impact from increased temperature on PTB from week 34 to 36 of gestation. For lower gestations however, the direction of the relationship changed, with a 5.2% (95% CI –9.9, –0.4) decrease in PTBs per 5.6 °C increase in apparent temperature. There are no previous studies investigating vulnerable periods of gestation concerning the risk of stillbirth from exposure to temperature.

5.3.3 BIOLOGICAL MECHANISMS

I found a significant effect of exposure to high temperatures on preterm infants (weeks 28–36), and at term gestational ages (≥ 37 weeks). This might be explained by the fact that as the pregnant woman gets closer to term, she also increases in size and the exertion posed by the big womb increases exponentially. Among preterm gestational ages, the risk of birth increased with increasing temperatures above 20 °C (Figure 4.17). Among post-term gestational ages however, the risk increased at temperatures from 12 to 21 °C and levelled out at higher temperatures (Figure 4.18 and Figure 4.19). The reason for this may be that whilst 12 °C would be a pleasant temperature for a woman in the earlier parts of her pregnancy, it might be too hot for a woman in the post-term period, who has a much bigger womb.

For stillbirth, the early parts of the third trimester (< 28 weeks and 28–36 weeks) were the most vulnerable (Figure 4.20). This is plausible as the fetus' immune system is under-developed earlier in the pregnancy. One possible explanation for the increased vulnerability in this early period of gestation may be the development of the central nervous system (CNS). The brain and the CNS keeps developing well into the postnatal period with brain growth peaking approximately four months into the postnatal period (Rice & Barone, 2000). In the early part of the third trimester, the development of the human brain is particularly vulnerable to hypoxic, ischemic and infectious insults, which can result in brain lesions (Pitcher, Henderson-Smart & Robinson, 2006). The mechanism causing temperature to affect brain development in humans is not clear, but hyperthermia has been shown to influence brain development in rodents and guinea pigs (Edwards & Beatson, 1984; Hinoue, Fushiki, Nishimura & Shiota, 2001). In humans, insults during the development of the CNS may also result in severe congenital abnormalities, with one study reporting a frequency of 0.74–1.89 cases per 1,000 births (Reznik & Minkov, 1993). These birth defects include conditions that produce extremely severe functional shortages including hydrocephaly, and herniation of the spinal cord, which may be incompatible with life (Rice & Barone, 2000). Damages on the fetus during this vulnerable period of brain development could therefore be the reason for increased risk of stillbirth from temperature during these periods of gestation.

5.3.4 MISSING ABORTIONS

Even though the brain is vulnerable to environmental exposures early in the third trimester, the CNS is developing most rapidly during the first months of gestation. Exposure to a variety of factors in this period has also been shown to be associated with birth defects (Park-Wyllie et al., 2000; Ritz et al., 2002; Zhang & Cai, 1993). I could not investigate the acute temperature exposure in this group however, as stillbirths occurring before 20 weeks of gestation (spontaneous abortions) were not included in the Brisbane birth registry. I could therefore only investigate vulnerable weeks and periods after week 20 of the pregnancy. Missing these births does have the potential to affect investigations of the effects of temperature on gestational age and stillbirth. It is possible that the mechanism causing the abortion is the same as for PTB and stillbirth, meaning that the results only reflect part of the picture. Another possibility is that the ‘harvesting effect’ described in studies investigating temperature and mortality is also present in birth outcome studies. A harvesting effect is typically identified by the occurrence of fewer deaths than expected following a heatwave, as those who died during the heatwave had a poor inherent health status to begin with and would have died soon regardless of the temperature (Toulemon & Barbieri, 2008). In birth outcome studies, this would take the form of vulnerable fetuses dying before week 20 (abortion) resulting in fewer stillbirths after week 20. This study based on births after 19 weeks could underestimate the dangers of environmental exposure. It is therefore important for new studies to collect data prospectively from an early gestation to capture these potentially important abortions.

5.3.5 CONCLUSION

I found that the effect of temperature on gestational age is highest among preterm infants (weeks 28–36) and among post-term infants (week 41 and 42). The effect of high temperatures on live births after 37 weeks of gestation however, is not as important as it is not dangerous to the fetus. I found that the temperature effect on stillbirth is highest in the shortest gestational ages (< 28 weeks) and the period between 28 and 33 completed weeks. This study is one of the first studies to explore vulnerable periods and weeks of gestation to the effects of temperature exposure, and it therefore provides valuable new information on the relationship between temperature and birth outcomes.

5.4 ALTERNATIVE EXPLANATIONS AND POSSIBLE CONFOUNDERS

5.4.1 AIR POLLUTION

In the cohort, the adjusted seasonal pattern of gestational age had a significant peak in winter. In Brisbane, air pollutants also have a seasonal pattern with higher PM_{10} and O_3 levels in spring; and higher NO_2 levels in winter (Wang, Tong, Verall, Gerber & Wolff, 2006). Darrow and colleagues (2009) found that daily PTB rates were associated with average NO_2 concentrations in the six weeks preceding birth. A review of the literature revealed that eight out of 13 studies investigating the effect of PM found 10–20% increased risk of PTB with increasing PM concentrations (Empana et al., 2009). Since PM_{10}, $PM_{2.5}$, O_3, CO and NO_2 all had a seasonal pattern in the study period (Figure 4.3), they could be contributing to the seasonal pattern of birth outcomes found in the cohort. I did not control for air pollutants when assessing the seasonal variation of birth outcomes in the study, but the most likely determining air pollutant would be NO_2, as it peaks in winter, approximately six weeks before the peak in live birth risk the cohort. I also observed a peak in stillbirth risk (even though not statistically significant) in winter after adjusting for temperature. A few studies have linked air pollution to stillbirth in the past (Pereira et al., 1998; Pope et al., 2010) and Pereira and colleagues found that the air pollutant most strongly associated with stillbirth was NO_2.

Air pollution has the potential to confound the association between temperature and birth outcomes. Air pollutants have a seasonal pattern, and are correlated with temperature (Table 4.3). I adjusted for one air pollutant at a time and did not find that air pollution is a significant confounder of the effect of temperature on birth outcomes.

5.4.2 SUNLIGHT

Another factor that varies by season is sunlight exposure and maternal vitamin D. Ultraviolet (UV) radiation-induced synthesis in skin following sun exposure is the main sthece of Vitamin D (Moan, Porojnicu, Dahlback & Setlow, 2008). Because of the seasonal variation in UV light, vitamin D nutritional status is best in summer and autumn and poorest in winter and spring (Nesby-O'Dell et al., 2002). The vitamin D pool of the fetus is highly dependent on the mothers (Salle, Delvin, Lapillonne, Bishop & Glorieux, 2000). Recent data suggest that vitamin D influences fetal-placental development and has anti-inflammatory effects (Evans, Bulmer, Kilby & Hewison, 2004; Schleithoff et al., 2006). Therefore, it may act as a protective agent for the pregnancy. It is possible that low levels of vitamin D during the winter months are contributing to the seasonal pattern in gestational age and stillbirth risk. McGrath and colleagues (2005) reported that fetuses exposed to low levels of vitamin D were slightly heavier than fetuses exposed to adequate levels of vitamin D. In New Zealand, researchers found that exposure to bright sunshine in the first trimester increased the birth weight of the child (Waldie et al., 2000). Arora and Hobel (2010) found a relationship between vitamin D deficiency and PTB and Morley et al. (2006) found that pregnancies of mothers with low vitamin D status were shorter (by 0.7 weeks; 95% CI −1.3, −0.1), and the babies had poorer intrauterine long bone growth. There is also a statistically significant relationship between vitamin D and bacterial vaginosis (Bodnar, Krohn & Simhan, 2009), a condition strongly associated with PTB. Haugen et al. (2009) reported that pregnant women receiving 400–600 UI/day of vitamin D had a 27% reduction in the risk of pre-eclampsia (PE) compared to those not taking supplements, and Algert et al. (2010) found that sunlights was correlated with pregnancy-induced hypertension

(PIH). As PE and PIH are strong determinants of both PTB and stillbirth, this relationship is important for understanding seasonal determinants of adverse birth outcomes.

5.4.3 CONCEPTION RATES

In Texas, USA from 1994 to 1998, a seasonal pattern of conception rates was reported ($p < 0.01$) with highest rates from November to January (Tita, Hollier & Waller, 2001). Seasonal patterns in conception rates cause seasonal patterns in gestational ages. For example, 36 weeks after a peak of conception rates, there will be a peak of 36 weeks old fetuses. These fetuses have a much higher chance of being born prematurely than fetuses of for example 20 weeks of gestation. Darrow and colleagues (2009) reported that the average expected rates of PTB in their cohort were highest in August, when a larger proportion of fetuses at risk were in late gestation (i.e., week 36), and lowest in May, when a smaller proportion of fetuses were in late gestation. They found that not accounting for the seasonal pattern in the distribution of gestational ages would lead to an 8% increase in rates of PTB in August compared with May. The seasonal pattern in conception rates can therefore appear as seasonal pattern in gestation. This confounding is however controlled for in the study as I only compared fetuses at the same stage of gestation using a survival model.

5.4.4 SOCIO-DEMOGRAPHIC FACTORS

Different seasonal patterns of conception and birth rates have been found between different socio-demographic groups including maternal age, education level, marital status, birth order, and ethnicity (Bobak & Gjonca, 2001; Darrow, Strickland, et al., 2009). A study in New York found that ethnicity modifies seasonal patterns.

After stratification by ethnicity (black, Puerto Rican, and white) the relationship between season of birth and birth weight was statistically significant only in black subjects (p= 0.002, after adjustment for study site, sex, gestational age, maternal education, maternal age, maternal BMI and birth order) (van Hanswijck de Jonge et al., 2003). However, those differences were not significant after adjustment for confounding variables for the white (p= 0.8) or the Puerto Rican subjects (p= 0.8). A study in Chile investigated socio-economic factors contributing to the bimodal pattern of birth weights. The authors reported that socio-economic factors were unlikely to contribute to the pattern because when they added socio-economic variables in their model, the bimodal pattern remained the same and was still statistically significant (Torche & Corvalan, 2010) .

