DEMOGRAPHIC RISK FACTORS FOR LATE PREGNANCY STILLBIRTH IN SASKATCHEWAN WOMEN

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ABSTRACT

Statistics Canada data indicates that between 2002 and 2006, the late stillbirth incidence (≥ 28 weeks gestation) was 3.0/1000 and 4.0/1000 among Canadian and Saskatchewan births respectively. This difference questions the characteristics and associations of late losses in our province; this work aims to assess late Saskatchewan stillbirths in regard to incidence, causes, characteristics, and area-level factors.

Accessing Vital Statistics cases (1987 to 2007, n=1119), descriptive statistics and incidence were examined utilizing Chi-square testing and Poisson regression. Associations between variables were evaluated by log-linear models. Area-level factors relating to incidence within census divisions were explored using Poisson regression.

Although some variation existed by time and region, women were most often ≤ 35 years, of moderate parity, non-Aboriginal, had no previous stillbirths, and were not carrying multiple fetuses. Approximately half of the losses were preterm and half were inadequately grown. Incidence per 1000 births differed significantly for Saskatchewan (3.86) and Canada (3.43) with only Canada declining. Several division values were also higher than Saskatoon's Division 11. Associations were seen between characteristics; most notably the combination of Aboriginality, increased maternal age, and large-for-gestational-age appeared over-represented compared to live births. Regions with higher proportions of Aboriginal preschoolers or land area with herbicide application had higher incidence (RR = 1.53 and 1.55, $p \leq 0.001$). Further work is required to understand Saskatchewan's lack of decline, what can be done about areas where incidence is increased, the significance of the associated characteristics as actual risk factors, and how Aboriginality and herbicide influence risk at the individual level.

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Finally, this work is dedicated to 1 119 Saskatchewan women who never heard their babies cry. Your loss is remembered.

DISCLAIMER

The analysis performed in this thesis was based in part on non-identifiable data provided through the cooperation of the Government of Saskatchewan's Information Services Corporation (Department of Vital Statistics) and Saskatchewan Health. Additional aggregated data from Statistics Canada was also utilized. The findings, interpretations, and conclusions in this document do not necessarily represent those of any of the above organizations.

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LIST OF ABBREVIATIONS

IDLS: Internet Data Library System

IUGR: intrauterine growth restriction

BMI: body mass index

SGA: small for gestational age

LGA: large for gestational age

AGA: appropriate for gestational age

CI: confidence interval

OR: odds ratio

SES: socio-economic status

DEET: N,N-Diethyl-meta-toluamide

CD: census division

CMA: census metropolitan area

CA: census agglomeration

WHO: World Health Organization

ICD: International Classification of Disease

MBC: Modified Beale Code

RBC: Revised Beale Code

GEE: generalized estimating equations

GLM: generalized linear model

CHAPTER 1:

1.0 INTRODUCTION

A study cannot be truly effective without an understanding of the real world problem and why its investigation matters. This brief chapter aims to provide a basic understanding of stillbirth occurrence, particularly in the Saskatchewan context.

1.1 Stillbirth Overview

Over the last century, advances in pregnancy care have led to the general expectation of a viable outcome, particularly as gestation reaches its latter months. Indeed, within the context of the developed world, the vast majority of infants are live born (1); in Canada less than one percent of pregnancies are lost after 20 weeks gestation (2, 3). When such a loss does occur, however, the grief and its impact on relationships is often substantial (4).

Stillbirth, recognized in Canada as the death of a fetus at or beyond twenty weeks gestation or weighing at least 500 grams[1] (5), is typically subdivided into the categories of early stillbirth (from 20 weeks up to, but not including, 28 completed weeks gestation) and late stillbirth (28 completed weeks and beyond) (5). Although the use of this division is somewhat arbitrary, particularly given recent advances in neonatal care, it does roughly separate pregnancies in which the fetus may have been mature enough for delivery from

[1] Quebec only requires stillbirth registration at a fetal weight of 500 grams (5).

those that would most likely have been inadequately developed for survival outside the uterus (6). A separation of earlier and later stillbirths is also important in studying the etiology of pregnancy loss; even after autopsy, late stillbirths are more often left unexplained (7). Within medical literature, stillbirths are further subdivided into antepartum and intrapartum losses, reflecting fetal death occurring before and during labor respectively. Given that more than 90% of stillbirths in Canada are antepartum events, this study will focus on deaths that occur prior to labour whenever possible (8).

Multiple etiologies for stillbirth exist. Recognized causes include maternal death, birth injury, placental/umbilical cord lesions or events, hydrops fetalis, complications of multiple pregnancy, lethal congenital anomalies, and infections (9). Similarly, the numerous risk factors for stillbirth appear to reflect this wide variety of underlying causes. Relevant literature consistently identifies increased maternal age, black and Aboriginal ethnicity, obesity, previous stillbirth, pre-pregnancy diabetes, thrombophilia, pre-existing hypertension, smoking, pre-eclampsia, multiple pregnancy, post-term gestation, and intrauterine growth restriction (IUGR) as risk factors. Studies around these associations will be reviewed in Chapter 2.

1.2 Study Rationale and Objectives

Within Saskatchewan, the overall five-year incidence of stillbirth spanning 2002 to 2006 was similar to the whole of Canada at 6.6/1000 total births and 6.2/1000 total births respectively (2,3). However, when late pregnancy is the focus, Saskatchewan had a higher 2002–2006 incidence of 4.0 per 1000 live births, compared to the Canadian calculation of 3.0 per 1000 live births for the same time period. Although this incidence difference suggests that women in Saskatchewan are at greater risk of late pregnancy

loss, its statistical significance and trend must be evaluated to give context to this concern. Regional consistency in this risk throughout the province is also unknown. Thus, this study will examine the statistical significance of this difference, trends in incidence over time, incidence variation throughout the province, factors that may influence incidence values, and the attributed causes of late fetal loss. The objectives of this study are:

1. To describe provincial and regional late stillbirth characteristics, incidence, causes of death, and their trends.
2. To examine the relationships between individual-level risk factors identified in the research literature.
3. To explore factors at the area level that are associated with increased late stillbirth risk in Saskatchewan women.

CHAPTER 2:

2.0 LITERATURE REVIEW

There has been a proliferation of literature in the area of stillbirth research in the past two decades. Efforts to capture the "big picture" risk factors as well as the relationships between specific individual variables have increased but with limited success. Stillbirth etiology is a difficult research area for several reasons. As there appears to be multiple chains of causation leading to fetal demise (10), pregnancies resulting in stillbirth may have very different characteristics. Acquiring an adequate number of cases may be challenging as stillbirth is a relatively rare event in developed countries (1). As a result, registries are frequently used, with limitation in the number, nature, and format of the variables collected. The information gathered may span large time intervals, subject to temporal effects.

The resultant studies have also been difficult to build upon. Work by different investigators is often not clearly comparable as definitions of both dependent and independent variables vary widely. For example, Scandinavian, British, and Canadian research tends to differ in the gestational age threshold for stillbirth as these regions register stillbirths at twenty-eight (11), twenty-four (11), and twenty weeks gestation (12) respectively. The definition of stillbirth has also changed over time, based on gestational age alone, weight alone, or a combination of these aspects; the Saskatchewan

provincial definition has been modified twice since 1994 (13). Stillbirths may also be combined with early neonatal deaths to create a composite perinatal death outcome. This combined variable results in a blurred understanding of the relationship between risk factors and either original outcome. As previously noted, data on the independent variables has often been collected for administrative purposes and studies subsequently vary as to which covariates are adjusted for and how they are defined.

2.1 Included Stillbirth Risk Factors

Information on several of the risk factors identified in the literature is available for the Saskatchewan women in this study. This section reviews the research around those variables that will be considered in the analysis.

2.1.1 Maternal Age

Certain demographic risk factors have been relatively consistent in their reported associations with stillbirth, of which increased maternal age appears to have been most frequently documented. A recent Canadian review by Huang et al. found a statistically significant association in thirty of the thirty-seven studies examined, with odds ratios ranging from 1.20 to 4.53 (14). The subgroup of ten studies that compared women age 35 years and older to women 34 years of age and younger had a narrower range of odds ratios between 1.26 and 1.92. These results are similar to Usta and Nassar's review of maternal age and stillbirth which provided values of 1.41 to 2.39 (15). Bateman and Simpson also noted that studies examining women over age 40 have generally reported odds ratios greater than 2, suggesting a dose-response relationship (16). Although the usefulness of creating categories with 35 years as the point of division has been debated (14), this dichotomous variable is commonly used in published literature (14) and reflects

the increased stillbirth risk that has been noted with relative consistency at this age (16-19).

The mechanism through which increased maternal age increases stillbirth risk is unclear. Currently age appears to be an independent risk factor for stillbirth, with its relationship changing very little when controlling for various confounders including parity, smoking, education, race, chronic illness, prenatal care, body mass index (BMI), pregnancy complications, and multiple pregnancy (14,16,19,20). Miller, in investigating the relationship between age and placental insufficiency, did not find strong evidence to implicate placental inadequacy as the underlying mechanism causing increased stillbirth rates in older women (21). This result is further supported by work which indicates that older women generally do not show an increased tendency towards small-for-gestational-age (SGA) infants, an expected outcome of poor placental function (22-24). Compared to younger mothers, losses in older mothers occur more frequently throughout pregnancy, but the risk difference is greatest after 37 weeks gestation (16). Fretts and Usher, using the McGill stillbirth database for 1978 to 1995, compared stillbirth etiology between women less than 35 years old with those 35 years and older (25). Stillbirths among older women were more likely to be attributed to infection at a statistically significant level; abruption, malnutrition, and diabetes were of borderline significance. This study also found that older women were 2.2 times more likely to have an unexplained stillbirth (95% CI 1.3-3.8), even with a 97% autopsy rate for this registry. Interestingly, fetal anomalies had an odds ratio of 0.2 (95% CI 0.03-1.5) among stillbirths occurring in older women, attributed to increased early detection and termination of non-viable fetuses.

At the opposite end of the age continuum, women less than 20 years of age also appear to have an increased tendency to fetal loss, with crude stillbirth rates increasing as age decreases (18). After controlling for multiple covariates, however, Wilson et al. determined an adjusted hazard ratio of 1.2 for mothers aged 15 to 19 years when compared to mothers 20 to 24 years of age (26). In contrast, mothers less than 15 years continued to have an elevated adjusted odds ratio of 2.3 for antepatum stillbirth. Utilizing a large nationwide American sample, Bateman found women less than 20 years of age to have only a slightly increased adjusted odds ratio of 1.11 (95% CI 1.08-1.14) when compared to women age 20 to 34 years (16). These findings are in keeping with an Australian study by O'Leary et al. which concluded that "the increased risk of stillbirth in young mothers can, for the most part, be explained by sociodemographic factors" (27), although residual risk does appear to remain in extremely young mothers (26). As previously highlighted, this explanation does not appear to hold for older women (27).

Few studies have looked at the changes in stillbirth risk for different age groups over time. O'Leary et al. found that in Western Australia, rates across age groups were relatively constant between the intervals of 1984-1993 and 1994–2003, with the only statistically significant improvement occurring in women age 35 to 39 years (27). Analysis from northern England found that the pattern of risk across age categories was similar between 1982-1990 and 1991-2000, although women in all groups saw a similar and statistically significant decrease in risk between intervals (28). This study, by standardizing rates seen in the latter interval to the maternal age distribution of the previous interval, also calculated a lower age-adjusted stillbirth rate than was actually

seen in the later period. Thus, even though risk had decreased in all age groups, an increase in the number of older mothers in the population over time limited the actual overall rate reduction. This demographic change has been highlighted by concerns that rates of stillbirth in the United Kingdom have stopped declining as maternal age increases (29).

Within Canada, Fretts et al. using the McGill Obstetrical Neonatal database compared the association of increased maternal age with stillbirth for the periods of 1961-1974 and 1978-1993 (19). Although increased maternal age was not a significant risk factor in the earlier period, it was recognized as an important predictor in the second period, largely attributed to the decreased stillbirth incidence among younger women during the later interval.

Considered together, the above studies indicate that deferred childbearing has a significant influence on stillbirth rates. Of greater concern is the suggestion that the increased risk introduced by advanced maternal age may not be easily modified.

2.1.2 Ethnicity

Several studies have recognized ethnic background to have a relationship with stillbirth, particularly in increasing the risk among black women; odds ratios in these investigations ranged from 1.26 to 2.09 (14, 15, 28-31). Using Missouri Vital Statistics data from 1989 to 1997, Getahun et al. undertook a detailed examination of differences in stillbirth risk factors between black and white women (31). Overall, black women were less likely than white women to have a stillbirth in the preterm period, but risks converged and appeared to cross over as pregnancy progressed; black women were subsequently at greater risk as gestational age reached term. Although similar

antepartum stillbirth risk factors were recognized, risk factors for intrapartum stillbirth differed between black and white women. These authors also noted persistent disparities between African-American and white antepartum stillbirth risks among subgroups of women who were between 20 and 30 years of age, had low or high levels of education, had a BMI<25 kg/m^2, were single, were multiparous, smoked, or were carrying a male fetus. These differences were present even after multivariable adjustment, suggesting that race may truly increase stillbirth risk in certain subpopulations, although unrecognized confounding within these groups cannot be ruled out. Black women also had more antepartum stillbirths than white women when pregnancies were complicated by pre-existing hypertension, pregnancy induced hypertension, premature rupture of membranes, or placental abruption; these findings introduce the possible role decreased prenatal care may play in the influence of race. In contrast, Balchin et al. in their study of British women found that the stillbirth risk in black women became non-significant after adjustment for multiple factors, but South Asian ethnicity remained an independent risk factor (32).