In Australia, the Indigenous population has poorer birth outcomes than the non-Indigenous population. This means that if Indigenous pregnancies in the cohort have a different seasonal pattern than non-Indigenous pregnancies, this may look like a seasonal pattern in adverse birth outcomes. This would also be the case with adolescents, who have been reported to have a different seasonal pattern in conception rates than adults (Petersen & Alexander, 1992). This group has poorer birth outcomes than older mothers (Conde-Agudelo et al., 2005) which could potentially create an artificial seasonal pattern of adverse birth outcomes. Again, if these seasonal patterns of birth outcomes happened to coincide with a season with high temperatures, it would make it look like high temperatures were related to adverse birth outcomes. I adjusted for both Indigenous status and maternal age in the study and should therefore have eliminated the potential for this bias.

5.4.5 SMOKING

Smoking during the pregnancy is a strong determinant of adverse birth outcomes (Ward et al., 2007). Only one previous study in this field has adjusted for smoking status (Bodnar & Simhan, 2008). In the United States, tobacco sales have been reported to be seasonal with a significant drop in winter (January–February) and an increase during the summer months (June–August) (Chandra & Chaloupka, 2003). Climatic factors such as temperature may be the reason for the seasonal pattern, as smokers have to go outside to smoke most places in the United States. According to the authors, other possible explanations include the timing of tax changes (December–January or June–July), the timing of the new fiscal year (June–July), the timing of school year (August–June), and the timing of quitting efforts tied to New Year's resolutions (December–January). As the pattern is seasonal, it may contribute to the seasonal patterns previous studies. No study has been undertaken in Australia on the seasonal pattern of tobacco sales or smoking. However, I adjusted for the confounding effects of smoking in the study.

5.4.6 AIR-CONDITIONING

I did not have the postcode of the pregnant mother. One thing that differs between areas is the use of air-conditioners. In general, humans have greater means of protecting themselves from the cold (by the use of high quality housing, indoor heating, warm clothing and blankets, for example) than from the heat (Wells, 2002). Houses in Queensland are often designed to create air flow through the house because of the mild winters and hot summers (Australian Bureau of Statistics, 2006). This may not be enough on extremely hot days when air-conditioning is the only way of cooling down. Pregnant women in Queensland may therefore be particularly vulnerable to hot rather than cold temperatures if their houses do not have air-conditioning. However, I did not have information about the density and uses of air-conditioners across different areas in the cohort. This prevented us from investigating the potential modifying effect of air-conditioning.

5.4.7 PHYSICAL ACTIVITY

Pregnant women may be less physically active during cold days in winter and hot days in summer. Physical activity has been shown to have a positive effect on birth outcomes (Leiferman & Evenson, 2003) and a sedentary lifestyle has been associated with lower birth weight (Both, Overvest, Wildhagen, Golding & Wildschut, 2010). I found a significant lower risk of stillbirth in March. As from March, it starts to cool down in Brisbane after a hot and humid summer, so it is possible that pregnant mothers (and everyone else) became more active at this time, thus reducing their risk of adverse birth outcomes. Detailed individual level data on physical activity was not available in this study, and prospective cohort studies are needed in order to better measure this seasonal confounder.

5.4.8 INFLUENZA

The seasonal epidemiology of influenza is well characterised and a clear seasonal pattern with more cases in winter months is observed. One study found no significant increase in adverse birth outcomes associated with respiratory hospitalisations during influenza season (Hartert et al., 2003). However, it is suggested that infectious diseases can cause stillbirth through several mechanisms including placental damage, or direct fetal infection, and that as much as 24% of all stillbirths are associated with infections (McClure, Dudley, Reddy & Goldenberg, 2010). Some studies have investigated the underlying reason for the seasonality and found that in guinea pigs the transmission of a human strain of influenza was highly sensitive to temperature and relative humidity (Lowen, Mubareka, Steel & Palese, 2007). Influenza is therefore a possible confounding factor of the relationship between temperatures and birth outcomes. I did not have information about infections during the pregnancy and thus could not adjust for it.

5.4.9 MENTAL HEALTH

Mental health varies by season and studies have found that depression is highly seasonal (Huibers, de Graaf, Peeters & Arntz, 2010). This type of depression is called Seasonal Affective Disorder (SAD) and occurs each year at the same time, normally starting in autumn or winter and ending in spring (Lam, Tam, Yatham, Shiah & Zis, 2001). Benzodiazepine (an antidepressant) has been shown to be highly associated with PTB and other adverse birth outcomes (Calderon-Margalit, Qiu, Ornoy, Siscovick & Williams, 2009) and may contribute to the winter peak in PTB.

5.4.10 NUTRITION/BODY WEIGHT

Humans have a clear seasonal variability in food intake and body weight (Mercer, 1998). There is a tendency towards weight gain in winter and weight loss in spring and summer (Ma et al., 2006) and temperature has been shown to be negatively correlated with body weight. Poor nutritional status during the pregnancy is related to PTB, and pregnancy complications (Ehrenberg et al., 2003). If pregnant mothers weigh less in summer due to high temperatures, it may confound the temperature-birth outcomes relationship, as it may be nutritional status and not the actual temperature that causes poorer birth outcomes. The lack of data on nutrition and other individual level confounders is a key limitation of this study.

5.4.11 METHOD OF DELIVERY

As the pregnancy progresses and the mother gets bigger and less tolerant towards hot temperatures, she may be more likely to initiate induced birth by caesarean during hot periods. The temperature effect on induced births by caesarean may therefore contribute to the temperature effect on the risk of birth, especially in term or post-term pregnancies.

5.5 METHODOLOGY

5.5.1 SURVIVAL ANALYSIS

This study is the first investigation of the relationship between temperature and birth outcomes using survival analysis. With this method, I was able to avoid the potential confounding described by Darrow and colleagues (2009), caused by the risk of being born (live born or stillborn) increasing exponentially with increasing gestational age. This issue arises only when defining an exposure window relative to the date of birth (e.g. last week or last trimester before birth) and not when defining an exposure window relative to conception (e.g. first trimester). This is because when comparing fetuses in their first trimester they will all be at the same gestational age (first trimester), but when comparing fetuses in their last trimester or week of birth, they will have different gestational ages. To examine exposure during the last week, month or trimester before birth however, has been a relatively common approach in birth outcome studies (Flouris et al., 2009; Lee et al., 2008; Porter et al., 1999; Yackerson et al., 2008). In this study, I only compared fetuses at the same stage of the pregnancy, thus eliminating this issue.

5.5.2 TIME-DEPENDENCE

Survival analysis has been proven effective when investigating time-varying exposures during pregnancy and their effects on birth outcomes by several previous studies (O'Neill et al., 2003; Suh et al., 2009). When a covariate of interest varies over time it can be fitted as a time-dependent variable (Fisher & Lin, 1999). O’Neill and colleagues (2003) performed a sensitivity analysis, in their study of urinary tract infection and preterm delivery, to prove that the HR is a better estimate than the OR. Later, the method was applied to a study of smoking during pregnancy and its effect on fetal and infant death, and smoking status was fitted as a time-dependent variable (Platt et al., 2004). More recently, the method was applied in a study investigating air pollution and its effect on PTB (Suh et al., 2009). The study examined the relationship using both a logistic model and an extended Cox proportional hazard model. They found that the survival method was more effective when investigating time-varying exposures than conventional approaches. They reported that air pollution had a greater effect on fetuses with shorter gestational age and that the method helped them identify the most vulnerable periods.

5.5.3 COMPETING RISKS

A further extension of the extended Cox proportional hazard model is to include competing risks. This is not a new concept (Berry, Ngo, Samelson & Kiel, 2010; Glynn & Rosner, 2005), but when examining birth outcomes, only a few studies have applied the method (Michalowicz et al., 2006). When competing risks are present, there are three ways to analyse the data: (*a*) analysis of the event of interest ignoring the competing risk, (*b*) analysis of joint events as a single end point, and (*c*) analysis of competing risk (Kim, 2007). In any situation when more than one outcomes is possible (e.g. live birth and stillbirth) a competing risk model would better account for the entire at-risk population without excluding any group of pregnancies. I included the complete at-risk population by modelling live birth and stillbirth as competing risks.

5.6 MEASURES

5.6.1 TEMPERATURE MEASURES

Most previous studies have used mean temperature (Elter et al., 2004; Flouris et al., 2009; Lawlor et al., 2005; Matsuda et al., 1998), but minimum and maximum temperatures have also been used (Lee et al., 2008; Murray et al., 2000). The models included mean temperature, as it reflects the temperature exposure during the whole day. Barnett et al. (2010) investigated many different measures of temperature and found that there was little difference in terms of the predictability of mortality.

The effect of relative humidity on the sensation of feeling hot is well known, and when the humidity is high, it feels warmer. Six studies have considered this. Four studies have controlled for relative humidity (Elter et al., 2004; Lee et al., 2008; Wells & Cole, 2002; Yackerson et al., 2008) and two studies estimated apparent temperature by calculating a heat-humidity index (Lajinian et al., 1997; Porter et al., 1999). I adjusted for relative humidity in the model. I also calculated a heat-index to get an estimate of the combined effect of heat and humidity on birth outcomes. The heat-index however, could only be used at temperature above 27 °C and at humidity levels above 40%. With the mean temperature in Brisbane in the warmest month being 25.1 °C (January), this study would miss large parts of the relationship between temperature and birth outcomes if I had only focused on these periods.

I used splines to capture a possible J- or U-shaped relationship between temperatures and birth outcomes. My results show however, that as an overall effect, only hot temperatures were associated with adverse birth outcomes in Brisbane, and that the relationship is close to linear. As Brisbane is a subtropical city with the mean temperature in the coldest month in winter being 15 °C, it is unlikely that this study would capture any harmful effects from cold temperatures on birth outcomes.

5.6.2 OUTCOME MEASURES

It has been common practice in epidemiology to use binomial outcomes measures such as PTB/term birth and LBW/normal birth weight. Only one study has previously examined gestational age as a continuous variable when investigating the effect of temperature (Porter et al., 1999). To treat the outcome on a continuous scale makes sure that I do not lose statistical power (Greenland, 1995). As an increased "risk" of live birth is hard to quantify in terms of shortened gestation, I also examined gestational periods to get a picture of the effect of temperature on PTB and extreme PTB.

It is difficult to compare this results with other studies investigating the risk of stillbirth, as it is defined differently in different countries. Torrey and colleagues (1993) reported a peak in stillbirth in winter in the United States. The authors did not give their definition of stillbirth and as the United States has no formal definition of stillbirth (Kowaleski, 1997). Researchers in Switzerland reporting a seasonal pattern in stillbirth with peaks in winter and spring covered more than a hundred years of birth data (Eriksson & Fellman, 2000). However, the stillbirth definition and reporting practices are likely to have changed considerably during this long period, complicating comparisons even further.

To get a better picture of the biological mechanism behind the adverse effect of hot temperatures on stillbirth, it would be valuable to know whether the fetus dies before birth (intrapartum) or during birth (antepartum). One previous study separated the two terms and found that the seasonal pattern was significant only among intrapartum stillbirths, and not antepartum stillbirths (Keller & Nugent, 1983). This suggests that the mechanism behind the effect of hot temperatures on stillbirth is that it causes the fetus to die inside the womb, and not that it shortens gestation resulting in death during birth. I did not have this information for this study, but future research should explore it to help explain the association between temperature and stillbirth.

5.7 STRENGTHS OF THE RESEARCH

This is the first study to explore the association between temperature and birth outcomes in Australia. As Brisbane is a subtropical city with an increasing number of warm days and heatwaves, it is of growing importance to assess possible adverse health effects of high temperatures. It is critical to identify vulnerable population groups such as pregnant women within the context of climate change. This will encourage them to protect themselves (and their babies) against excessive heat.

This study is also the first to explore the impact of temperature on birth outcomes using a survival analysis approach, which is able to capture the competing risks of live birth and stillbirth. I also fitted temperature and air pollutants as time-dependent variables, so that I was able to examine temperature as it changes over the course of the pregnancy. My method compared only the fetuses at the same stage of the pregnancy, eliminating any biases arising from aggregating fetuses at different stages.

This study used a comprehensive dataset covering all births in Brisbane over a period of 4.5 years. I excluded the pregnancies at the start and the end of the study period to eliminate the fixed cohort bias. I included a range of potential confounders including pregnancy complications, previous pregnancies and smoking.

I explored the acute temperature effects over the last four weeks before birth, capturing not just the immediate effect but also any delayed effect of high temperatures on birth outcomes. I also examined if the relationship between temperatures and birth outcomes was U- or J-shaped. I fitted splines with 3 degrees of freedom to get a better picture of whether the relationship is U or J-shaped.

This is one of the first studies to explore vulnerable periods of the pregnancy in terms of temperature exposure. This is an important step towards understanding the underlying mechanisms of such a relationship. The biological mechanisms behind the relationship are poorly understood. By investigating especially vulnerable periods of the pregnancy, a more comprehensive picture and possible underlying causes of the relationship can be assessed.

5.8 LIMITATIONS

Although this study has adjusted for a large number of potential confounders, the list is still not complete. For example, information on postcode or suburb of residence was unavailable. These data could have been used to derive maternal socio-economic status (a well-known determinant of birth outcomes). I did, however, include smoking status that has been shown to correlate strongly with socio-economic status (Reid, Hammond & Driezen, 2010).

Due to no information about postcodes, my estimates of temperature and air pollution were based on a network of monitoring stations across the city, and may be a poor measure of actual exposure for some women (particularly those women who spend a lot of time indoors). However, measuring individual exposure for such a large cohort of women would be very expensive and time consuming. I also do not know whether the pregnant mother lived within Brisbane statistical division for the whole duration of the pregnancy. Studies have shown that approximately 12–20% of women move address during pregnancy and that approximately 60% of these moves within the same county (Fell, Dodds & King, 2004; Khoury et al., 1988). Canfield et al. (2006) found that studies of birth defects using maternal address at birth as a proxy for maternal environmental exposures during pregnancy, may lead to considerable non-differential exposure misclassification due to maternal mobility during pregnancy. A workshop on "Methodological issues in studies on air pollution and perinatal outcomes", concluded that in large studies over long periods the temporal variation in air pollution could be enough (Woodruff et al., 2009). Also, the main focus was on temperature rather than air pollution, and average air pollution concentrations should be appropriate to be used as control variables.

I did not have information about individual level physical activity, BMI, infectious diseases, or mental health, which may also confound the relationship between temperature and birth outcomes. Therefore, I cannot exclude that the associations found are due to changes in these factors. I did not include other meteorological factors such as sunshine and barometric pressure. These factors may contribute to the seasonality of birth outcomes (Akutagawa et al., 2007; Tustin et al., 2004).

Stillbirth is a rare outcome (only 0.6% in the cohort) and the influence of temperature is relatively small as demonstrated in the study. Thus, a large cohort over a long period is needed to achieve sufficient statistical power. Even though this study covered a cohort of 101,870 births over 4.5 years, I did not have enough power to investigate the interaction between socio-demographic variables (e.g., maternal age) and the effects of temperature. The effects of ambient temperature on adult mortality and morbidity have been shown to differ between age groups (Curriero et al., 2002). Based on this, and the wide confidence intervals when investigating vulnerable weeks and periods of the pregnancy, I believe that an even larger cohort is required to give more certain answers and narrower confidence intervals.

5.9 PUBLIC HEALTH IMPLICATIONS

This study found that exposure to high temperatures during the pregnancy is dangerous for the fetus, increases the risk of stillbirth, and shortens gestation. As our climate is changing and temperatures are on the rise, the research findings from this study may have strong public health implications. It is important that pregnant mothers be warned about the dangers their unborn baby is facing during hot summers and heatwaves. They should be encouraged to keep cool or stay in air-conditioned areas during hot periods and to protect themselves from overheating.

5.10 RECOMMENDATIONS FOR FUTURE RESEARCH

I found the competing risks model to be useful, and the approach should be developed by future studies. Future studies should use extended exposure windows and look at exposure during the whole pregnancy. However, confounding by season becomes a danger when examining longer periods (e.g., trimesters). Future studies should explore methods of overcoming this methodological challenge.

To get a more complete picture of the temperature effect on the pregnancy, future studies should include spontaneous abortions. A good approach would be to follow women prospectively from early pregnancy. A drawback with this method, however, is the limited cohort size due to its costs, and limited power to detect small effects from temperature. In larger retrospective studies, birth records could be merged with datasets containing abortions in the same statistical district by the date of conception. That way, the study would capture the temperature effect on all stages of the pregnancy, and determine vulnerable periods during the whole course of the pregnancy.

The Queensland Health Perinatal Data Collection Unit (and probably birth registers in other countries) do separate between intrapartum and antepartum stillbirth in their birth records. Thus, future studies should aim to collect more detailed data on this issue.

It would be useful to include more information about confounding factors when collecting data on adverse birth outcomes. Socio-economic status has been shown to be a strong determinant of birth outcomes (Farley et al., 2006; Kramer, Séguin, Lydon & Goulet, 2000) and should be considered and adjusted for in future studies. Air-conditioning is an important effect modifier in studies investigating the health effect of high temperatures. If possible, air-conditioning data should be collected, preferably at an individual level, but if this is not available, density of air-conditioners in a neighbourhood could be used as a proxy for individual exposure. In addition, the method of delivery should be included in future analysis as it may play a role in the temperature-birth outcomes relationship (5.4.11).

This study found that the seasonal pattern of birth outcomes changed greatly after adjusting for temperature with higher risk of stillbirth and shorter gestations in winter months. Alternative explanations to this may be a decrease in vitamin D as exposure to sunlight decreases. Sunlight is important also in terms of the temperature effect, as exposure to sunlight increases the feeling of heat. Future studies should include ultraviolet radiation in their models when investigating the temperature-birth outcomes relationship. A possible synergistic effect of air pollution and temperature on birth outcomes should also be examined by future research.

As our climate is changing and the frequency and intensity of weather extremes and natural disasters is increasing, the need to assess the impact of temperature on human health is urgent. Future research should focus not only on temperature, but also on extreme weather conditions such as heatwaves and their impact on birth outcomes. Because of limited time, this study only focused on gestational age and stillbirth. The impact of temperature on birth weight could also be examined using a survival analysis approach, and this approach would minimise any biases caused by gestational age.

Finally, to achieve sufficient power to detect a small effect when investigating vulnerable weeks of the pregnancy and interactions between the covariates, future studies should aim to include as big a sample as possible. However, this will lead to a trade-off between good quality data from small prospective studies and lower quality data from larger retrospective studies.

5.11 CONCLUSIONS

This study identified and quantified the nature and magnitude of the association between temperature and birth outcomes after adjustment for the effects of a range of potential confounding factors including season, humidity and air pollutants in Brisbane, Australia. I found a seasonal pattern of gestational age and stillbirth risk that changed after adjusting for temperature. I also found that exposure to high temperatures during the pregnancy affects birth outcomes adversely. As the temperature increases, the risk of stillbirth and PTB increases. This risk is highest at preterm gestational ages for live birth and at earlier gestational ages for stillbirth. The findings have important implications for maternal and antenatal care policy and planning, and they have demonstrated the value of keeping cool during pregnancy. Reducing the occurrence of PTB and stillbirth will not only save a lot of physical and psychological problems for a family, but will also benefit our society economically and reduce the burden on an already strained health system. I believe that it is necessary and feasible to build on the current knowledge to reduce and prevent the occurrence of adverse birth outcomes and to ensure that newborn babies get a good start to their life, or even get to start their life at all.