The influence of Aboriginal ancestry on stillbirth has also been examined. In the Saskatchewan context, Eduard et al., utilizing provincial health data from 1980 to 1986, appear to have undertaken the most recent analytical work (34). Crude annual stillbirth rates in this study were approximately 1.5 to 2 times higher in Aboriginal women. The authors also highlight that when stratifying rates by maternal age, a J-shaped pattern was evident for non-Aboriginal women as maternal age increased. This finding contrasted the much more linear age-related increase in stillbirth rates that occurred among First Nations women.

The increased stillbirth incidence among Aboriginal women has been highlighted in other parts of Canada. Recently, a Manitoba study calculated a stillbirth rate of 8.9 per 1000 First Nations births versus 5.7 per 1000 births in the province with a corresponding adjusted odds ratio of 1.72 (95% CI 1.53-1.94) (35). Analysis of the Quebec indigenous population in the mid 1980s to mid 1990's also observed overall stillbirth rates that were higher in Inuit and Indian women compared to French and English speaking women (36). The overall adjusted odds ratio for this study was similar to the Manitoba result at 1.53 (95% CI 1.09-2.15) after controlling for education levels, maternal age, single motherhood, parity, infant gender, community size and community-level factors. Among Indian women, a statistically significant increase could be seen when crude rates from the early part of the period were compared with the latter part of the period. The authors indicate that the effect of ethnicity did not appear different when the analysis was restricted to small town and rural settings.

The increased stillbirth risk among indigenous women has been documented globally as well. Aboriginal Australian women have been noted to have twice the risk of stillbirth compared to non-Aboriginal women (37). Native American women are also at increased risk of stillbirth (16,33). The consistency of race as a risk factor for stillbirth across cultures highlights the need for further analysis towards a better understanding of its mechanism.

Related to race, and the following section on place of residence, is the influence that immigrant status has on stillbirth. The few studies that have looked at this factor have produced mixed results. Swedish work undertaken during the 1970's found the Swedish immigrant population to have lower rates of perinatal death, possibly due to the

selection of physically and socially advantaged individuals for immigration (38). French work from the same time period found a persistent stillbirth risk among immigrant women, particularly those from North Africa (39). Immigrant women were also reported to be less likely to access prenatal care in the French context, even when socio-economic status was adjusted for; increased perinatal pathology was still noted, however, even when adequate levels of care were accessed (40). More recently Swedish work among twin pregnancies found African and Asian immigrant women to have a stillbirth odds ratio of 12.3, although adjustment for confounders appears limited in this work (41). These authors raise speculation that a high prevalence of consanguinity may have contributed to this high association. American work in 2003 found an increased risk for fetal mortality in Asian Indian immigrant women that could not be explained by socio-economic factors. Paradoxically, the fetal mortality rate in this group was actually higher than in Mexican immigrants, a group that typically has more socio-economic barriers but lower rates of perinatal pathology (42).

2.1.3 Place of Residence

Relatively little has been done to compare the risk of stillbirth in urban and rural contexts as place of residence is infrequently considered in stillbirth studies. Aljohani et al's recent Manitoba study did not find a significant difference in stillbirth rates between urban and rural settings considering postal code areas with a population density ≤400 people per square kilometer as rural (35). Luo and Wilkins, however, took a different approach when examining Quebec births, categorizing place of residence according to the influence of a census metropolitan area or census agglomeration (43). They found that a statistically significant association between areas with weak metropolitan influence

and increased stillbirth risk persisted even after adjustment for age, mother tongue, education, marital status, parity, multiple gestation, and infant gender (OR 1.36, 95% CI 1.12-1.64). A statistically significant trend was seen as crude rates increased with increasing remoteness (p-value = 0.0001). Of interest, this Quebec study also found that "rates of all observed birth outcomes were nearly identical comparing rural areas with strong metropolitan influence against urban areas." In light of this observation, a definition of rural based on population size alone potentially ignores the protective influence that individuals in small centers close to large cities gain, diluting the significant risk of rural residence farther away. This is in contrast, however, to Australian work in which "remote" mothers, defined only according to community size, were more likely to have a stillbirth (44), while teen mothers whose place of residence was assessed according to accessibility were not statistically more likely to have a stillbirth based on remoteness after adjustment (45). In the latter study, mothers with the greatest degree of remoteness were clearly at increased risk of a stillbirth (OR = 2.91) but after adjustment for age, smoking, parity, and obstetrical/medical complications, the odds ratio decreased to 1.21 (95% CI 0.17-8.76).

Related to place of residence is the role of environmental exposures, and particularly among rural women, the effect of pesticide exposure on pregnancy. For many rural women, pesticide exposure is related to employment; studies examining the association between occupational pesticide exposure and stillbirth will be examined in Section 2.1.5. Savitz et al. in examining at-home exposures to pesticides undertook a case-control study using the National Natal and Fetal Mortality Survey (46). Among the 1 497 American cases exposed to insecticides, rodenticides, herbicides, or fungicides

at home, an adjusted stillbirth odds ratio of 1.5 (95% CI 1.3-1.7) was determined. Odds ratio for paternal home exposure was 1.3 (95% CI 1.1-1.5). Examining exposure in each trimester separately, Pastore et al. determined weak, non-significant associations for maternal insecticide use in the home and stillbirth from all causes; the association was more convincing, however, between stillbirths due to congenital anomalies and exposures occurring during the first eight weeks gestation (47). The personal use of DEET as an insect repellant, applied in daily, topical, standardized amounts for fifteen weeks between the third and seventh months of pregnancy has shown no increase in stillbirth risk (48).

Pesticide exposures not directly at the home but in areas surrounding the home have also received some evaluation. The above work by Savitz et al. also found respective odds ratios of 1.6 (95% CI 1.1-2.2) and 1.4 (95% CI 1.0-1.9) for maternal and paternal exposures around place of residence (46). In largely suburban areas of San Francisco that were aerial sprayed with malathion to combat fruit fly infestation, the relative risk of late stillbirth was 1.95 among women whose residential area was sprayed up to one month prior to delivery. This adjusted association did not, however, reach statistical significance (95% CI 0.88-4.35) (49).

Bell et al. have attempted to show association between rural residential pesticide exposure, assessed according to Californian township, range, and section, and fetal deaths due to congenital anomalies (50). Adjusting for age and county of residence, they found the highest levels of association for all categories of pesticide when exposure occurred within the 3 to 8 week gestational window. Associations were highest for halogenated hydrocarbons (OR 2.3, 95% CI 1.2-4.4.) and pyrethroids (OR 4.9, 95% CI

1.9-12.9) sprayed within the section of residence or the surrounding eight sections, compared to non-exposure to any class of pesticide (50,51). The associations generally increased if spraying occurred within the section of residence itself and did not change if the chemical was applied by air or on the ground. It should be noted that the definition of fetal death in this study included live born infants who died of a congenital anomaly within the first twenty-four hours; these neonatal deaths constituted more than half the cases. In a separate study, these authors also examined similarly defined fetal deaths that were not due to anomalies and found that their relationship to pesticide was much weaker (52). Halogenated hydrocarbon exposure within the fourth or fifth month of gestation produced an adjusted hazard ratio of 1.4 (95% CI 1.0-2.0); carbamate acetylcholine esterase inhibitor exposure in the third or fourth month had a similar association. These associations were similar whether exposure occurred within the section of residence or the surrounding sections.

In the Canadian context, White et al., citing a seasonal pattern of stillbirths in the St John's River basin, undertook a case-control study to analyze the relationship between both agricultural and forestry application of pesticide and rates of birth defects and stillbirths in New Brunswick (53). Exposure to agricultural chemicals during the second trimester was associated with increased stillbirth risk, although much of the exposure was assessed from maps of soil capability and suitability for production rather than actual pesticide application or estimates derived from type of crop grown.

2.1.4 Socio-economic Status (SES)

As highlighted by Stephansson et al. (54), the relationship between SES and stillbirth risk has been recognized for more than sixty years (55); even so, its influence is

poorly understood. In the past two decades, multiple studies have included this variable in analysis, some finding low status to be an independent predictor (54,56,57), while others not (20,24). Studies vary in the indicators used to determine low SES. Swedish blue-collar and low level white-collar workers were 1.5 to 2 times more likely to have a stillbirth than women with higher positions, associations which remained after adjustment for age, country of birth, body mass index, height and smoking (54). Controlling for the number of prenatal visits, involuntary childlessness, pregestational or gestational diabetes, pre-eclampsia or eclampsia, smoking, and body mass index had only minor effect on the association between occupation and stillbirth in this study. A Danish study by Olsen and Madsen, examining all singletons born in Denmark during 1991 and 1992, noted that the crude stillbirth risk decreased gradually with increasing level of education up to upper secondary school (58). With adjustment for age, parity, and smoking, however, the increased odds ratios seen at lower education levels markedly decreased and the overall trend disappeared, suggesting that stillbirth risk is actually independent of education level. Analysis done in Nova Scotia used education level, Blishen Index (a measure of occupational status), and household income to quantify SES (56). Of these, only household income (<$60 000 annually) was found to be a significant predictor of stillbirth. Although pre-pregnancy obesity did not confound the association between income and stillbirth, smoking did account for 18.5% of the relationship. This study also found no association between neighbourhood SES and stillbirth.

Recent work in British Columbia also considered the effect of disparity in neighborhood income quintiles on birth outcomes, both in rural and urban settings (59). Using data from 1985 to 2000, these investigators found disparities for stillbirth rates

according to quintile only during the late 1990's and only for women in urban areas. This study found that in general, birth outcomes are not significantly different according to rural neighborhood income quintile, due at least in part to the smaller difference in income across the rural quintiles. In urban areas, however, neighbourhood income varied much more, with richest and poorest areas subsequently showing the largest disparity in outcomes and mid quintiles being relatively similar to each other. The disparities in income level across rural neighborhood quintiles declined during the fifteen years investigated in this study but increased in urban areas. The authors also noted that the adjusted rate ratio between the urban neighbourhoods with the lowest and highest income level had increased over this time period. Unfortunately, this study could not examine the role of individual level income within the context of neighbourhood income. Work undertaken in Quebec, however, did find that neighbourhood income level appears to have an association separate from personal education level in urban women (60). Incidentally, this study also found that low personal education level was significantly predictive of increased stillbirth risk in urban settings and borderline significant in rural settings.

2.1.5 Occupation

Certain types of employment have also been associated with stillbirth, with much of the research in this area having occurred in the 1980's and 1990's. These studies have, however, been frequently troubled by difficulties in the measurement of exposures, the classification of exposures, and the assessment of confounding.

A variety of maternal occupations have been assessed in connection with stillbirth. American janitors and textile workers have been reported to have an increased risk of

stillbirth with adjusted odds ratios of 2.5 (95% CI 1.4-4.3) and 2.0 (95% CI 1.2-3.4) respectively when compared to clerical workers (61). Borderline significant associations were also seen for pregnant women working in personal service[1] and food service employment. A large study undertaken in Montreal during the mid 1980's found that stillbirth risk was significantly increased for women in leather or textile manufacturing, sports/dance, agriculture, and horticulture (63). Women working as operating room nurses, radiology technicians, and in metal/electrical manufacturing also had a statistically significant risk of fetal death, although the outcome variable included both late spontaneous abortions and early stillbirths. In this work, stillbirth risk also appeared to increase in occupations requiring physical effort, vibration, long periods of standing, and solvent exposure, reported as observed-to-expected ratios ranging from 1.5 to 2.8 with p-values <0.05. Heavy lifting, long hours, noise exposure and cold exposure were only statistically significant in the group that included both late spontaneous abortions and early stillbirths. Industrial exposure to rubber, synthetics and plastic production as a combined category and exposure to lead have been found to have stillbirth odds ratios of 1.8 and 1.6 respectively, although the calculated confidence intervals for both associations contained one (95% CI 0.8–4.0 and 0.8–3.1 respectively) (64).

In the specific area of agricultural employment, study results have again varied. Stillbirth odds ratios among women with agricultural job titles have ranged from 1.0–5.6 (63-65). The closely related factor of occupational pesticide exposure has also been examined. Californian survey based case-control study by Pastore et al. found that

[1] A combined category of funeral directors, housekeepers, estheticians, travel guides and attendants, childcare providers, and related job titles (62)

women with occupational exposure to pesticides in the first or second trimester had approximately 1.3 to 2.7 times the risk of stillbirth from any cause, adjusting for smoking, alcohol, race, age, county of residence, previous pregnancy loss, and season of conception (44). Stillbirths due to cord, placenta, and membrane abnormalities were 1.2 to 4.8 times more frequent in exposed pregnancies than in pregnancies that were unexposed. The odds ratio for lethal congenital anomalies with occupational exposure in the first two months was 2.4 (95% OR 1.0-5.9). It should be noted that the outcome variable in this study was again a composite of stillbirths and neonatal deaths; approximately one-quarter of cases were live born. These authors also highlight the stronger associations often seen between pesticide exposure and stillbirth among women with agricultural occupations compared to those with pesticide exposure in other types of employment (47). This difference could be attributed to confounding by additional factors related to agricultural employment or, as Goulet et al. pointed out, pesticide exposures in the latter studies may be grouped together with other exposures such as fungicides and germicides (65). Exposed occupations would then potentially include nurses, cleaners, laundry workers, etc (65). It would seem that such broad groupings would likely invalidate inference of stillbirth risk among women with agricultural pesticide exposure from occupational exposures in general.