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Appendices

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APPENDIX A: PAPER PUBLISHED IN BMC MEDICAL RESEARCH METHODOLOGY

Strand *et al. BMC Medical Research Methodology* 2011, 11:49
http://www.biomedcentral.com/1471-2288/11/49

BMC Medical Research Methodology

RESEARCH ARTICLE **Open Access**

Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes

Linn Beate Strand, Adrian G Barnett* and Shilu Tong

Abstract

Background: Many previous studies have found seasonal patterns in birth outcomes, but with little agreement about which season poses the highest risk. Some of the heterogeneity between studies may be explained by a previously unknown bias. The bias occurs in retrospective cohorts which include all births occurring within a fixed start and end date, which means shorter pregnancies are missed at the start of the study, and longer pregnancies are missed at the end. Our objective was to show the potential size of this bias and how to avoid it.

Methods: To demonstrate the bias we simulated a retrospective birth cohort with no seasonal pattern in gestation and used a range of cohort end dates. As a real example, we used a cohort of 114,063 singleton births in Brisbane between 1 July 2005 and 30 June 2009 and examined the bias when estimating changes in gestation length associated with season (using month of conception) and a seasonal exposure (temperature). We used survival analyses with temperature as a time-dependent variable.

Results: We found strong artificial seasonal patterns in gestation length by month of conception, which depended on the end date of the study. The bias was avoided when the day and month of the start date was just before the day and month of the end date (regardless of year), so that the longer gestations at the start of the study were balanced by the shorter gestations at the end. After removing the fixed cohort bias there was a noticeable change in the effect of temperature on gestation length. The adjusted hazard ratios were flatter at the extremes of temperature but steeper between 15 and 25°C.

Conclusions: Studies using retrospective birth cohorts should account for the fixed cohort bias by removing selected births to get unbiased estimates of seasonal health effects.

Background

Worldwide, it is estimated that 2.2% of all babies are stillborn [1] and 9.6% of all births are preterm (less than 37 completed weeks of gestation) [2]. Preterm babies are at greater risk of poor health and early death, require longer periods of hospitalisation after birth, and are more likely to develop disabilities [3-5].

Environmental and meteorological factors may be a cause of adverse birth outcomes [6]. Increases in air pollution [7] and temperature [8] have been associated with adverse birth outcomes. Air pollution and temperature usually have a strong seasonal pattern, meaning that one method of examining environmental factors is to explore seasonal patterns. Research has shown that the risk of preterm birth varies by season of birth [9,10] and season of conception [11]. Seasonal patterns of preterm birth differ from country to country, and peaks have been shown to occur at both hot and cold times of the year. For example, in a London cohort of almost 500,000 live singleton births, babies were more likely to be born preterm in winter than in spring (odds ratio = 1.10, 95% confidence interval (CI) 1.07-1.14), with the highest risk of preterm birth in November and December (probability of 0.76 per 1,000 fetuses at risk compared to 0.64 in April) [12]. However, in Greece preterm birth rates were highest in summer and spring [9], and in The Gambia preterm birth rates peaked in summer and autumn [13]. In Japan peaks of preterm

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births were reported in summer and winter [14]. The peak in winter was dominant among the northern latitudes and the peak in summer was dominant among the southern latitudes, suggesting that the seasonal pattern was dependent on factors differing between geographic locations (such as temperature) [15]. Different statistical methods may partly explain the differences in the seasonal patterns in the studies discussed above [16]. In particular, some studies assumed a sinusoidal seasonal exposure, whereas others looked at individual months or seasons.

Studies in developing countries have hypothesised that seasonal patterns in birth outcomes are due to seasonal changes in nutrition, infectious diseases, and seasonal work [13]. These factors are not as important in developed countries, but seasonal patterns in birth outcomes still occur, possibly because of seasonal changes in Vitamin D, air pollution or temperature [7,8,17,18]. As we show in this paper, seasonal patterns can also be due to biases in the selection of the study sample.

The fixed cohort bias

For birth cohorts the population at-risk is constantly changing, as new pregnancies start and existing pregnancies end [19]. In retrospective birth cohort studies, when using a study period based on the date of birth (e.g., all births from 1 January 2005 to 31 December 2005), the population at-risk is different at the start and end of the cohort. The differences are shown in Figure 1 using three groups of three births, where each group has the same conception date. The shortest pregnancy registered in Brisbane statistical Division between 1 July 2005 and 30 June 2009 was 19 weeks and the longest was 43 weeks. For pregnancies conceived more than 19 weeks before the study start date, only those with a longer gestation will be included, and those with a shorter gestation will be missed because they gave birth before the start of the study. Similarly, for pregnancies conceived less than 43 weeks before the end of the cohort, mothers with longer gestations will give birth after the end of the study. Birth cohorts that prospectively follow women from conception to birth (or from their first antenatal visit to birth), do not experience this problem because the complete pregnancy history is known and no deliveries are missed.

The pattern shown in Figure 1 has the potential to bias seasonal patterns of gestation length by including only the longer pregnancies at the start of the study and only the shorter pregnancies at the end of the study. It also has the potential to bias studies of environmental exposures such as temperature. Just one example of how this could lead to biased estimates were if there was an unusually hot month in the first trimester of those women captured at the start of the study, which could mean that high temperatures were wrongly associated with longer gestations. We refer to this bias as the *fixed cohort bias*.

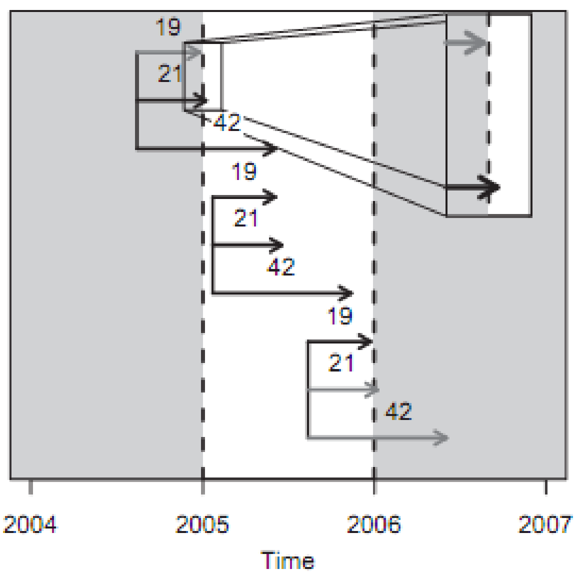

Figure 1 How the population at-risk changes according to birth date using a birth cohort based on all births in 2005. Black arrows show births included in the cohort and grey arrows show births that were missed. The number above each arrow shows the gestation length in weeks. The plot shows three groups of three births, each group represents one conception date.

The arrows shown in Figure 1 call to mind to the well-known issue of left and right censoring in survival analysis [20], where either the start or end times are unknown. However, the fixed cohort bias is a different issue because it occurs when *both* the start and end times are unknown. These subjects will be missing from the at-risk population which will therefore be too small, and hence the consequences of the bias are similar to those caused by censoring.

The purpose of this paper is to demonstrate the potential effects of ignoring the fixed cohort bias, and to show how it can be avoided. We show the bias when estimating the effects of season, and the seasonal exposure of temperature.

Methods

The Brisbane cohort

We requested data on a cohort of all singleton births in the Brisbane Statistical District from 1 July 2005 to 30 June 2009 (n = 114,947) from the Queensland Health Perinatal Data Collection Unit. We only examined singleton births, so twins or triplets were excluded.

Simulated cohorts

To investigate the fixed cohort bias we simulated a retrospective birth cohort with no seasonal pattern in gestation. The simulated cohort was based on the Brisbane cohort and had the same start and end dates (1 July 2005 to 30 June 2009). We randomly sampled gestation lengths from the Brisbane cohort (with replacement) using the original sample size (n = 114,947). We randomly simulated conception times from 43 weeks prior to the start of the study period (3 September 2004) until the end of the study period using a discrete Uniform distribution. Using these non-seasonal conception times and randomly sampled gestation lengths meant there was no seasonal pattern in gestation lengths or dates of births in the simulated cohorts, and that the distribution of gestation lengths was the same as the Brisbane cohort. Simulated births with a date of birth outside the cohort start and end dates were excluded, as these births would have been missed by a fixed cohort. Missing these births is the cause of the fixed cohort bias. The simulations were made using the R software (version 2.11.1).

Statistical analyses

We ran a survival analysis of gestation length to analyse the effect of the fixed cohort bias on the seasonality of birth outcomes. We used a Cox proportional hazards model with a dependent variable of gestation length (in days) and an independent variable of conception month. A hazard ratio greater than one means an increased chance of giving birth, and hence shorter gestations. Whereas a hazard ratio less than one means a reduced chance of giving birth, and hence longer gestations.

We suspected that the effects of the fixed cohort bias would vary depending on the start and end dates of the study. To investigate this, we moved the end date of the study (using the simulated cohort) backwards in time (one month at a time) and repeated the survival analysis. We repeated this analysis for 100 simulated cohorts and calculated the average hazard ratios in each conception month.

We propose a method to avoid the fixed cohort bias by removing some pregnancies from the cohort. The adjusted cohort is created by limiting the included pregnancies to those with conception dates between:

1. 19 weeks before the cohort started, and
2. 43 weeks before the cohort ended.

We used 19 and 43 weeks as cut-offs since these were the longest and shortest gestation lengths observed in the Brisbane cohort. This ensures that the long pregnancies at the beginning of the cohort, and the short pregnancies at the end of the cohort, are excluded. We then repeated the survival analysis using the original Brisbane cohort and the adjusted cohort with month of conception as the single independent variable.

To investigate the effect of the fixed cohort bias on the effect of seasonal environmental exposures, we fitted a similar survival model but with the time-dependent variable of mean temperature in the last four weeks. We used polynomial splines for mean temperature [21]. The degrees of freedom of the spline control the degree of smoothness of the estimated temperature-gestation association. To allow for non-linear shapes, we used three degrees of freedom to describe the association between temperature and gestation length. We used the mean temperature in Brisbane (21°C) as the reference temperature where the hazard ratio was 1. We adjusted for mean humidity (in the last four weeks), baby sex, maternal age, Indigenous status, marital status, maternal smoking, number of previous pregnancies, and pregnancy complications (yes/no). We used both the original and adjusted Brisbane cohort. All models were fitted using the R software (version 2.11.1).