Timing of work may also be important to pregnancy viability. A recent, large, retrospective cohort from Denmark determined an adjusted hazard ratio of 1.92 for late stillbirth among women engaged in consistent nighttime work as compared to daytime employees (66). Unfortunately, this estimate lacked both statistical significance and precision (95% CI 0.59-6.24).

A few studies have undertaken assessment of paternal occupational exposures and stillbirth risk. Savitz et al, using the National Natality and Fetal Mortality surveys from 1980, examined several occupations and stillbirth risk (67). Among men working in the textile industry, stillbirth risk in their partners had an adjusted odds ratio of 1.9 (95% CI 1.2-2.9). Weaker associations were also seen for fathers working in paper/wood industries (OR 1.4, 95% CI 1.0-1.9) and construction (OR 1.2, CI 95% 1.0-1.5). Associations with specific occupational toxins, including several forms of hydrocarbons, metals, minerals, and alkylating agents were near 1.0 and non-significant. Paternal dioxin exposure within milling or manufacturing has also showed no clear association with stillbirth (67,68). Exposure assessment, which was largely based on job titles, has been recognized as a limitation in these studies.

More specifically, stillbirth risk introduced by paternal occupational pesticide exposure has also undergone some evaluation but again with generally weak associations; the majority of these studies have been summarized in at least two major review articles (69,70). Among male Vietnam veterans exposed to Agent Orange, stillbirth associations in their offspring have generally ranged from 0.87 to 3.2, although statistical significance, evidence of a dose-response relationship, good assessment of exposure, and adjustment for confounding are frequently lacking (71-73). General pesticide exposures in fathers working in floriculture (74) or as aerial sprayers (75) have not been found to have a relationship with stillbirth, although the previously mentioned methodological weaknesses are again present. Unprotected organochlorine, organophosphate, and synthetic pyrethroid exposure in non-smoking, male cotton field workers in India, however, was associated with a crude relative stillbirth risk of 2.49

($p<0.05$) (76). Savitz et al. found that men exposed to pesticides at work have an odds ratio of 1.2 (95% CI 1.0-1.5) (46), which decreased further when assessed by job title only; fathers employed within the category of agriculture, forestry or fishing have been found to have an odds ratio of 1.0 (64).

2.1.6 Fetal Gender

Fetal gender is frequently included in the statistical modeling of birth outcomes, with some studies finding maleness to increase the risk of stillbirth. In publications with positive findings, adjusted odds ratios typically range from approximately 1.2 to 1.5 (20, 28, 77). Engel et al. recently noted that among women in an Australian study, 20% of male stillbirths occurred at 37 to 40 weeks, differing significantly from the 10% of female stillbirths that occur at this gestation (77). Median gestational age was subsequently later for male stillbirths than female stillbirths (30.5 weeks versus 25 weeks) in this study.

2.1.7 Multiple Pregnancy

Multiple pregnancies (pregnancies involving twins, triplets, or more fetuses) have consistently been recognized to be at increased risk for stillbirth. Twinning has been reported to have a frequency of 2.7%, a stillbirth incidence of 12/1000, and an odds ratio for stillbirth of 1.0-2.8 (6). Work from northern England has provided a similar description of twinning and stillbirth (28). These authors also noted an increase in twinning frequency between 1982 and 2000 (2.0% to 2.4%) but a statistically significant 36% decrease in stillbirth risk for twins. This respective increase and decrease have been reported in other countries including Sweden, the United States, and Canada, although not all have reached statistical significance (78-81). Among Australian pregnancies twenty weeks gestation and beyond, Mohsin et al., using data from 1998 to 2002, found

an adjusted odds ratio of 3.35 (95% CI 2.87-3.91) for stillbirth among multiple pregnancies, even after controlling for low birth weight and gestational age (20). Certain subgroups, such as monochorionic twins, are recognized to be at higher risk (82). The prospective risk of stillbirth is increased in twins over singletons at all time points in the second half of pregnancy (83), although the majority of the overall risk difference appears to occur as a disproportionate increase in stillbirth incidence among twins after thirty-three weeks gestation (84).

2.1.8 Gestational Age

Among recent stillbirth literature, an important study examining the significance of gestational age on stillbirth risk was undertaken by Reddy et al. (17). Using population-based data for more than five million pregnancies in thirty-six American states during the period of 2001 to 2002, these investigators described stillbirth risk by gestational week, subdivided according to maternal age. For all women, forty-one weeks gestation was the period of greatest risk, but stillbirth incidence appeared to begin increasing for all age groups earlier at approximately thirty-eight weeks. This result concurs with previous work by Hilder et al. (85) and subsequent work by Bahtiyar et al. (86). Hilder et al. showed a marked increase in stillbirth risk towards term; risk increased six-fold between 37 and 43 weeks gestation, from 0.35 per 1000 ongoing pregnancies to 2.12 per 1000 ongoing pregnancies. In the work by Reddy et al. and Bahtiyar et al., however, there is also evidence of interaction between maternal age and gestational age, with older women having a remarkably sharper increase in stillbirth risk with advancing gestation than younger women. Reflecting the general influence of this risk factor, Gulmezoglu et al. in a systematic review determined that routine induction of

labor among women at forty-one completed weeks gestation resulted in a statistically significant reduction in total stillbirth incidence (87).

In considering the influence of gestational age, it is worth noting Hilder et al.'s emphasis on the necessity of using of the correct denominator to determine risk at specific gestational ages. First pointed out by Yudkin et al., the true number of fetuses at risk is not the number of total births in a particular time period but the number of ongoing pregnancies at that time (88). To highlight the importance of this principle, Hilder et al. re-examined the same data using total births at specific weeks of gestation as the denominator and noted that the risk created by prolonged pregnancy was no longer apparent (85).

2.1.9 Intrauterine Growth Restriction

Multiple studies have evidenced that fetuses with inadequate growth are at risk for stillbirth (31, 89-92). Intrauterine growth restriction (IUGR) is often used interchangeably with small-for-gestational age (SGA) although not all fetuses that are small for their gestation have pathological smallness (93). Population-based birth weight percentiles have been typically used in this assessment, but there is concern that fetuses that are small simply due to their genetic constitution are inappropriately labeled as IUGR, potentially resulting in unnecessary worry for parents and clinicians while biasing associations among researchers (94). In contrast, the possibility of missing a truly IUGR fetus that appears of adequate size by population standards but is smaller than it should be by its genetic makeup also exists (94).

There has been considerable discussion in research literature as to how inadequate growth should be determined. Although population based growth curves

have been traditionally use in this assessment, Gardosi et al. first suggested the use of customized growth charts in 1992 (94), and multiple authors have since confirmed their usefulness (95). These growth trajectories are based on ultrasound assessed intrauterine fetal weights with adjustment for physiological characteristics that are thought to influence fetal size such as fetal gender, maternal height and weight, parity, and ethnicity (94). This differs from more common population-based fetal growth curves which are determined from the birth weights of infants born at specific gestational ages. These weights are recognized as typically being lower than those of fetuses at the same gestational age that remain in utero; subsequently "normal" population curves at earlier gestations are generated from preterm deliveries predisposed to pathological smallness (94). Gardosi et al. found that when applying the customized curves to their British sample of 4 179 pregnancies, approximately one-quarter of pregnancies recognized as SGA by population standards would have been considered appropriate by the customized standard and a quarter who were SGA by the customized standard were considered appropriate by population standards (94). Overall the two standards for assessment agreed on smallness in 89% of births.

In 2001, Clausson et al. compared perinatal outcomes among all women in the Swedish Birth Register who gave birth between 1992 and 1995 (96). Births were labeled as either SGA or non-SGA, using the tenth percentile as the cut-point, by both population based curves and customized standards. These two methods agreed on classification of fetal size in 86% of stillbirths and 95% of pregnancies overall; among those assessed as SGA by both methods, there was a strong risk of stillbirth (OR 5.1, 95% CI 4.3-5.9). Among those who were only SGA by customized curves, the odds

ratio increased to 6.1 (95% CI 5.0-7.5), while those that were only SGA by population based curves were not at an increased risk for stillbirth. Overall, fetuses that measured below the tenth percentile on their customized curve had an odds ratio of 5.3, while those below the tenth percentile on a population based curve had an association of 3.4, suggesting that customized assessment is better at recognizing stillbirth risk.

Zhang et al., using an extension of this registry up to 2001, confirmed the degree of agreement between assessment methods and calculated similar odds ratios (97). These authors, however, also subsequently adjusted the odds ratios for gestational age with a significant reduction in the association between SGA and stillbirth. This result led them to suggest that the majority of the relationship determined through customized assessment is generated by the use of an intrauterine fetal weight standard that improves classification in preterm fetuses and is not the result of the other maternal characteristics incorporated into customized assessment (97,98). Subsequent work by several of the same authors using the same data found that customized assessment (intrauterine derived growth curves customized to individual pregnancy characteristics) versus non-customized intrauterine based curves produced very similar associations, leading them to conclude that maternal variables, which are often unavailable from birth registries, are not necessary for appropriate size categorization (99). These results are similar to the findings of Lyon et al.'s autopsy assessment of growth restriction in stillborn infants (100). These authors concluded that intrauterine derived growth curves customized for physiological variables were no better in determining IUGR, confirmed by brain to liver weight ratios, than non-customized intrauterine derived curves.

In additional work, Gardosi et al. also determined a stillbirth odds ratio of 6.2 (95% CI 3.3-11.5) for fetuses considered SGA by intrauterine-weight based but non-customized standards (90). A significantly higher proportion of preterm than term stillbirths were SGA (53% versus 26%, OR 3.3, 95% CI 1.6-6.5). Although among term stillbirths there were fewer babies that were SGA as defined, the non-SGA stillbirths also tended to be smaller than live births, with eighty percent weighing less than the fiftieth weight percentile.

Froen et al. in looking at the subgroup of pregnancies that ended in a sudden unexplained intrauterine death also found SGA status to be a significant risk factor (OR 7.01, 95% CI 3.27-15.06) (101), agreeing with Gardosi et al. who also examined this outcome (90). Froen et al. did not, however, find a difference in the occurrence of SGA according to gestational age at the time of fetal death. Additionally, smoking was associated with stillbirth in SGA fetuses but not in non-SGA fetuses. This finding suggests that either the risk of stillbirth among smokers depends on whether or not the fetus is appropriately grown or that IUGR lies on the causal pathway between smoking and stillbirth. The latter seems more likely, based on the association between smoking and SGA that was also noted by these authors and multiple other investigators (102).

In the same work, Froen et al. also found that increased body mass index elevated the risk for both non-SGA and SGA unexplained stillbirth (OR 5.77, 95% CI 1.99-15.77 and OR 2.77, 95% CI 1.1-7.0 respectively) (101). As discussed by these authors, obesity or the excessive caloric intake leading up to it, may directly impair growth, leading to stillbirth, but based on the above odds ratios, this does not appear to be the exclusive mechanism. Overall, the risk of unexplained stillbirth was remarkably

high when the fetus was SGA and carried by an overweight or obese woman, compared to the corresponding risk in a pregnancy that had neither complicating factor (unadjusted OR 71, 95% CI 14-350).

2.1.10 Parity

There is evidence that past obstetrical history has a predictive relationship with stillbirth risk. One of most commonly considered but inconsistent aspect is parity. Fretts et al., using the McGill Obstetrical Neonatal Database found that regardless of maternal age, women pregnant for the first time, or in contrast, pregnant women with a parity of three or more, were at increased risk of stillbirth during the 1960's and early 1970's (19). Repeat analysis of a second time period from the mid 1970's to the early 1990's saw increased risk remain only for women with higher parity. Sipilka et al.'s work among Finnish women also found the influence of nulliparity to have weakened when comparing stillbirth risk factors between the mid 1960's with the mid 1980's (103). Looking at the more recent time periods of 1984-1993 and 1994-2003, O'Leary et al. found no statistically significant change in a variety of stillbirth predictors, including parity, among Australian women (27). When examining only the subgroup of unexplained stillbirths from a Montreal tertiary care hospital, Huang et al. found nulliparity to remain a significant predictor across the 1960's to the mid 1990's with a higher odds ratio in the subgroup of older mothers (104). The significance of high parity (3 or 4 previous pregnancies) appeared to increase across this interval. A recent American study by Reddy et al. using national data from 2001 and 2002, found that stillbirth risk, when stratified by maternal age, was increased for nulliparous women compared to multiparous women in all age groups (17). This large work also suggests

that nulliparity remains a risk factor in addition to the association of higher levels of parity highlighted above.

2.1.11 Previous Stillbirth

It is also recognized that women who have experienced a previous stillbirth have a two to ten fold increased risk of recurrence (105-107). Work by Sharma et al. using Missouri cohort data from 1978 to 1997 supports this conclusion and suggests that this risk is comparatively higher in women who experience an early rather than late stillbirth in their previous pregnancy (107). Similarly, there is some evidence to support a doubling of stillbirth risk among women who have previously experienced a spontaneous abortion (108,109)

2.2 Additional Significant Risk Factors

In addition to the variables that are available for this analysis, research literature identifies several other important characteristics have been connected to increased stillbirth risk. Maternal characteristics/behaviors [increased BMI (30,110-112), smoking (16,20,57,89,113-116), substance abuse (117-120), no seatbelt use (121-123)], prenatal complications [pre-eclampsia/eclampsia (124-126), placental abruption (127), umbilical cord knots (128,129), fewer than 4-5 prenatal visits (8,104,130,131)], past obstetrical history [previous small-for-gestational age infant (105,132,133), Caesarean section (133,134)], and maternal disease/injury [chronic hypertension (135-137), clotting disorders (138,139,141), pre-pregnancy diabetes (20,34,142-144), mental illness (145-147), physical abuse (148-150,151-155)] have been noted to increase stillbirth risk.

2.3 Causes of Stillbirth

According to Korteweg et al., no less than thirty classifications have been developed for the examination of perinatal death which includes stillbirth (156). This surprisingly large number of approaches appears to reflect differing purposes for classification. Among those most commonly used are the extended Wigglesworth classification, developed to highlight the pathophysiological cause of death, and the modified Aberdeen classification which categorizes the clinical factor that initiated the events leading to death (157). The main criticisms of these particular classifications, however, are their failure to recognize poor growth and placental pathology as contributing to death, their inability to retain important information about the stillbirth, and relatively poor inter-rater agreement (158-161). More recently proposed classifications include the ReCoDe system, which aims to identify conditions that have contributed to death rather than the cause (158), the Tulip classification which examines underlying pathology and mechanism of death (156), and the de Galan-Roosen classification which classifies by the initiating maternal, fetal or placental clinicopathology (159), among others. Vergani's et al.'s comparison of these systems found a lower proportion of unexplained stillbirths (14-18%) when employing the latter three than when the extended Wigglesworth classification was used (47%) (160). Much of this decrease appears to be due to recognition of growth restriction as a category in itself. Similarly, Flenady et al. recently found several newer classifications, including ReCoDe and Tulip to perform better in a number of aspects than either the extended Wigglesworth or the modified Aberdeen (161).

A clear epidemiological description of stillbirth causes is also problematic due to differing approaches within research literature. A recent review by Silver et al. reported that infection, chromosomal abnormalities, and maternal-fetal hemorrhage are among the major causes of stillbirth (10-15%, 6-12%, 3-14% respectively) with fetal growth restriction seen in approximately half of cases (9). Smith and Fretts recently published Scottish stillbirth data reporting that 59% of cases were unexplained, 15% were due to hemorrhage, 10% were due to fetal abnormality, and 7% were due to pre-eclampsia (162). In examining the autopsy results of late stillbirths in a large Montreal series between 1980 and 1988, Fretts et al. reported 21% to 41% of all stillbirths as unexplained, 7% to 33% as the result of fetal growth retardation (defined in this study as fetal weight less than the 2.5th percentile), and 12% to 18% as due to abruption; the ranges of these percentages reflect different gestational ages (7). Using data spanning 1985 to 1995, Ogunyemi et al. reviewed 115 stillbirths twenty-five weeks gestation and beyond and reported 37% to be related to placental causes, 28% due to cord complications, and 15% due to fetal factors such as major anomalies and twin-to-twin transfusion (163). The variation in the reporting of results for these four studies alone exemplifies the difficulty in trying to compare and summarize results across the research literature.

A few authors have examined trends in stillbirth causes within specific populations. Bell et al. in comparing Northern England singleton stillbirth causes between 1982-1990 and 1991-2000 noted statistically significant decreases in losses due to congenital anomalies, antepartum hemorrhage, pre-eclampsia, and intrapartum causes; unexplained rates were essentially unchanged (164). Stillbirths caused by maternal

conditions such as hypertension, diabetes, and isoimmunization appeared to decrease but did not reach statistical significance. Antepartum death with cord compression appeared to increase but with borderline significance, while infectious causes showed a statistically significant increase, possibly due to improved detection. Fretts et al. in drawing comparisons among Montreal stillbirths between 1961-1969 with 1980-1988 found statistically significant decreases for stillbirths attributed to isoimmunization, intrapartum asphyxia, malformations, and growth restriction, as well as for antepartum stillbirths that remained unexplained (7). Again diabetic and abruption-related losses decreased but were not statistically significant, while stillbirths caused by infection and high blood pressure increased, also without definite significance. More recent American work looking at term stillbirths in the interval of 1996 to 2005 found that although rates in this group did not show a significant decrease during this time period, the incidence of unexplained losses declined (165). Placental and cord causes did not show a significant trend during this interval.

Method and intensity of investigation is also important in determining stillbirth causes. The previously mentioned work by Ogunyemi et al. (163) found that 28% of pathology results were inconclusive, falling in the range also reported above by Fretts et al (7). Pathology assessment was still crucial, however, as these reports provided the only diagnosis in forty percent of the cases (163). This is similar to other studies that have reported autopsy as diagnostic in approximately 30% of otherwise unexplained fetal deaths (166, 167). Carlidge et al. also reported that autopsy changed the clinical diagnosis in 12% of cases (168), while Saller et al. found that among cases with a clinical diagnosis, autopsy changed or added to the diagnosis in 54% (166). It appears that in

many cases, perinatal autopsy also provides additional information that is unavailable through prior prenatal ultrasound (169). Ahlenius et al. found that with an extensive postmortem testing protocol, the proportion of fetal deaths that remained unexplained was as low as 12% (170). Similarly Petersson et al. reported that 11.5% of otherwise unexplained losses could be attributed to viral infection if polymerase chain reaction testing was added to assessment (127). Clearly the amount of recognized pathology is proportional to the effort put into the search for it.

Deriving a solid overall description of stillbirth causes from current literature is challenging due to differences in classification, intensity of testing, gestational age under investigation, and variation as to whether certain characteristics, such as poor fetal growth, are treated as risk factors or causes. Further work is required to better define stillbirth causes, including efforts to improve understanding of basic mechanisms of stillbirth. As Smith and Fretts summarized, "A definitive classification system will probably continue to be elusive until the pathophysiology underlying the large number of cases without a clear direct cause is elucidated" (162).

2.4 Literature Gaps

As previously highlighted, this area of research is generally hindered in several ways, including a lack of standardization in clinical workup and cause of death classification. It would also seem that there is also inadequate knowledge of significant risk factors; after taking into account the major recognized associations of increased age, high parity, smoking, low education, no prenatal care, low BMI, chronic medical conditions, pre-eclampsia, abruption, SGA, and congenital anomalies, Getahun et al. could only calculate a total population attributable risk proportion of approximately 50%

(31). Thus there is still a large proportion of stillbirths in the general population that cannot be explained, and the exploration of previously unrecognized risk factors is required. Two such factors that appear to have received little assessment, particularly in the developed world, are that of diet and physical activity; further work is also needed to better quantify the influence of depression, stress, and partner violence on stillbirth risk. Other risk factors such as parity and place of residence have been inconsistently associated with stillbirth and require further evaluation. Even among well-recognized risk factors such as ethnicity, low socio-economic status, or increased maternal age, the underlying mechanisms of influence and interplay of these factors is not known. Exemplifying the former, Goy et al. found that 80% of variance in stillbirth risk across socioeconomic levels could not be explained by known factors (56).

Acquisition and analysis of data has also been somewhat limited. A large number of relevant studies have been retrospective in nature, dependent on administrative data from birth registries and health records. This results in limitation of exposures available for assessment both in nature and format. Although perhaps impractical due to the relative infrequency of this outcome, stillbirth research would benefit from a large prospective cohort study, specifically designed to adequately assess obstetrical outcomes while obtaining detailed information on all recognized and potential covariates. Additionally there appears to be relatively little assessment of interaction between covariates in existent research. For example, Huang et al. noted in their systematic review of the relationship between stillbirth and maternal age, only three of the thirty-seven studies examined tested the potential interaction of parity with age, an important

consideration in an era where increasingly more women are having their first child at an older age (14).

From the above literature review, it also appears that relatively little investigation into stillbirth has occurred within the Canadian context. When undertaken, the focus has typically been on specific associations with little work to create a more composite picture of the risk factors that influence stillbirth among Canadian women. The majority of the work that has been done has examined populations in Nova Scotia and Quebec alone, although many of the investigated associations are of interest to western Canada as well. Major findings include evidence that stillbirth risk is increased among Aboriginal women (36) and women residing in areas with weak metropolitan influence (43), factors of particular relevance to the prairie provinces. Given that the Saskatchewan population has one of the highest proportions of Aboriginal people in Canada (171), and that approximately 25% of Saskatchewan women age fifteen to forty-four years live in areas of little or no urban influence (172), the need to assess the role of these factors, among others, in this province's relatively high late stillbirth rate is apparent.

Although this study was clearly not anticipated to address most of these concerns, the proposed methodology was directed towards providing a description of Saskatchewan women who experience a late pregnancy loss. It was intended to examine interrelationship of individual risk factors, offering additional clues as to the individuals who are at specific risk and the mechanisms behind certain recognized associations. It also aimed to explore the association area-level characteristics have with late stillbirth risk in Saskatchewan, reflecting both individual factors and certain social and economic community characteristics.

CHAPTER 3:

3.0 DATA

In order to meet the stated objectives, two sources of data were required. For examination of the inter-relationships between late stillbirth characteristics as indicated in the second objective, a provincial data source able to provide individual case information rather then aggregated data was needed. As such, the Department of Vital Statistics at Saskatchewan Health[1] seemed most likely to have recorded this information. The third objective required area-level information such as education levels, changes in population numbers, etc. both for reproductive-age women and the larger populations in which they live. Statistics Canada seemed the most likely source for such information at a variety of geographic levels (e.g. census tract, census subdivision, census division, etc.) The first objective could be met using a combination of data from both these sources.

3.1 Saskatchewan's Vital Statistics Database

The Saskatchewan government records basic demographic data about all stillbirths occurring within Saskatchewan in the Vital Statistics Database. This database dates back to the late 1970's and, in accordance with provincial law, records all fetal deaths in the province. Information is reported per standardized form from both parents and the attending physician within fifteen days of the stillbirth (Appendix B). Although

[1] The Department of Vital Statistics is no longer a department within Saskatchewan Health but at the time of writing is part of the Government of Saskatchewan's Information Services Corporation (ISC).

additional information is recorded on the forms, variables recorded electronically for each fetal death include maternal age, parity, residence, duration of the pregnancy, fetal weight, type of pregnancy (singleton versus twin, triplet, etc.), Registered Indian Status (when disclosed) as well as cause of death.

A request was made to the Department of Vital Statistics to access de-identified data from this database. Data was extracted by agency employees and approval of its release was subsequently granted by the department registrar. As data was requested at the level of the census division, it was felt that identification of specific individuals would be unlikely given the relatively large area covered by each region. This data was provided without personal identifiers (e.g. name, address, birth date, etc.) and variables were requested in categorical form where scientifically reasonably to limit detailed description of cases and possible recognition. Ethical approval from the University of Saskatchewan's Research Ethics Board to use this data has been received under the constraints that any tabular data with cells counts less than five will not be published or presented and that all results will be stated in aggregate (Appendix C).

3.2 Study Population

3.2.1 Sample Size Estimation

For the determination of sample size, emphasis was placed on adequacy for Objectives 2 and 3, given their more analytical nature. An expected minimum of five cases per cross-classified cell has typically been advised for Chi-square testing and its use in log-linear modeling (173-175). It was impossible to know a priori how many variables, and subsequently the exact number of cases, would be required for Objective 2. Due to potential complexity of interpretation, however, the number of variables included in log-

linear models appears to be generally limited between three and five (174,175). For this study, it was hypothesized that a typical model might categorize the subjects according to the presence or absence of a metropolitan area in their census division of residence (no metropolitan area = 23% (176)), relative fetal size (small for gestational age = 50%[2] (90,96)), their Aboriginal status (estimated proportion of stillbirths that occur in Aboriginal mothers = 19% (134)), and number of deliveries (four or more = 21% (177)). To ensure that a minimum of five cases per cell would remain after progressively categorizing the data on all of these variables, a total of 1090 records would initially be required (5/(0.23*0.50*0.19*0.21)= 1090). In reviewing annual provincial vital statistics reports, it appeared that twenty-one years of data would be adequate to meet the calculated value with reasonable potential for the creation of models of greater depth, particularly those containing the noted variables of importance to Saskatchewan births. It was recognized that less frequently seen characteristics such as multiple gestation (9.5%), previous stillbirth (0.9%), and post term delivery (1.1%) would likely be limited in the depth to which their relationships with other variables could be investigated (20,107,178).