Results

Table 1 describes the demographics of the original Brisbane cohort (n = 114,947). Figure 2 shows gestation lengths by month and year of conception. The births in the cohort conceived in September 2004 must have had a gestation of at least 40 weeks to be included, because any shorter pregnancies gave birth before the start of the study period (1 July 2005). The closer to the start of the study period, the more possible it became for women with shorter pregnancies to enter the cohort. In the middle of the cohort, gestation lengths were relatively stable, as all pregnancies were included and none were excluded because of their length. Towards the end of the cohort it became impossible for women conceiving during the study period but with longer pregnancies to be included, because they gave birth after the end of the study period. After removing the pregnancies conceived more than 19 weeks before the study start and less than 43 weeks before the study end, the adjusted cohort had 101,870 pregnancies (88.6% of the original sample).

Simulation results

Our simulated data had no seasonal pattern in gestation length. Figure 3 shows that an artificial seasonal pattern occurred for every end date except June 2009. The seasonal pattern varied according to the end date, so an end date of April 2009 meant that the shortest gestations were for conceptions in July (highest hazard ratio for giving birth), whereas an end date of January 2009 meant the shortest gestations were for conceptions in May (highest hazard ratio for giving birth). The bias was

Table 1 Demographics of the Brisbane cohort (births between 1 July 2005 and 30 June 2009)

	n	%
Total births	114,947	100.0
Gender		
Male	59,317	51.6
Female	55,630	48.4
Marital status		
Married/De facto	98,888	86.0
Never married	14,240	12.4
Separated/Divorced	1,788	1.6
Not stated	31	< 0.1
Indigenous status		
Indigenous	2,568	2.2
Non-Indigenous	112,301	97.7
Not stated	78	0.1
Smoking		
Non-smoker	94,283	82.0
Smoker	19,845	17.3
Not stated	819	0.7
Pregnancy complications		
No complications	108,946	94.8
Pre-eclampsia	6,001	5.2
Previous pregnancies		
0	34,857	30.3
1-2	55,670	48.4
3-4	17,393	15.1
5+	7,027	6.1
Mother's age (years), mean (SD)	29.6 (5.8)	
Gestation length (weeks), mean (SD)	38.8 (2.3)	

SD = Standard deviation

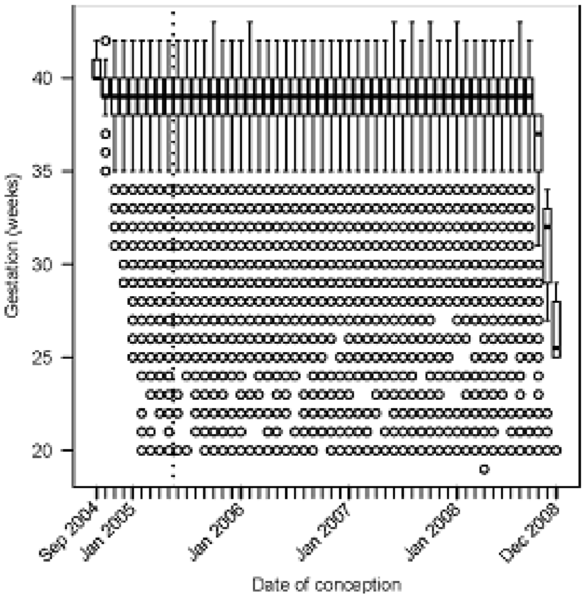

Figure 2 Box plots of gestation (weeks) by month of conception for the Brisbane cohort. Boxes show the inter-quartile range; outliers are circles. The dotted vertical line shows the start of the cohort based on birth dates (1 July 2005). The last birth was 30 June 2009 and the last gestation was in December 2008. Gestations for conceptions in September 2004 were all 40 weeks or longer, whereas those in December 2008 were all shorter than 30 weeks.

avoided when the day and month of the end date (31 June - ignoring year) were just before the day and month of the start date (1 July). This is because the shorter pregnancies at the end of the study period were balanced by the longer pregnancies at the start of the study.

Brisbane results

We further illustrate the fixed cohort bias using the Brisbane cohort in Figure 4. The estimated seasonal pattern in gestation length was strongly dependent on the end date of the study. For an end date of September 2008 the hazard ratios for many conception months were significantly lower than January (e.g., the hazard ratio for June relative to January was 0.95, 95% CI: 0.92, 0.98) meaning that gestations were longer for June conceptions. Conversely for an end date of March 2009 the hazard ratio for June relative to January was 1.04, 95% CI: 1.01, 1.07, meaning that gestations were shorter for June conceptions. After adjusting the cohort by removing births conceived more than 19 weeks before the cohort started, and less than 43 weeks before the cohort ended, the estimated seasonal pattern remained almost the same regardless of the study end date. The estimated seasonal pattern using the adjusted cohort was very close to that shown for an end date of June 2009, an end date which avoids the fixed cohort bias for this analysis because the end day and month are just before the start day and month (regardless of year).

Temperature results

The effect of the fixed cohort bias in a study investigating temperature is shown in Figure 5. In the original cohort, longer gestations (reduced hazard ratios) occurred at temperatures from 12°C to 15°C, there was no change from the average gestation length between 15°C and 25°C, and average gestation lengths were shortened from 25°C and upwards. The estimated hazard ratios using the adjusted cohort were quite different. The hazard ratio of birth increased (gestation decreased) almost linearly from 15°C to 25°C. At very low and high temperatures the confidence intervals were wide, making it difficult to make any inferences.

Discussions

Artificial seasonal patterns can occur in retrospective birth cohorts depending on the study's start and end

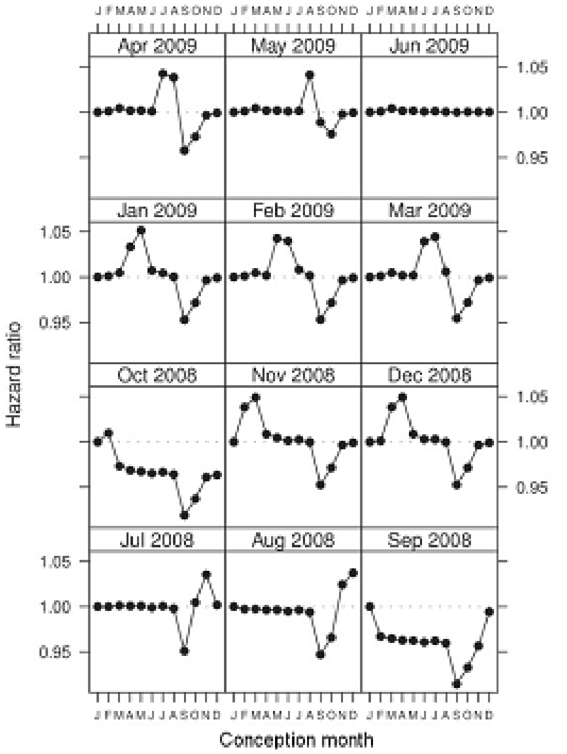

Figure 3 Estimated seasonal pattern in gestation length by conception month for 12 end dates using 100 simulated cohorts (January is the reference month). Each panel shows the estimated seasonal pattern for a different end date. The start date was 1 July 2005. The data was simulated with no seasonal pattern.

dates (Figure 3). The cause is the great difference in pregnancy lengths between those births included at the start and those included at the end of the study. In our Brisbane cohort the median gestation length was 40 weeks at the start of the study, 39 weeks in the middle part of the study and as low as 25.5 weeks during the last conception month (Figure 2). The artificial seasonal patterns caused by the fixed cohort bias have a shape similar to an expected seasonal pattern, meaning that it could easily be wrongly attributed to a seasonal exposure (e.g., temperature). It is possible to remove the bias at the cost of a loss of sample size. We demonstrated how the bias was avoided by removing the pregnancies that were conceived earlier than 19 weeks prior to the start of the study period and later than 43 weeks before the end of the study period (Figure 4).

The biases are not caused by the well-known issues of censoring in survival data, which occurs when the start or end time of a subject are unknown. The bias demonstrated here is because both the start and end times are unknown. It is a bias caused by subjects who were completely (and unknowingly) missed from the cohort, not because of subjects who were partially observed.

The potential biases due to changes in the at-risk population when examining the effect of time-dependent exposures on pregnancy have been addressed by two recent studies [19,22]. These studies showed substantial biases due to ignoring seasonal patterns in pregnancies [19], and due to ignoring the week of gestation at study entry [22]. A recent study demonstrated the value of using time-dependent exposures as part of a Cox proportional hazards model when estimating the effects of air pollution on pregnancy, and concluded that this method was more effective than conventional approaches for estimating key exposure periods [23]. We also recommend the use of methods that adjust for the at-risk population and use time-dependent exposures to correctly estimate the effects of environmental exposures on pregnancy. However, we caution that when using these methods the fixed cohort bias needs to be considered. Our paper makes an important contribution to this developing area as it shows the potential size of the fixed cohort bias and a simple way to avoid it.

Our results show how the size of the fixed cohort bias can be substantial, causing great changes in the months that most effect gestation length (Figure 3, 4), and changing the estimated effect of temperature on gestation length (Figure 5). The results in Figure 3 showing the erroneous seasonal pattern were based on four years of data. To remove the seasonal pattern we excluded pregnancies with conception dates 19 weeks before the cohort started and 43 weeks before the cohort ended. These were around 13% of all pregnancies, and so represent a relatively large proportion of the sample, which explains the relatively large bias.