Sample size considerations for the area-level analysis were complicated by the repeated assessments of census division count data at three different time points (1992-1996, 1997-2001, 2002-2006). As such, the correlation between counts within the same census division should be accounted for and a methodology that would do so, generalized estimating equations (GEE), was taken into consideration when evaluating the sample size (179). As sample size for GEE depends upon the number of clusters and

[2] 50% is a combined estimate based on the two indicated references

not the number of time points, the area level sample size was limited to eighteen census divisions by the geographic level of the data available (180). It has been suggested that although GEE requires at minimum twenty-five clusters for reliability, analysis with less than twenty clusters may be improved if model based variance estimates are used rather than the robust versions (180,181).

As Objective 1 was largely descriptive, sample size estimation was less of a concern. Even so, as identifying census divisions where incidence varied was a priority, it was important to consider if recognized differences across five year periods could legitimately be statistically significant on Chi square assessment given twenty-one years of data. Assuming a provincial late stillbirth incidence at 4/1000 total births as noted in Chapter 1 (2,3) and the estimated number of live births in five year periods from Statistics Canada (182), anticipated marginal probabilities and expected counts were calculated. This sample size appears reasonable for this aspect of the analysis as 18.1% of the expected values were less than 5.

3.2.2 Predictor Variables

3.2.2.1 Individual-level Variables

The information collected by Vital Statistics on each stillborn case is relevant to the examination of this issue in Saskatchewan; several of the predictor variables recognized in the literature are included in the electronic record. Table 3.1 indicates the variables requested from Vital Statistics and the format in which they were received. The majority were categorical, in formats reflecting typical groupings found in the literature. Only fetal size and pregnancy duration were specifically requested in continuous form as the weight at which a fetus is deemed small for gestational age is

very different from 28 weeks to 42 weeks gestation. The size categorization for fetuses at varying gestations based on a single cut-point value would frequently lead to misclassification. Both variables were, therefore, requested in continuous form and were used to appropriately categorize fetal size.

TABLE 3.1 Variables received for each stillbirth recorded by the Department of Vital Statistics, Government of Saskatchewan, 1987-2007

Variable	Type	Coding
Year	Continuous	Recorded as calendar year
Maternal age	Categorical	0 = less than 35 years 1 = 35 years and older
Parity	Categorical	0 = one delivery 1 = 2 to 3 deliveries 2 = 4 or more deliveries
Previous stillbirth	Categorical	0 = no previous stillbirth 1 = one or more previous
Place of residence	Categorical	1 to 18 by census division
Ethnicity	Categorical	0 = non-First Nations 1 = First Nations status
Fetal size	Continuous	Recorded in grams
Fetal gender	Categorical	0 = female 1 = male
Pregnancy duration	Continuous	Recorded in completed weeks
Multiple pregnancy	Categorical	0 = single fetus 1 = twin, triplet, or other
Cause of Stillbirth	Categorical	International Classification of Disease (ICD) 9 or 10[1] cause of death (183,184)

[1] ICD-10 used as of January 1, 2000

The purpose of categorizing residence according to census division was three-fold. Firstly, it allowed assessment of case regionality while maintaining a reasonable degree of anonymity; data acquisition at the more exact levels of postal code or census

subdivision was not possible without violating privacy safeguards. Secondly, it also provided opportunity to assess relative proximity to a census metropolitan area. As indicated in the literature review, influence of an urban centre may be more related to stillbirth risk than rural/urban status defined by population numbers. Thirdly, it allowed analysis of corresponding regional census data for characteristics such as income which are not available from the vital statistics information.

3.2.2.2 Area-level Variables

The area-level variables of interest in Table 3.2 are all available from Statistics Canada and the corresponding data was located for all census divisions at the three census time points of 1996, 2001, and 2006 (185-208). Their selection is largely based on pertinent associations noted in the literature review and availability for all three time intervals.

TABLE 3.2: **All variables considered for area-level analysis**

Income
Median household income
Median family income
Education level
Proportion of reproductive age females with no diploma or degree
Proportion of reproductive age males with no diploma or degree
Proportion of total adult population with no diploma or degree
Proportion of reproductive age females with high school diploma or equivalent as highest education
Proportion of reproductive age males with high school diploma or equivalent as highest education
Proportion of total adult population with high school diploma or equivalent as highest education
Proportion of reproductive age females with undergraduate-level degree or certificate as highest education

Proportion of reproductive age males with undergraduate-level degree or certificate as highest education

Proportion of total population with undergraduate-level degree or certificate as highest education

Proportion of reproductive age females with graduate degree as highest level of education

Proportion of reproductive age males with graduate degree as highest level of education

Proportion of total population with graduate degree as highest level of education

Ethnicity

Proportion of the population who are Aboriginal

Proportion of children age 0 - 4 years who are Aboriginal[1]

Proportion of reproductive age women who are immigrant

Proportion of total population who are immigrant

Proportion of reproductive age women who are black

Occupation

Proportion of reproductive age women in primary production work[2]

Proportion of reproductive age men in primary production work

Proportion of total population involved in primary production work

Proportion of reproductive age women working in agriculture

Proportion of reproductive age men working in agriculture

Proportion of total population working in agriculture

Proportion of adult female population who are farm operators

Proportion of the adult male population who are farm operators

Proportion of total adult population who are farm operators

General census division characteristics

Population density (per square km)

Population change between census years (%)

Largest community size

Estimated average age[3]

Proportion of reproductive age women who are ≥35 years

Ratio of children 0 - 12 years to reproductive age women[4]

Proportion of families with lone female parent

Proportion of land area sprayed with pesticide

Proportion of land area sprayed with herbicide

Proportion of land area sprayed with fungicide

Modified Beale Code (MBC)

Revised Beale Code (RBC)

[1]This variable was chosen as a reflection of Aboriginal pregnancies that occurred in the 5 year period under assessment. Although it too is an ecological variable, it would be expected to have a closer relationship to the outcome than the proportion of Aboriginal women in the reproductive age group.

[2] Labor involved in harvesting (including aquaculture/marine), landscaping/grounds maintenance, mining, oil/gas drilling or servicing, logging/ forestry (62)

[3]Calculated as a weighted midpoint average for five year age categories.

[4]Values for parity not available

3.2.2.3 Offset Variable

While not truly a predictor, a specific variable included in the Poisson regression both for trend/region assessment and area-level modeling is that of the offset, a variable which provides context for the count outcome. For this analysis the offset is the total number of births per given region and/or time period, having been estimated from the total number of live births available from Statistics Canada data (182). Unfortunately live birth numbers by census division encompassed the calendar from July 1 of one year to June 30 of the next year, rather than January 1 to December 30, with subsequent misalignment from the corresponding stillbirth count data by six months. Given that live birth counts only change in relatively small increments from year to year (only three values changed more than 20% between successive years) and recognizing the large difference between outcome and offset, a large over or underestimation of the birth counts would be required before the results would change substantially. Even so, to create the best approximation possible for the number of total births occurring during a January through December year, live births for each two successive twelve month periods were averaged with late stillbirths then added in. In the analysis the final values were used in their natural log form.

National live birth data was also used to create an offset values for incidence comparison between Saskatchewan and the rest of Canada in Objective 1 (3). These values were also utilized as natural logs and appear to cover a typical calendar year.

3.2.3 Outcome Variables

The vital statistics dataset as outlined provided the number of cases which, when counted by specific time interval and region, could be modeled as the outcome variable for trend analysis in Objective 1. This information was also used in conjunction with annual national data on the number of late stillbirths for incidence comparison (2). For Objective 2 the vital statistics data allowed the count of cases with particular combinations of characteristics to be assessed and modeled. As the residential census division and year of stillbirth for each case was also available from this data, the number of stillbirths per census division per five year period was available to be modeled as the outcome variable in meeting Objective 3.

CHAPTER 4:

4.0 METHODS

This chapter will describe both the theoretical and practical steps taken in the analysis of the data. After data cleaning and categorization, analysis itself included basic descriptive procedures for case characteristics, Poisson regression to examine trends in incidence, examination of descriptive associations between characteristics of cases, and area-level analysis of regional characteristics in relation to local late stillbirth incidence.

4.1 Data Preparation

Prior to formal analysis, data assessment began with overall examination of the information, inspection of missing values, and recognition of inconsistencies between variables. Additional categorization of fetal weight, pregnancy duration, census division, and cause of death were also undertaken as preliminary steps. All preparation and subsequent calculations were undertaken using PASW[1] Statistics 18 (SPSS Inc., Chicago, IL.).

As noted in the Chapter 3, each fetal weight was categorized in relation to its corresponding pregnancy duration. Reflecting the literature reviewed pertaining to fetal size assessment, the ultrasound based fetal weight standard determined by Hadlock et al was used to label stillbirths weighing less that the tenth percentile for their gestational

[1] PASW was a temporary name change of the well-known SPSS software

age as small for gestational age (SGA) and those above the ninetieth percentile as large for their gestational age (LGA) (Appendix D) (209). The specific mathematical equation underlying this growth curve was used in all the studies reviewed that compared population birth weight curves and ultrasound-based curves in relation to stillbirth risk (90,94,96,97). Although debate continues as to whether an ultrasound standard may be further improved by customization (210), the variables required to do so are largely unavailable from this dataset. Even so, the reviewed literature as a whole suggests that an ultrasound-derived standard is a reasonable means to assess fetal size and much improved over population-based birth weight curves (210). As this standard only measures fetal size up to forty weeks, any stillbirths occurring after this gestation were classified according to a Canadian birth weight standard (211), a reasonable alternative given that the major advantage of an ultrasound-derived growth curve appears to be the assessment of fetal size at preterm gestations (97-99). Pregnancy duration was more simply categorized by the clinical obstetrical definitions of preterm (<37 completed weeks), term (37 to 42 completed weeks), and post term (>42 completed weeks) (212).

Census divisions were also further categorized according to both Modified Beale Codes (MBC) and Revised Beale Codes (RBC). In considering the multiple definitions of rural, du Plessis et al. (213) described Modified Beale Codes (also known as Ehrensaft's codes) as a classification based on the work of Calvin Beale at the United States Department of Agriculture and adapted for Canadian census divisions by Philip Ehrensaft (214). This coding system allows assessment of the relationship that combined census metropolitan area proximity and local community size has with stillbirth risk.

Briefly, location of residence is categorized according to metropolitan and non-metropolitan regions, depending on whether or not the census division in which it is contained also contains a census metropolitan area. Non-metropolitan divisions are further sub-classified according to the size of their largest settlement and whether or not the division itself is adjacent to a metropolitan area. This classification is outlined in Table 4.1 (213,214).

TABLE 4.1 Modified Beale Codes

Metropolitan Regions

Major metropolitan:
Central and fringe census divisions (CDs) of urban settlements of 1 million or more people
Code 0 – Central CDs of urban settlements of 1 million or more people
Code 1 – Fringe CDs of urban settlements of 1 million or more people

Mid-sized metropolitan:
Code 2 - CDs containing urban settlements of 250,000 to 999,999 people

Smaller metropolitan:
Code 3 – CDs containing urban settlements of 50,000 to 249,999 people

Non- Metropolitan Regions

Non-metropolitan small city zone:
Non-metropolitan CDs containing urban settlements of 20,000-49,999 people
Code 4 – adjacent to a metropolitan area
Code 5 – not adjacent to a metropolitan area

Small town zone:
Non-metropolitan CDs containing urban settlements of 2,500 to 19,999 people
Code 6 – adjacent to a metropolitan area
Code 7 – not adjacent to a metropolitan area

Predominantly rural:
Non-metropolitan CDs containing no urban settlements (i.e., no places of 2,500 or more people)
Code 8 – adjacent to a metropolitan area
Code 9 – not adjacent to a metropolitan area

Northern hinterland:
Code 10 – CDs that are entirely or in major part north of the following parallels by region: Newfoundland, 50th; Quebec and Ontario, 49th; Manitoba, 53rd; Saskatchewan, Alberta, and British Columbia, 54th; and all of the Yukon, Northwest Territories, and Nunavut

Du Plessis also indicated that census divisions can be classified according to Revised Beale Code, a variant of the Modified Beale Code classification. Although initially developed to remedy issues of data sparseness that may occur with the multiple Modified Beale Codes, in the Saskatchewan context Revised Beale Codes allow a more generalized assessment of remoteness. As noted in the literature review, this aspect of a woman's place of residence may be more important than population size. Revised Beale codes are defined in Table 4.2 (215) and Appendix E provides the assignment of Modified and Revised Beale Coding for specific Saskatchewan census divisions.

TABLE 4.2 Revised Beale Codes

Code	Description	
0	Large Metro	Central and most populous census division of a CMA with a population greater than 1 million
1	Large Metro Fringe	Remaining census division(s) within or partially within a CMA with a population greater than 1 million
2	Medium Metro	Census division(s) containing, within, or partially within a CMA with a population between 250,000 and 999,999
3	Small Metro	Census division(s) containing, within or partially within a CMA/CA with a population between 50,000 and 249,999
4	Nonmetro-Adjacent	Census divisions that share a boundary with a CMA/CA and the CMA/CA has to have a population greater than 50,000
5	Nonmetro-Nonadjacent	Census divisions that do not share a boundary with a CMA/CA that has a population greater than 50,000

Cause of death, supplied as International Classification of Disease codes (ICD-9/ICD-10), was further categorized at the outset according to the fetal cause of death

classification employed by the Canadian Perinatal Surveillance System of the Public Health Agency of Canada (216). This classification system was selected for its epidemiological nature, its applicability to stillbirth data in ICD form, its comparability for cause of death analysis at the national level, and its broad categorization of outcomes that may have had a limited or uncertain diagnostic work up. The categories include congenital anomalies (ICD codes 740-759.9 or Q00-Q99), maternal complications of pregnancy (761 or P01), complications of placenta/cord/membranes (762 or P02), intrauterine hypoxia and birth asphyxia (768 or P20, P21) and unspecified (779.9 or P95, P96.9). As several cases had an alternate cause of death or no cause of death provided at all, two additional categories outside of those provided by the Perinatal Surveillance System were also created to classify these cases as "other" or "not stated" respectively. The detailed categories of ICD-10 can be found in Appendix F.

4.2 Descriptive Statistics

4.2.1 Late Stillbirth Characteristics

Efforts to describe late stillbirth characteristics were largely straightforward. Because the majority of variables pertaining to cases were categorical, most could only be examined as percentages (i.e. number of cases with the characteristics of interest divided by the total number of late stillbirths in the dataset multiplied by 100). Pregnancy duration and fetal weight were also in continuous form, allowing assessment of their mean, median, range, and standard deviation in addition to categorical percentages.

As Objective 1 was directed towards better understanding late Saskatchewan stillbirths over time and in different locations, Chi-square contingency testing between

stillbirth characteristics and both five year period and location was undertaken. Chi-square testing compares the expected counts of cells in a two way contingency table based on marginal probabilities (i.e. the number of cases across a particular column or row divided by the total number of subjects in the entire table). The row and column probabilities are multiplied to provide the probability that any given subject could be found within the cell corresponding to this particular row and column. Multiplying the cell probability by the total number of subjects in the table provides the expected number of subjects for that cell, which is then compared against the actual number and this difference as a percentage of the expected is summed for all cells in the table. This calculated Chi-square statistic is then examined against the Chi-square test distribution and statistical significance is determined as to whether or not the column proportions are substantially different for different rows and similarly, that the row proportions are different for different columns. If so, there is dependence between the rows and columns (i.e. the distribution of subjects over rows depends on which column they are in and vice versa). The major assumptions of Chi-square testing is that no more that 20% of the expected counts are less than 5 and that all expected counts are at least 1 (217).

Although Chi-square testing will indicate the statistical probability that there is an association between certain characteristics, it does not in itself indicate which rows and columns show association, the strength of their relationship, or if there is a linear component. Cramer's V statistic was assessed to measure the strength of the relationship overall between two variables if at least one was nominal (e.g. Modified Beale Code) and standardized residuals were examined for each cell to localize which cell or cells had counts that were far from the predicted values.

If the variables were ordinal, linear-by-linear association testing results (Mantel-Haenzel Chi-square test) were noted. This measure indicates that as one variable either increases or decreases, the other also changes in a linear fashion beyond what could be expected by chance alone (218). Mantel-Haenzel Chi-square testing is a much stronger test for determining associations between ordinal variables than Pearson's Chi-squared or likelihood ratio Chi squared (219). This result is limited in its interpretation as it provides no indication of the direction of the trend and, as such, Spearman's correlation coefficients were also calculated. As correlation coefficients are recognized as a poor way to assess strength of such relationships if the variables are discrete and unbalanced in their marginal totals, Spearman's correlation coefficient was relied on only to provide directionality to the trend, not the magnitude of the relationship (219).

If the variables were a combination of nominal and either continuous or ordinal with a scalar nature and a relatively large number of categories, eta was determined. This measure of association does not differentiate between linear and non-linear relationships and is always a positive value (220).

As indicated in Section 4.1, cause of death for each stillbirth was categorized according to groups used by the Canadian Perinatal Surveillance System. Proportionate mortality, the percentage of all cases in each category, was then described and Chi square testing was again used to determine differences in proportions for different time points and regions. Cause-specific incidence values were also determined and examined for trend using Poisson regression.

It should be noted that when the associations examined above included the variable of five year time period, cases occurring in 2007 were removed.

4.2.2 Incidence

National, provincial, and regional late stillbirth incidence was calculated as in Equation 4.1, examining one year periods for national or provincial incidence, and five-year, ten-year, or twenty-year periods for regional incidence (221). Although the outcome of stillbirth can be thought of as a binomial event and each pregnancy as a successive trial, suggesting a binomial distribution, rare events with a probability of less than 0.05 and more than twenty trials have outcome probabilities that approximate the Poisson distribution (222). As such, 95% confidence intervals for provincial and regional incidence were calculated by multiplying the standardized denominator of the incidence value (e.g. "per 1000") by upper and lower limit factors provided by Haenszel et al. for the calculation of confidence intervals for Poisson-distributed variables (Appendix G) (223). The numbers of Canadian cases and total births, however, were obviously much larger; as such the binomial distribution approximates the normal distribution and 95% confidence intervals for Canadian incidence were calculated by utilizing Equation 4.2, where p is the probability of stillbirth and n is the total number of deliveries (217). Once all incidence values had been determined, regional results were mapped using ArcGIS-10 software (Ersi, Redlands, CA) to provide visual distribution of the incidence throughout the province.

$$\text{Incidence} = \frac{\text{Number of late stillbirths per geographic area per time period}}{\text{Total number of births per geographic area per time period}} \qquad (4.1)$$

$$95\%\ \text{CI} = \text{Incidence} \pm 1.96\sqrt{p(1-p)/n} \qquad (4.2)$$

Confidence intervals were thought to be of value even though incidence values involved population-level data rather than a population sample with subsequent inference. They suggest whether observed differences could have arisen from chance under a similar set of influences or if they are more likely the result of true differences in influential factors (224).

Two possible concerns pertaining to the Equation 4.1 are worthy of mention. The denominator as stated would contain infants delivered before twenty-eight weeks in addition to those born later. These very premature births, however, comprise less than 1% of all births and would have minimal impact on incidence calculations (2,225). Secondly, in evaluating incidence among census divisions, the total number of births from available Statistics Canada data encompasses the calendar year from July 1 of one year to June 30 rather than January to December, as highlighted in Chapter 3 (182). This is also not likely to have considerable impact on the results given the reasons previously discussed in Section 3.2.2.3.

4.2.3 Trends

Poisson regression was also used to meet Objective 1 as well as Objective 3. Poisson regression models are part of the larger family of generalized linear models (GLM). GLMs are models that link explanatory variables with an outcome variable through a function that can make otherwise non-linear relationships linear. This is typically done by taking the linear predictors represented as η_i and equating it to the mean outcome μ_i through the presence of the linking function g in the format $g(\mu_i) = \eta_i$. In the situation of Poisson regression this linking function is the log of the count and thus is referred to as a log link function. Specifically for Poisson regression, the model can be

written as $\log(\mu_i) = x'_i\beta$, where μ_i is the expected count, x_i' is a vector of explanatory characteristics of interest, and β is a summary of their parameter estimates (174,180).

As mentioned in the assessment of confidence intervals, the Poisson distribution is used to model count data as the outcome variable, typically for rare events. It is commonly used to model true rates (e.g. events/person-years) but can also be used to assess counts over space or some other index of size (174). An important assumption of the Poisson distribution is that of equality between the mean and the variance. Should the variance of the outcome variable exceed its mean, it is considered to be overdispersed; similarly if the variance is less than the mean, the data is underdispersed. Over or underdispersion is problematic as it will lead to exaggerated or understated significance respectively (226,227). This assumption can typically be evaluated from statistical output by examining the ratio of the deviance to the degrees of freedom (175). Remedies to the more typical overdispersion situation include improving the model to decrease the variance, using a negative binomial model, or adjusting the scale parameter of the variance which otherwise has a value of one (180,226,227).

Frequently used as a method to assess trends in counts by including time as a factor of interest, Poisson regression was applied to the assessment of trends in stillbirth counts for various regions. As the outcome variable is count, an offset variable of subjects at risk, that of all deliveries for the time period, was employed and the Pearson Chi squared scale factor was adjusted as needed for over/underdispersion.

4.3 Log-linear Modeling

4.3.1 Theoretical Basics

To meet Objective 2, log-linear modeling, a form of Poisson regression, was undertaken. This statistical technique has the specific purpose of examining the relationship of variables in terms of their interactions with each other. No one variable is viewed as either an outcome or causal factor, but it is combinations of factors that are of interest in regard to their count. As described in Section 4.2.1, expected associations between two categorical factors can be assessed from their marginal probabilities and dependence between the rows and columns can be evaluated. In a similar fashion, log-linear modeling allows extension of the tables beyond two factors into three or more dimensions, allowing assessment of higher order interactions between multiple characteristics.

Similar to the more typical form of Poisson regression, log-linear models are part of the larger family of generalized linear models. The link function is again the log of the count but rather than modeling the number of specific outcome events, the number of subjects with the specific combination of variables under study is used. The degree of excess or inadequacy of the observed count compared to the expected is indicated by the parameter lambda (λ) and can be displayed in the following model for a simple two dimensional table (228):

$$\ln F_{ij} = \mu + \lambda_i + \lambda_j + \lambda_{ij} \qquad (4.3)$$

where μ = a baseline "overall effect" (i.e. a reference group) (175) or the average of the logs of all individual cell frequencies (228)

λ_i = additional influence of column i

λ_j = additional influence of row j

λ_{ij} = additional influence of combining column i and row j

ln F_{ij} = the natural log of the count in the cell corresponding to column i and row j

This model is considered to be saturated as it contains all possible interactions of its main effects and will therefore fit the data perfectly. The question arises, however, as to whether or not the data could be adequately modeled without the interaction, improving parsimony. Therefore, adequacy of fit for the unsaturated model is compared to that of the saturated model, evaluated by calculation of the Pearson's chi-square value or the likelihood ratio (175).

Lambda values are calculated by PASW for main effects as well as the interactions terms. The main effects parameters are generally not interpreted as they simply reflect the count for a particular row or column characteristic above that of the designated baseline (i.e. reference group or mean log of all frequencies) (228). Interactions of the main effects are much more useful. When the final row and column are designated for the absence of the characteristics of interest, exponentiation of the interaction lambda value will produce an odds ratio comparing the counts of subjects with the specified effect against the count of subjects without that effect (i.e. the odds) in the presence of the other factor in the interaction and in its absence (229). It should be noted that this interpretation applies to the PASW command series "analyze" and then "loglinear" followed by "general" which generates estimates in relation to reference categories. Were "model selection" utilized as the third step, estimates would be generated in relation to the overall average of the logs of the individual cell counts and

would require further minor manipulation to arrive at the same conclusions (219). Further interpretation of lambda parameters will be provided in Chapter 5.

4.3.2 Log-linear Model Building

A basic assumption of log-linear modeling is that of well populated tables (230). In preliminary exploration of the data, it became evident that cross-classification of multiple variables quickly led to many expected cell counts of less than five, indicating data sparseness and potential for biased results (174). Subsequently, the determination of characteristics most likely to interact with others was undertaken by assessing them in multiple simple two factor log-linear models, similar to univariate analysis as a preliminary step in other common model building strategies. To evaluate combinations of variables for adequacy of expected counts, each variable was progressively cross-classified on the others until more than 20% of cells had expected counts less than five. Thus multiple smaller models were generated, examining relationships between a smaller number of factors; this provided a sufficient number of observations to avoid inaccuracy while allowing the assessment of relationships at increased depth.

The model building strategy used for each group of variables was based on an example provided by Zelterman (175). All effects for each order were added progressively and their goodness of fit was assessed. Adequacy of fit was determined by examining the significance of the likelihood ratio; a model was deemed to be sufficient when the p-value was greater than 0.05, suggesting that the fit of the current model was not statistically different than the perfectly fitting saturated model. In the interest of parsimony, the strength of effect was then evaluated for each individual term in the highest order by removing all terms in that order and reintroducing them individually,

noting their effect on the likelihood ratio and degrees of freedom. Once evaluated and ranked, the terms were re-entered into the model in the order of decreasing effect until the model showed adequate fit and all terms of major influence were included. All models were hierarchical, in which lower order terms included in higher order terms were also included individually. Models are displayed according to their generating class, typical notation for hierarchical log-linear models in which individual variables are shown only at their highest order.

It should be noted that in all log-linear analysis, SPSS's default addition of 0.5 to each cell was reset to zero. This addition, while avoiding problems with model convergence in sparse tables, reduces power (174) and its removal has been recommended (230).

4.4 Area-level Analysis

4.4.1 Analytical Approach

Information compiled from three census time points as outlined in Chapter 3 was initially recognized to represent repeated measurements on eighteen subjects (i.e. census divisions) rather than fifty-four independent subjects. It was expected that this would require compensation for correlations in the outcome between the first, second, and third measurements of each census division (i.e. the within-subjects variation). As the outcome variable was not normally distributed, indicating that a random effects model was not appropriate, GEE was initially considered as a reasonable methodology to analyze this information as mentioned in Chapter 3 (179). GEE is an extension of the generalized linear model that allows for repeated measurement and permits modeling of outcomes that are not normally distributed, such as count. It is frequently used to

analyze repeated measures as it can provide consistent estimates using the robust version of the technique even if the relationship between the correlated observations is not well understood. However, this was recognized to be problematic as the robust estimator of the within-subject variance generates a substantial risk of Type 1 error with small sample sizes and it has been suggested that the model based estimator be used instead with sample sizes less than twenty (181,231). On examination of the outcome (incidence) across measurements, however, correlation values were found to be -0.24, 0.42, 0.13 indicating relatively small and sometimes negative associations. As GEE is based on positive correlations, the work of Hanley et al suggests that the best approach in the situation of negative values, at least in the context of binary data, appears to be to assume an independent correlation structure (232); little guidance is otherwise available from the literature. Thus the use of a model based estimator, with an independent covariance structure essentially reverted the methodology to a generalized linear model with a Poisson distribution. Using this technique, all observations were then viewed as independent (n = 54) and a potential increase in the possibility of Type 1 error due to the unaccounted correlation will be considered in the interpretation of results.