As shown in Figure 3, the fixed cohort bias is avoided when the day and month of the cohort's end date are a day before the day and month of the cohort's start date (regardless of year). A design with these 'matching' start and end dates is the most common for previous birth cohort studies [11,18,24,25]. However, the balancing of the bias will not occur for time-dependent exposures. For example, if there was an unusually hot month in the first trimester of those women captured at the start of the study, then high temperatures could be wrongly associated with longer gestations. The bias would only be avoided if there was an equally unusually hot month at end of the study period, when the women captured in the cohort have shorter gestations. We examined this potential bias in the original and adjusted Brisbane cohort and confirmed that the fixed cohort bias changed the effect estimates of temperature on gestation length (Figure 5). Ignoring the fixed cohort bias meant the biggest changes in the hazard ratios were at the extremes of temperature, whereas the adjusted estimate shows the biggest changes for more moderate temperatures. So if

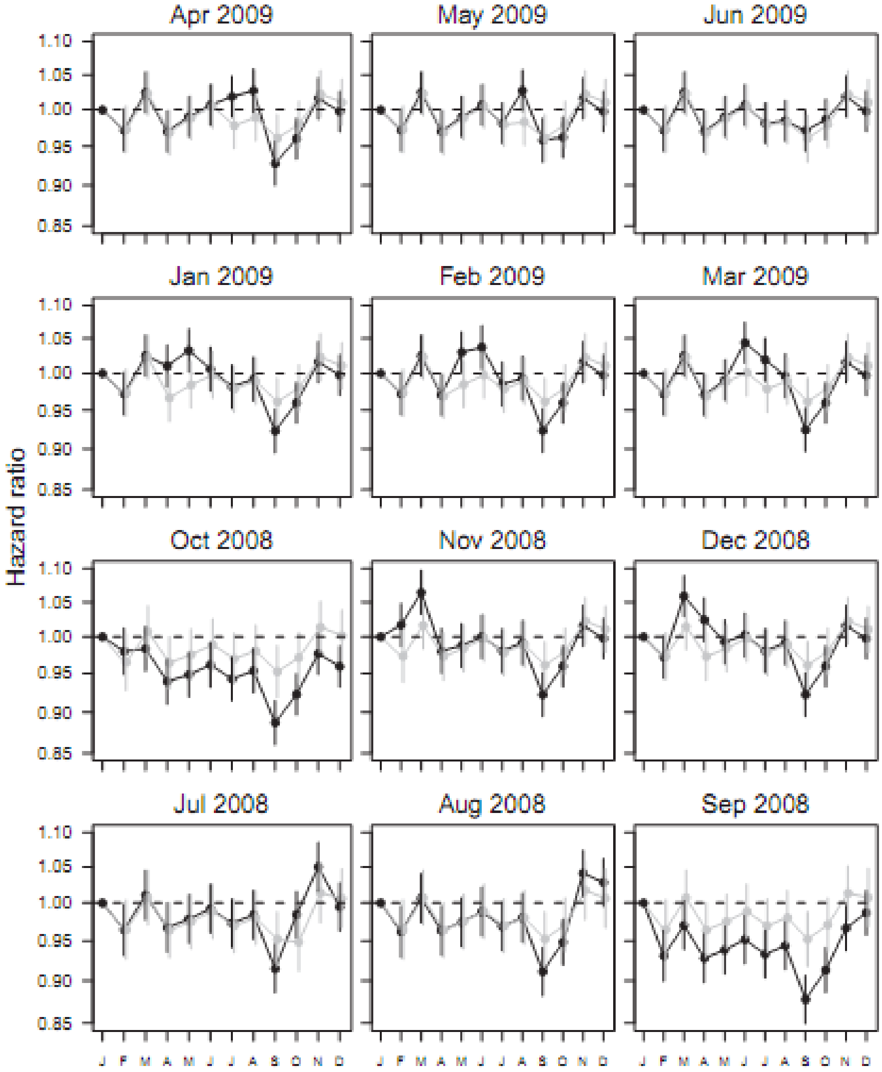

Figure 4 Estimated seasonal pattern in gestation length by conception month for the Brisbane cohort. Each panel shows the estimated seasonal pattern for a different end date. The black lines show the estimated seasonal pattern ignoring the fixed cohort bias. The grey lines show the estimated seasonal pattern after adjusting for the fixed cohort bias. Mean hazard ratios (dots) and 95% confidence intervals (vertical lines).

we ignored the fixed cohort bias we might wrongly advise that pregnant women avoid extreme temperatures (above 25°C), whereas the actual change in gestation length is for moderate temperatures (between 16 and 25°C). The fixed cohort bias can therefore not only bias the estimated effects of season (e.g., month of conception), but can also bias the estimated effects of seasonal exposures (e.g., air pollution and temperature).

A group of conceptions that were missed in this study were those occurring before 20 weeks (spontaneous abortions). These unfortunate cases are not added to the Brisbane birth registry. Rates of spontaneous abortions having reached at least five gestational weeks after last menstrual period vary from 11 to 16% [26-28]. Missing these cases has the potential to bias estimates of time-dependent exposures. Suppose an environmental exposure is strongly associated with spontaneous abortion, then a peak in this environmental exposure will cause an increase in spontaneous abortions and hence a decrease in the number of births that appear in the cohort. A study based on births after 19 weeks would miss the opportunity to detect the dangers of this exposure. Hence birth cohort studies should minimise their entry time, and clarify that the results only apply to pregnancies that have progressed to that time.

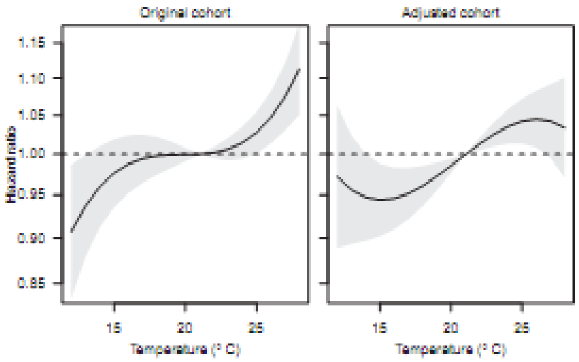

Figure 5 The estimated effect of temperature on gestation length in the original Brisbane cohort (left) and the adjusted cohort (right). The solid line shows the mean hazard ratio and the grey area the 95 confidence limits. The dotted horizontal line at 1 represents no change in gestation length. The reference temperature is 21°C.

An ideal study design is one that prospectively follows women from close to conception, as this ensures that no pregnancies are missed (and hence the fixed cohort bias is not an issue). However, these designs are much more expensive that those relying on routinely collected birth data. A good alternative is to adjust cohorts using our method, and so avoid artificially created patterns and wrongly estimated effects from seasonal environmental exposures on birth outcomes.

Our results in Figure 5 are consistent with three previous studies that found that exposure to high temperatures in the week of birth increased the risk of preterm birth [8,9,29]. Maternal hyperthermia has been associated with abortions and stillbirths with lags of days to several weeks [30]. A study investigating hot tub and Jacuzzi use during the pregnancy and its effect on abortions found that pregnant women using hot tub or Jacuzzi during the pregnancy were twice as likely to have an abortion than women who did not (hazard ratio: 2.0, 95% confidence interval: 1.3, 3.1). Another study found that application of heat to the abdominal wall of women in labour increased uterine activity [31]. Dehydration during warmer temperatures may also be the cause of the shorter gestations, as insufficient fluids in the mother can decrease the amount of blood available to the fetus and induce uterine contractions [32]. Our results suggest that pregnant women should avoid exposure to high temperatures.

Limitations

Although we controlled for Indigenous status we did not have data on other racial groups. As shown by Darrow et al [19] seasonal patterns in birth numbers by racial groups can cause seasonal patterns in birth outcomes. Therefore by only partially controlling for race the results in Figure 5 may be caused by a seasonal pattern in conception times in one or more racial groups. Also, we used data on ambient temperature and not the actual temperature experienced by the women which introduces a measurement error. For example, women with air conditioning would experience less exposure to high ambient temperatures.

We used a Cox proportional hazard model with a time-dependent exposure and therefore the results are presented as hazard ratios, and we were not able to give the estimated gestation length on the absolute scale of time (Figure 3). Using an accelerated failure time model or pooled logistic regression model [33] in place of the Cox model would mean the results could be given on a time scale.

Conclusions

Correctly estimating the effects of environmental exposures on pregnancy is vital because an unhealthy start to life can mean an unhealthy adulthood. The adverse health effects of preterm birth and low birth weight include: socio-emotional and educational problems [3], reduced cognitive function [4], impaired vision and hearing [5] and restricted growth [34]. New research into the possible effects of the temperature on pregnancy is particularly important because of climate change. Future changes are predicted to include an increase in 'mega-heatwaves' such as those experienced in Europe in 2003 and 2010 [35]. If higher temperatures increase the risk of preterm birth as shown here (Figure 5), then we can expect a greater future public health burden due to preterm birth.

Acknowledgements
Computational resources and services used in this work were provided by the High Performance Computer and Research Support Unit, Queensland University of Technology, Brisbane, Australia. The data were retrieved from Queensland Health Perinatal data Collection Unit.
LS was supported by a Queensland University of Technology Masters Scholarship and ST is funded by a National Health and Medical Research Council Research Fellowship (#553043).

Authors' contributions
LS and AGB discovered the bias and designed the method to avoid it. LS wrote the first draft of the manuscript. AGB ran the statistical analyses. ST supervised the study and contributed to the final draft. All authors contributed to study concept and design. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Received: 10 January 2011 Accepted: 18 April 2011
Published: 18 April 2011

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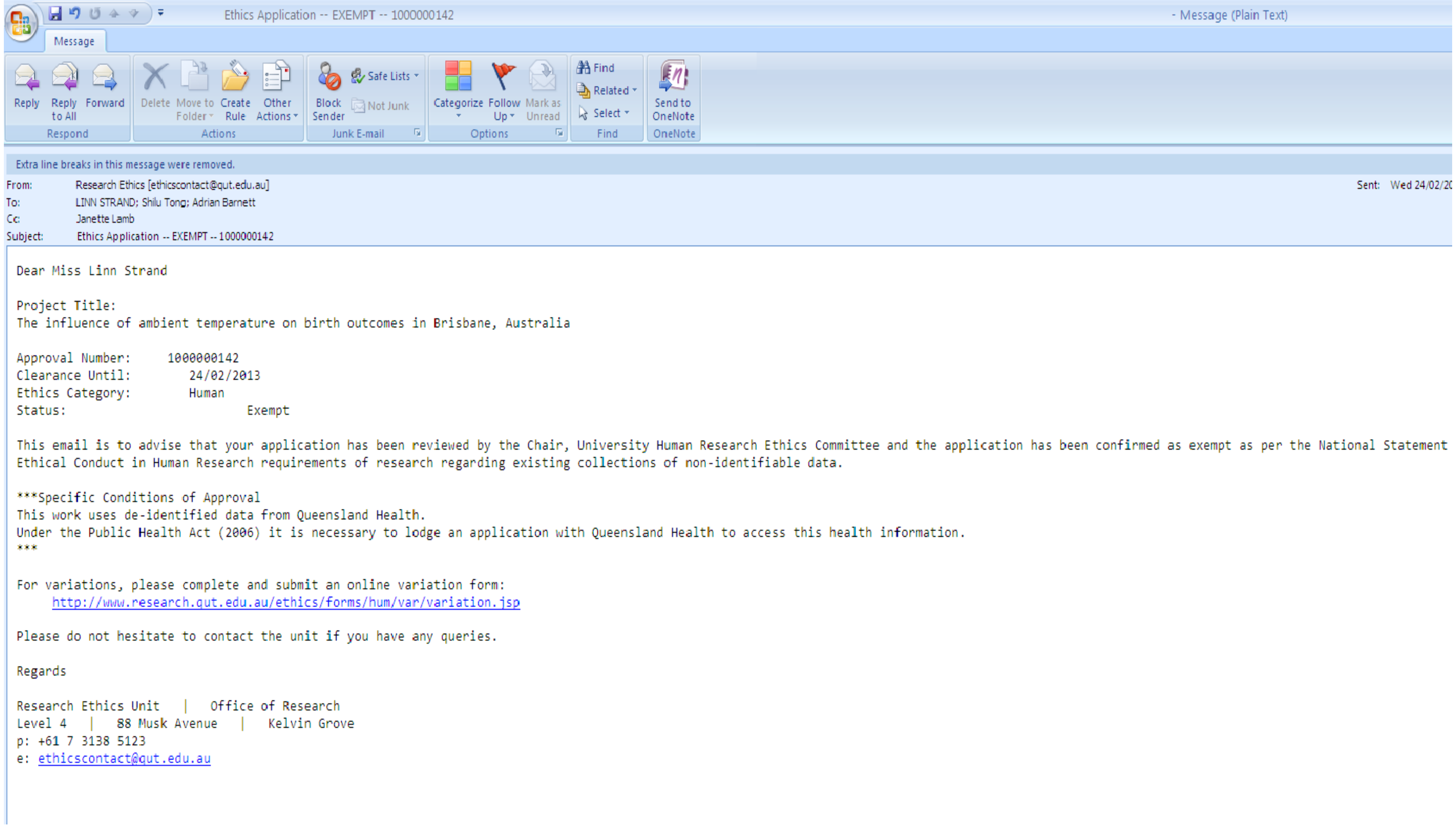
Pre-publication history

The pre-publication history for this paper can be accessed here: http://www.biomedcentral.com/1471-2288/11/49/prepub

doi:10.1186/1471-2288-11-49

Cite this article as: Strand *et al.*: Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes. *BMC Medical Research Methodology* 2011 11:49.

APPENDIX B: THE ETHICS APPROVAL



From: Research Ethics [ethicscontact@qut.edu.au]
To: LINN STRAND; Shilu Tong; Adrian Barnett
Cc: Janette Lamb
Subject: Ethics Application -- EXEMPT -- 1000000142
Sent: Wed 24/02/2

Dear Miss Linn Strand

Project Title:
The influence of ambient temperature on birth outcomes in Brisbane, Australia

Approval Number: 1000000142
Clearance Until: 24/02/2013
Ethics Category: Human
Status: Exempt

This email is to advise that your application has been reviewed by the Chair, University Human Research Ethics Committee and the application has been confirmed as exempt as per the National Statement Ethical Conduct in Human Research requirements of research regarding existing collections of non-identifiable data.

***Specific Conditions of Approval
This work uses de-identified data from Queensland Health.
Under the Public Health Act (2006) it is necessary to lodge an application with Queensland Health to access this health information.
***

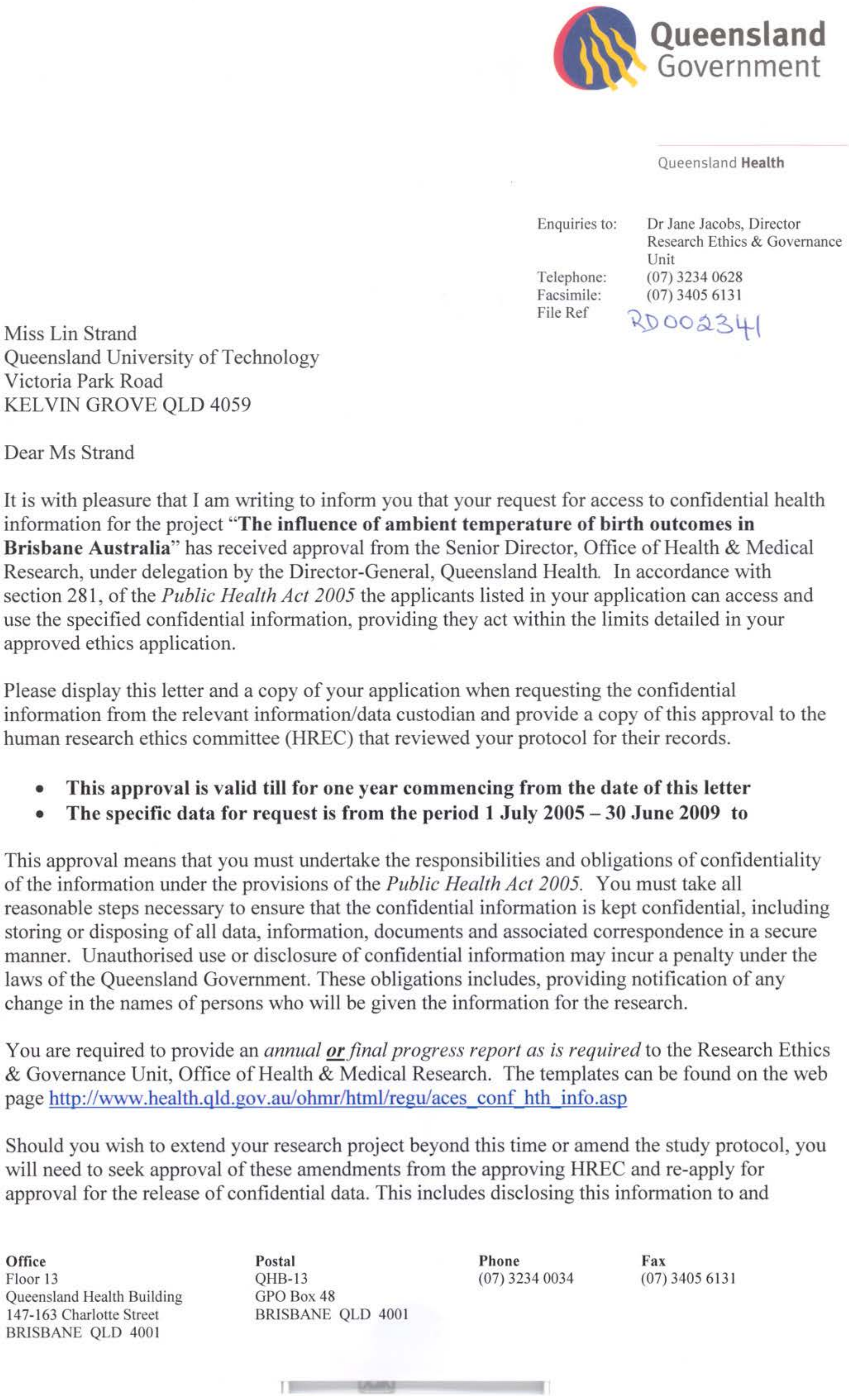
For variations, please complete and submit an online variation form:
http://www.research.qut.edu.au/ethics/forms/hum/var/variation.jsp

Please do not hesitate to contact the unit if you have any queries.

Regards

Research Ethics Unit | Office of Research
Level 4 | 88 Musk Avenue | Kelvin Grove
p: +61 7 3138 5123
e: ethicscontact@qut.edu.au

APPENDIX C: THE PUBLIC HEALTH ACT APPROVAL



Queensland Government

Queensland **Health**

Enquiries to: Dr Jane Jacobs, Director
Research Ethics & Governance Unit
Telephone: (07) 3234 0628
Facsimile: (07) 3405 6131
File Ref RD002341

Miss Lin Strand
Queensland University of Technology
Victoria Park Road
KELVIN GROVE QLD 4059

Dear Ms Strand

It is with pleasure that I am writing to inform you that your request for access to confidential health information for the project "**The influence of ambient temperature of birth outcomes in Brisbane Australia**" has received approval from the Senior Director, Office of Health & Medical Research, 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 approved ethics application.

Please display this letter and a copy of your application when requesting the confidential information from the relevant information/data custodian and provide a copy of this approval to the human research ethics committee (HREC) that reviewed your protocol for their records.

- **This approval is valid till for one year commencing from the date of this letter**
- **The specific data for request is from the period 1 July 2005 – 30 June 2009 to**

This approval means that you must undertake the responsibilities and obligations of confidentiality of the information under the provisions of the *Public Health Act 2005*. You must take all reasonable steps necessary to ensure that the confidential information is kept confidential, including storing or disposing of all data, information, documents and associated correspondence in a secure manner. Unauthorised use or disclosure of confidential information may incur a penalty under the laws of the Queensland Government. These obligations includes, providing notification of any change in the names of persons who will be given the information for the research.