4.4.2 Variable Formatting and Selection

At the outset, the variables of interest were individually examined both in scatterplot against stillbirth incidence and in univariate analysis of categorical and continuous forms to determine their most appropriate format. Categories were derived from quartiles, as suggested by Hosmer and Lemeshow in the context of logistic regression, with small adjustments for practical interpretation (e.g. a cut point of 34.12% may have been rounded to 35%) (233). Each variable was examined in continuous and

categorical forms in a generalized linear model with a Poisson distribution; adjacent categories were collapsed if estimates and confidence intervals appeared relatively similar. The Pearson chi-square scale factor was applied to all models to reduce complications of over/underdispersion. Those variables with p-values less than 0.25 were retained for further assessment in the format with the lowest p-value. As a high degree of correlation was expected given the similar nature of many of the variables, Spearman correlation was assessed; values of 0.7 or higher were noted and these combinations were examined separately to determine if their combined presence in a simple bivariable model resulted in larger standard errors and increased p-values. If present, substantial collinearity was suggested. In this situation, it was recognized that both variables could not be utilized and the one with the smaller p-value was selected for further assessment.

4.4.3 Model Building

A stepwise model building strategy was applied. Variables with p-values less than 0.25 were entered individually in order of decreasing significance and retained if p-values remained less than 0.10 at each entry. Once no additional variables could be introduced, any variables previously retained for their borderline significant nature (p-values of 0.05 to 0.10) were progressively removed from the model beginning with the least significant; all variables not included were individually re-tried at a 0.05 level of acceptability after each removal. Interaction between all main effects in the model and with those not included as main effects were considered; this yielded several statistically significant coefficients for a variety of combinations of variables. These associations were viewed skeptically; however, as sparse data can produce biased estimates (218).

Following this, the non-significant variables were again individually introduced and the lambda values were reassessed in order to evaluate confounding. Typically a change of 20% or greater suggested that the new variable was a confounder and should be added to the model. Several potential confounders were added as a group and in doing so, many of main effects were rendered non-significant at a level of 0.05. At this point, any variables still suggesting significance after adjustment (p-values approximating 0.10 or lower) were retained in the model. The emerging main effects were again assessed for their interaction with other main effects and with previously excluded variables.

In developing an area level model, it is important to recognize the complications introduced by its ecological nature. Model building in ecological research is often complicated by confounding and interaction that are difficult to control for (234). Research literature recognizes that control of confounding in ecological investigation can be attempted by either adjustment for covariates in the regression model or by adjusting both the outcome variable and each independent variable by all other covariates of interest and then performing the regression. Although the latter appears to have somewhat greater efficiency, it is cumbersome to perform when multiple covariates are present, stratified values may not be available to perform the adjustment, and not all variables are amenable to rate standardization (234). As all three of these obstacles impeded the more effective form of control in the model building process, attempts to adjust for confounding beyond simple addition of the covariates to the model were not made.

CHAPTER 5:

5.0 RESULTS

This chapter will present the results of the data and methodology outlined in Chapters 3 and 4. In keeping with the stated objectives, it will initially provide the descriptive aspects of late stillbirth, indications of stillbirth characteristics that are often present simultaneously, and the characteristics of regions with increased stillbirth incidence.

5.1 Objective 1

5.1.1 Late Stillbirth Characteristics

5.1.1.1 Descriptions

In the twenty-one years spanning 1987 to 2007, there were 1119 late stillbirths among Saskatchewan women. A single case was removed from the descriptive and log-linear analysis for inconsistency in its characteristics. The basic descriptive characteristics outlined in Table 5.1 were determined from the remaining 1118 cases.

5.1.1.2 Characteristics in Relation to Time and Region

Given that Objective 1 focuses on differences according to time and region, the characteristics in Table 5.1 were also examined for associations according to five-year period and location. Results are presented in Table 5.2

TABLE 5.1: Late stillbirth maternal and pregnancy characteristics, 1987 to 2007

Maternal Characteristics	Categories	Respective proportions
Maternal age	≥ 35 years, <35 years	12.8%, 87.2%
Parity (previous deliveries)	None, 1-2, ≥3	36.1%, 42.5%, 21.4%
Registered Indian Status	Yes, No	26.8%, 73.2%
Previous stillbirth	Yes, No	5.6%, 94.4%
Residential Modified Beale Code	3, 4, 6, 7, 8, 9, 10, not stated	40.5%, 12.0%, 9.1%, 24.6%, <1%, 2.9%, 4.7%, 5.8%
Pregnancy Characteristics		
Time period	1987-1991, 1992-1996, 1997-2001, 2002-2006[1]	28.4%, 26.3%, 23.0%, 22.2%
Fetal gender	Male, Female	52.1%, 47.8%[2]
Pregnancy duration	Preterm, Term, Post Term	54.0%, 44.4%, 1.6%
Size for gestational age	Small, Appropriate, Large	44.6%, 46.2%, 9.2%
Plurality (twin, triplet, etc.)	Yes, No	6.8%, 93.2%
Additional Continuous Variables	Mean, standard error	Median
Fetal weight	2354 g, 54.3 g	2340 g
Pregnancy duration in weeks	35.5 weeks, 3.9 weeks	36.0 weeks

[1]Cases from 2007 removed

[2]Total does not equal 100% as one case had no gender indicated

Chi square testing indicated that late stillbirths differed for maternal age, Aboriginal status, and fetal size for gestation according to time period. When both variables were considered as ordinal and the more powerful linear-by-linear assessment was applied, there also appeared to be a statistically significant trend for these characteristics, and quite possibly Revised Beale Code, over time. The positive Spearman's correlation indicated an increasing direction for all four. Similarly, examination of late stillbirths by Revised Beale Code also indicated that losses differed in Aboriginal status, associated parity, plurality, and fetal size by distance from a metropolitan center. Again based on the associated Spearman correlation coefficients,

Aboriginality, parity, and fetal size indicated an increase while plurality showed a decrease. Even after Bonferroni correction is applied to the significance cut point to compensate for multiple endpoint testing (e.g. 0.05/9 categories = 0.006), several of these associations, those in bold in Table 5.2, remain.

TABLE 5.2: Selected associations between characteristics of late stillbirths by time period and region

Associated variables		**Chi square p-value**	**Linear-by linear association p-value**	**Spearman's correlation coefficient (p-value)**
Chronological five year periods[1] (ordinal) with:	Maternal age	0.02	0.02	0.07 (0.02)
	Aboriginal	**<0.001**	**<0.001**	**0.15 (<0.001)**
	Revised Beale Codes	0.13	0.05	0.07 (0.03)
	Fetal size for gestation	0.04	**0.001**	0.06 (0.05)
	Duration	0.10	0.72	N/A
Increasing Revised Beale Codes (ordinal) with:	**Aboriginal**	**<0.001**	**<0.001**	**0.21 (<0.001)**
	Parity	**<0.001**	**<0.001**	**0.11 (<0.001)**
	Pregnancy type (singleton or multiple)	**0.005**	**0.003**	**-0.09 (0.003)**
	Fetal size for gestation	0.15	0.04	0.06 (0.07)
Modified Beale Codes (nominal) with :				**Cramer's V (p-value)**
	Aboriginal	**<0.001**	N/A	**0.28 (0.003)**
	Parity	**0.003**	N/A	**0.12 (<0.001)**
	Five year periods	0.08	N/A	N/A

[1]Cases for 2007 removed for this variable
[2]Bold indicates significance even after Bonferroni correction applied

These characteristics were again examined as Modified Beale Codes which allows the association of remoteness to be stratified by community size. Aboriginality and parity again were both noted to differ by categories. Although the overall strength of the associations are weak to moderate (235) as indicated by the Cramer's V statistics,

examination of the individual cells suggested that strong isolated associations exist, namely that stillbirths occurring in MBC 3 areas are much less likely to be associated with high levels of parity (≥ 3 previous deliveries) than expected (standardized residual = -2.9). Similarly, Aboriginality was also noted to be much more common among losses occurring in MBC 10 (standardized residual = 5.6) and much less common in the MBC 3 (standardized residual -4.5). Non-Aboriginality shows an inversion of this with MBC 3 and 10 standardized residuals of 2.6 and -3.2 respectively.

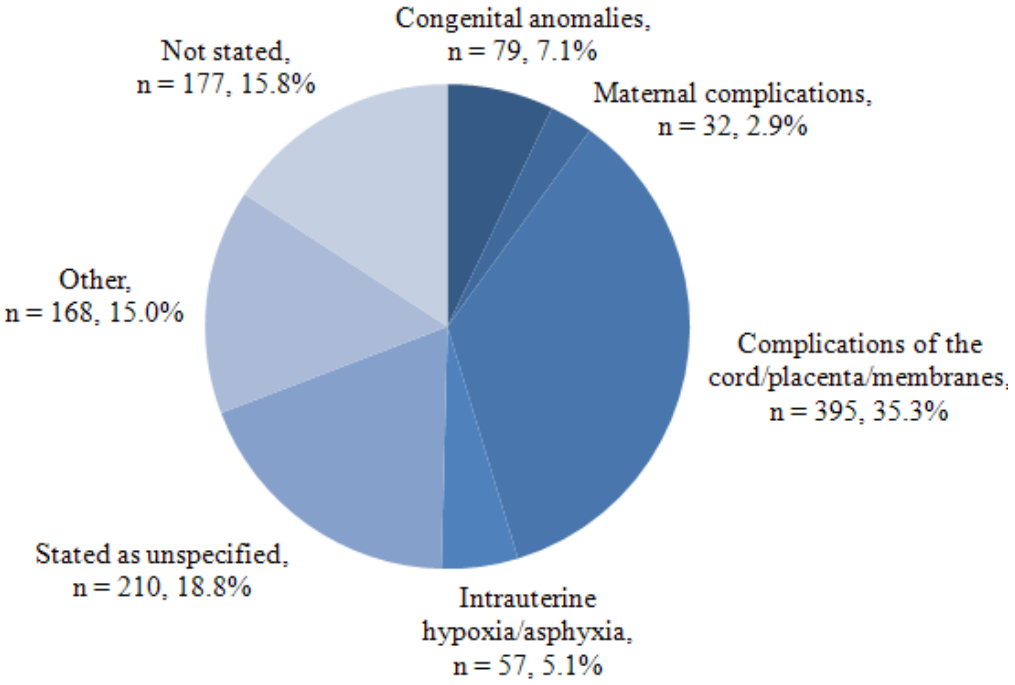
Included in Table 5.2 is one other association of interest, that of five year period and pregnancy duration. Although not statistically significant for Chi-square in its overall association ($p = 0.10$) or linear-by-linear association, a standardized residual of 2.2 was noted in isolation for post term stillbirth and the time period of 1987 to 1991. When this cross tabulation was collapsed into a two by two format (post term and non post term versus time period 1 and time periods 2,3 and 4 combined), Chi-square testing indicated a statistically significant association ($p = 0.01$).

5.1.1.3 Cause of Death

5.1.1.3.1 Proportionate Mortality

As noted in Chapter 4, cause of stillbirth was classified according to categories based on those utilized by the Perinatal Surveillance System of the Public Health Agency of Canada in the examination of fetal loss. Results for the entire twenty-one year period are provided in Figure 5.1 and a similar breakdown is available by census division in Appendix H.

FIGURE 5.1. Cause of death among late stillbirths by count and percentage, 1987 to 2007



These proportions were examined as to their consistency over time. Utilizing individual years, eta was determined to be 0.20, suggesting there is a weak to moderate relationship (235) between a certain year or consecutive years and specific causes of death although data was too sparse for Chi-square testing. To better quantify this, five year periods were examined in relation to causes of death with counts, proportions, and standardized residuals as displayed in Table 5.3. Chi-square testing with this categorization yielded a statistically significant association between cause of death and five-year time period (p-value <0.001). Large standardized residuals were seen in the category indicating no stated cause of death and isolated differences were also noted at different times for proportions due to membrane, cord, and placenta complications; non-specific causes; or other causes. When cases with no stated cause of death were

removed from the analysis, the significance of the Chi-squared assessment disappeared ($p = 0.28$).

In assessing whether or not the proportions of specific causes were changing with time, Spearman's correlation values suggested an increasing proportion of losses were indicated as unspecified and a decreasing proportion as unstated (linear-by-linear association p-value = 0.002, Spearman's correlation 0.094; linear-by-linear association p-value = <0.001, Spearman's correlation -0.196, respectively). These remain significant even after correction for examination of multiple endpoints (Bonferroni correction = 0.05/7 = 0.007).