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

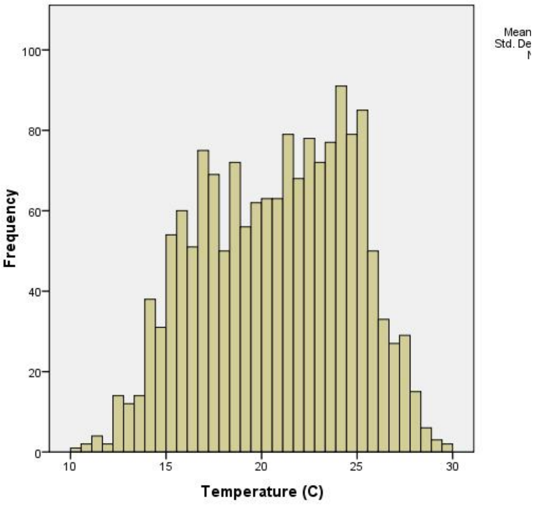
Should you wish to extend your research project beyond this time or amend the study protocol, you will need to seek approval of these amendments from the approving HREC and re-apply for approval for the release of confidential data. This includes disclosing this information to and recruiting additional people to this project. Please provide a copy of your HREC approval of the amendments when re-applying.

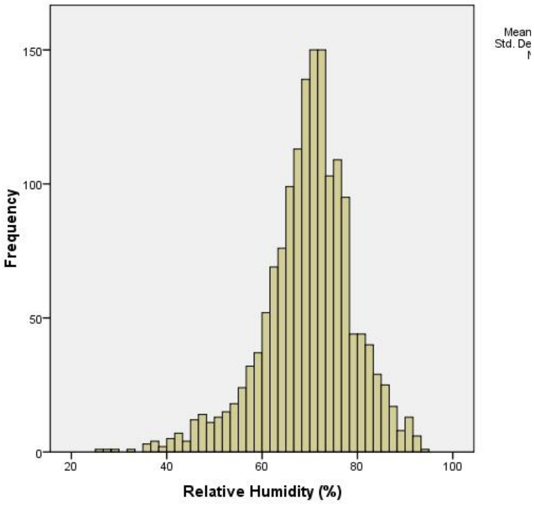
Should you have any queries regarding this approval, Deborah Hinchliffe, Ethics Administrator, Research Ethics & Governance Unit will be pleased to assist you and can be contacted on email regu@health.qld.gov.au or phone 07-32340034.

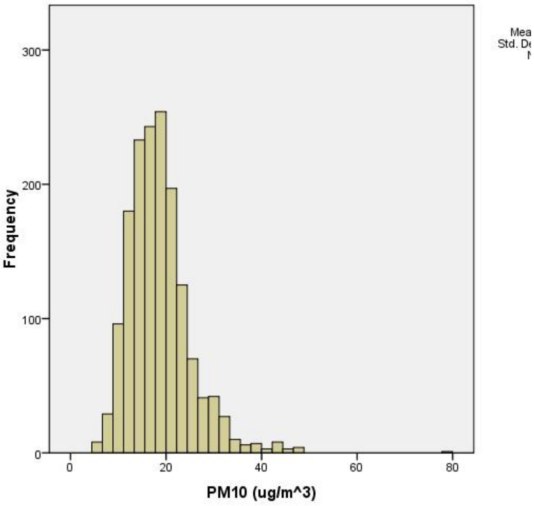
Yours sincerely

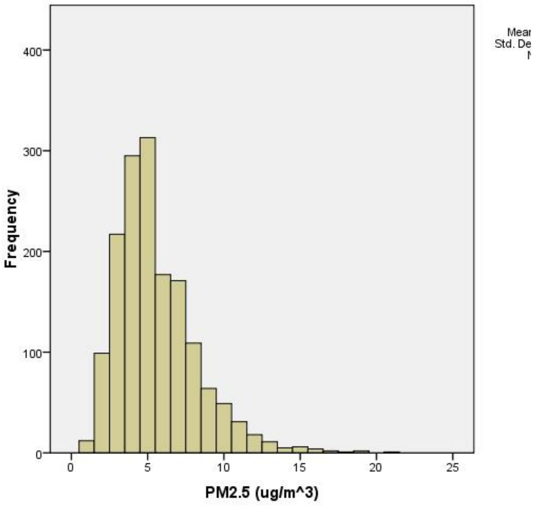
Professor Robin Mortimer
Senior Director
Office of Health & Medical Research
1 / 4 / 2010

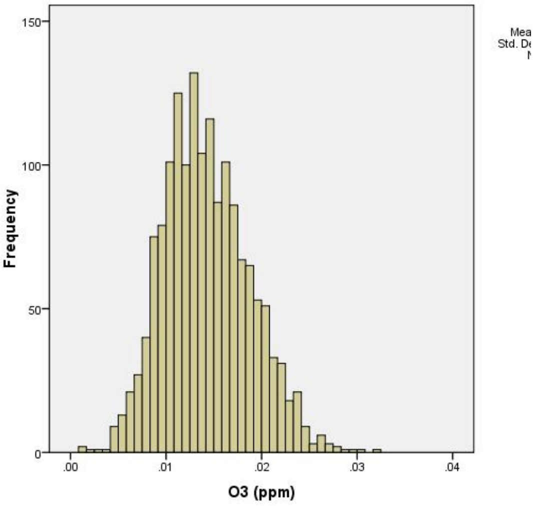
APPENDIX D: THE DISTRIBUTION OF THE VARIABLES

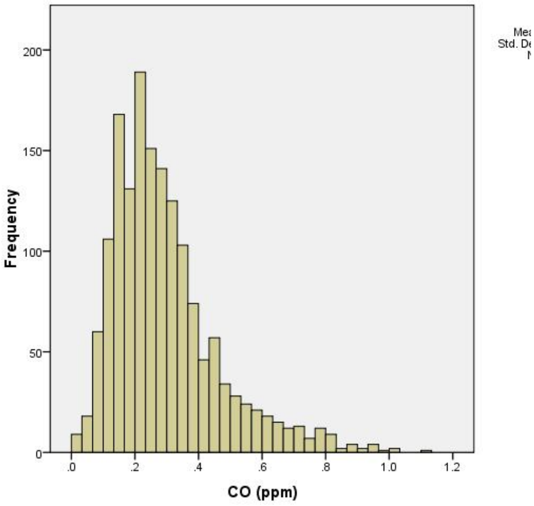












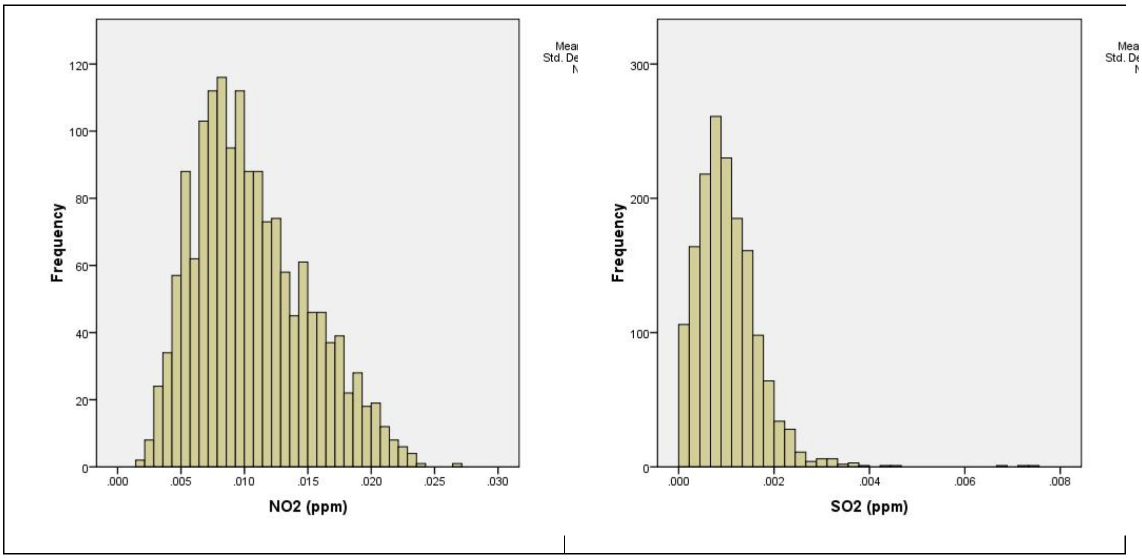


Figure D.1. The distributions of the weather variables.

APPENDIX E: THE BIVARIATE ASSOCIATIONS

Gestational age

Table F.1

Bivariate Associations between Dichotomous Demographics and Gestational age. Because Gestational Age was not normally distributed, we used a Non-Parametric Mann-Whitney U test

Variable	U	N_1	N_2	p-value
Birth outcome	6,246,305.5	101,217	653	<0.01
Indigenous status	1.03E8	2,263	99,531	<0.01
Smoking	7.16E8	83,548	17,559	<0.01
Pregnancy complications	1.87E8	96,606	5,264	<0.01
Sex	1.28E9	49,223	52,647	<0.01

Table F.2

Bivariate Associations between Categorical Demographics and Gestational Age using the Kruskal-Wallis test

Variable	H	df	p-value
Marital status	77.57	2	<0.01
Previous pregnancies	1086.62	3	<0.01
Antenatal visits	3550.65	2	<0.01

Stillbirth

Table F.3

Bivariate Associations between Categorical demographics and Stillbirth.

Variable	Chi-square	df	p-value
Indigenous status	9.451	1	0.002
Smoking	14.51	1	<0.01
Pregnancy complications	1.66	1	0.198
Sex	0.002	1	0.967
Marital status	18.25	2	<0.01
Previous pregnancies	16.16	3	0.01
Antenatal visits	2530.41	2	<0.01