Data was again too sparse to examine specific cause of death by Modified Beale Codes and as such these were collapsed into Revised Beale format. Overall, Chi-square testing did not suggest an association between specific causes of death and approximate distance from a major metropolitan center ($p = 0.72$). Examining specific causes of death, maternal complications had the only change in proportion of interest at borderline significance, a small reduction with increasing distance (Spearman correlation = -0.06, p-value = 0.06, proportions = 4.2%, 3.0%, 1.8%). This result was, however, far from the Bonferroni correction level of significance ($p = 0.007$).

TABLE 5.3 Cross tabulation of causes of late stillbirth, 1987 to 2006, and five year period

Years		Congenital anomalies	Maternal complica -tions	Membranes/ cord/ placenta	Hypoxia/ asphyxia	Stated as unspecified	Other	Not stated
1987-1991	Count	23	7	114	23	49	50	34
	Expected Count	20.4	9.1	105.8	15.9	57	43.7	48.2
	% within period	7.7%	2.3%	38.0%	7.7%	16.3%	16.7%	11.3%
	Standardized Residual	0.6	-0.7	0.8	1.8	-1.1	1.0	-2.0
1992-1996	Count	10	10	64	7	39	20	129
	Expected Count	19	8.4	98.4	14.8	53	40.6	44.8
	% within period	3.6%	3.6%	22.9%	2.5%	14.0%	7.2%	46.2%
	Standardized Residual	-2.1	0.5	**-3.5**	-2.0	-1.9	**-3.2**	**12.6**
1997-2001	Count	19	10	99	17	54	41	x
	Expected Count	16.6	7.4	86	12.9	46.4	35.5	39.2
	% within period	7.8%	4.1%	40.6%	7.0%	22.1%	16.8%	1.6%
	Standardized Residual	0.6	1.0	1.4	1.1	1.1	0.9	**-5.6**
2002-2006	Count	20	5	96	9	59	43	x
	Expected Count	16	7.1	82.8	12.4	44.6	34.2	37.8
	% within period	8.5%	2.1%	40.9%	3.8%	25.1%	18.3%	1.3%
	Standardized Residual	1.0	-0.8	1.4	-1.0	**2.1**	1.5	**-5.7**

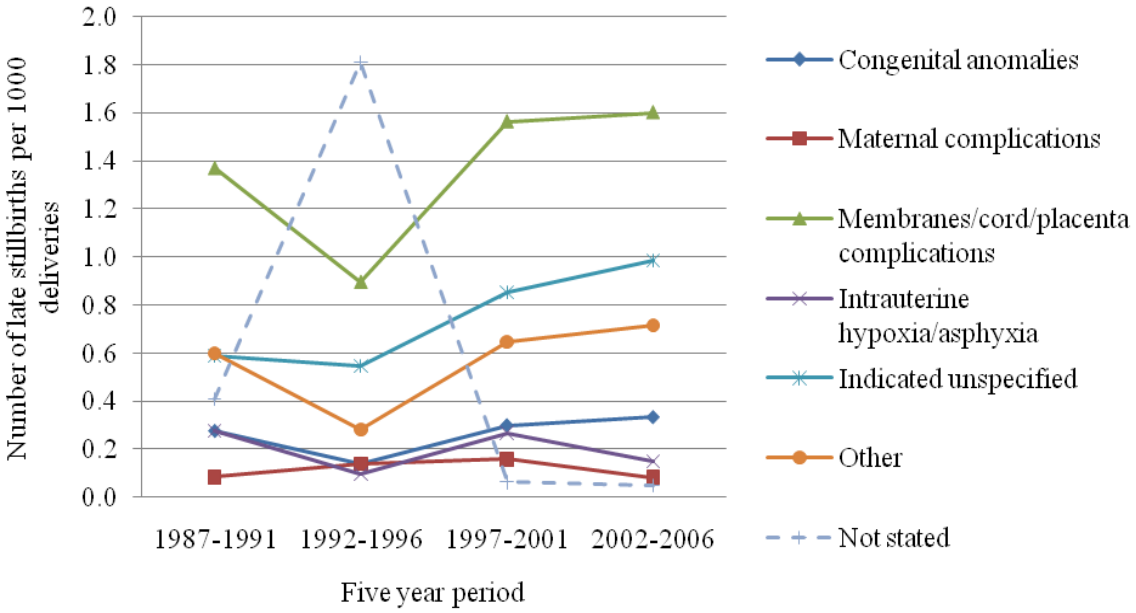
[1]x = values suppressed as cell count <5

5.1.1.3.2 Cause-specific Mortality

The cause-specific incidence was also calculated and graphed in Figure 5.2. Poisson regression, applying time period as a continuous predictor, was utilized to examine each cause-specific incidence separately; results indicated a statistically significant increasing trend for the incidence of losses stated as unspecified (p-value =

0.001). This finding remained significant when multiple testing was accounted for (α = 0.008).

FIGURE 5.2. Late stillbirth incidence by causes of death, 5 year periods, 1987 to 2006



5.1.2 Incidence

5.1.2.1. National and Provincial Incidence

In the twenty-one years spanning 1987 to 2007, there were 1119 late stillbirths among Saskatchewan women with an overall incidence of 3.86 per 1000 births (95% CI 3.63-4.09). This value represents a statistically significant difference from the corresponding twenty-one year incidence for the remainder of Canada at 3.43 (95% CI 3.39-3.47). Annual values for both Saskatchewan and the remainder of Canada are available in Table 5.4, and on initial inspection it appears that the Saskatchewan

incidence does not decline as the Canadian incidence does. Additional information on the numbers of cases and births per year is found in Appendix I

TABLE 5.4 Late stillbirth incidence per 1000 births, Saskatchewan and Canada[1], 1987-2007

Year	Stillbirth incidence		Stillbirth incidence	
	SK	95% CI[2]	Canada	95% CI[2]
1987	3.77	2.96, 4.79	4.27	4.05, 4.49
1988	3.18	2.36, 4.26	3.79	3.59, 3.99
1990	3.68	2.83, 3.68	3.83	3.63, 4.03
1991	4.01	3.09, 5.21	3.46	3.28, 3.64
1992	4.00	3.08, 5.20	3.78	3.58, 3.98
1993	3.81	2.93, 4.95	3.64	3.44, 3.84
1994	4.60	3.61, 5.84	3.55	3.35, 3.75
1995	4.19	3.23, 5.45	3.49	3.29, 3.69
1996	2.90	2.07, 3.94	3.39	3.19, 3.59
1997	3.42	2.49, 4.58	3.36	3.16, 3.56
1998	3.61	2.63, 4.84	3.14	2.94, 3.34
1999	3.85	2.86, 5.08	3.21	3.01, 3.41
2000	4.53	3.49, 5.89	3.22	3.02, 3.42
2001	3.87	2.82, 5.19	3.28	3.08, 3.48
2002	4.81	3.70, 6.25	3.12	2.92, 3.32
2003	3.97	2.89, 5.32	3.05	2.85, 3.25
2004	4.11	3.05, 5.43	2.88	2.70, 3.06
2005	3.43	2.45, 4.66	2.95	2.77, 3.13
2006	3.26	2.33, 4.43	3.03	2.85, 3.21
2007	5.01	3.86, 6.51	3.18	3.00, 3.36
Overall	**3.86**	3.63, 4.09	**3.43**	3.39, 3.47

[1] Canadian data does not include Saskatchewan

[2] A Poisson distribution is assumed for SK CI's; Canadian CI's assume a normal distribution

Poisson regression was used to more closely examine the association between place of residence (Saskatchewan or Canada, excluding Saskatchewan) and time on incidence. Initially the test of model effects for region and year (continuous) had estimated relative risks of 0.895 ($p = 0.013$) and 0.985 ($p = <0.001$) suggesting that

overall the Canadian incidence is 10.5% lower than that of Saskatchewan and that, on average, overall incidence decreases by 1.5% annually. The introduction of an interaction term between region and time in this format was statistically significant, indicating that these estimates are not reliable for all years and regions. Unfortunately with the addition of the interaction term, the model estimates appeared unstable and could not be confidently interpreted.

To further examine the aspect of interaction the data was then re-analyzed using both variables and their interaction as categorical; parameter estimates are presented in Table 5.5. Difference between regions is again suggested as Saskatchewan's risk was 58% higher than that of the remainder of Canada during the reference year, 2007. The significant interaction with time (model effect p-value = 0.009), however, again warns of substantial inconsistency in this difference according to year.

TABLE 5.5 Parameter estimates for Poisson regression assessment of trend

	Lambda [s.e.(Lambda)] $\hat{\lambda}[s.e(\hat{\lambda})]$	**RR**	**95% CI**	**p-value**
Region				
SK	0.456 (0.132)	1.58	1.22, 2.04	0.0010
Canada	Reference			
Year				
1987	0.29 (0.039)	1.34	1.25, 1.45	<0.001
1988	0.18 (0.039)	1.19	1.11, 1.29	<0.001
1989	0.24 (0.038)	1.27	1.18, 1.37	<0.001
1990	0.19 (0.039)	1.21	1.12, 1.30	<0.001
1991	0.084 (0.040)	1.09	1.01, 1.18	0.03
1992	0.17 (0.039)	1.19	1.10, 1.28	<0.001
1993	0.14 (0.039)	1.15	1.06, 1.24	0.001
1994	0.11 (0.040)	1.12	1.03, 1.21	0.005
1995	0.094 (0.040)	1.10	1.01, 1.10	0.02
1996	0.065 (0.041)	1.07	0.99, 1.16	0.11
1997	0.055 (0.041)	1.06	0.97, 1.15	0.18
1998	-0.011 (0.042)	0.99	0.91, 1.07	0.79

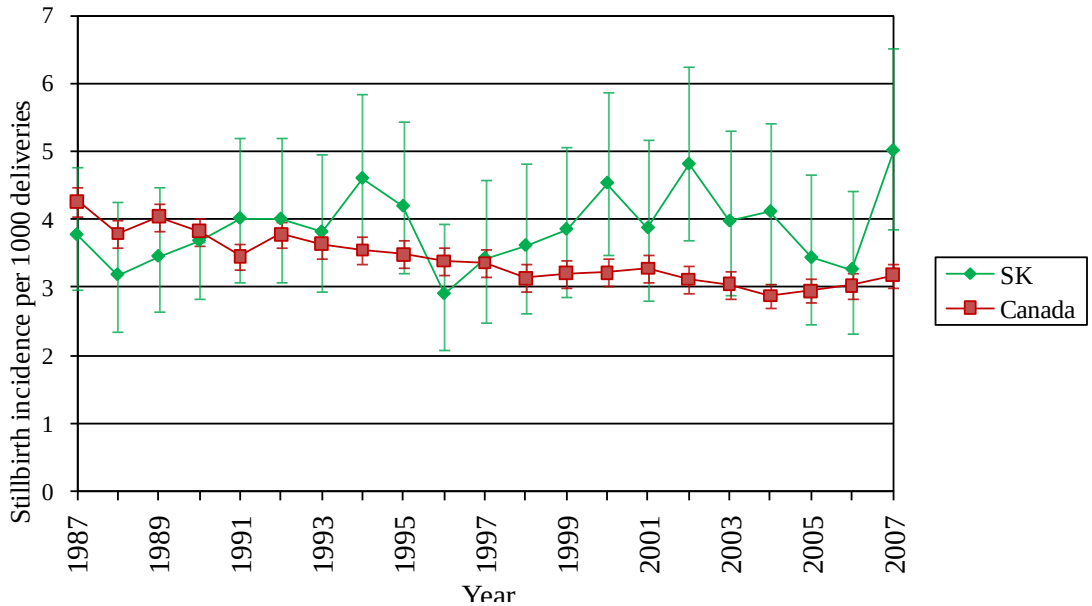
1999	0.011 (0.042)	1.01	0.93, 1.10	0.79
2000	0.014 (0.042)	1.01	0.93, 1.10	0.73
2001	0.031 (0.042)	1.03	0.95, 1.12	0.46
2002	-0.019 (0.043)	0.98	0.90, 1.07	0.66
2003	-0.039 (0.043)	0.96	0.88, 1.05	0.36
2004	-0.099 (0.043)	0.91	0.83, 0.99	0.02
2005	-0.074 (0.043)	0.93	0.85, 1.01	0.08
2006	-0.047 (0.042)	0.95	0.88, 1.04	0.27
2007	Reference			
Interaction[1]				
1987*SK	-0.58 (0.18)	0.56	0.39, 0.80	<0.001
1988*SK	-0.63 (0.19)	0.53	0.36, 0.78	<0.001
1989*SK	-0.61 (0.19)	0.54	0.37, 0.78	<0.001
1990*SK	-0.49 (0.19)	0.61	0.42, 0.88	0.01
1991*SK	-0.31 (0.18)	0.74	0.51, 1.06	0.10
1992*SK	-0.40 (0.19)	0.67	0.47, 0.97	0.03
1993*SK	-0.41 (0.19)	0.66	0.46, 0.96	0.03
1994*SK	-0.20 (0.18)	0.82	0.57, 1.18	0.29
1995*SK	-0.27 (0.19)	0.76	0.53, 1.10	0.15
1996*SK	-0.61 (0.21)	0.54	0.36, 0.82	0.00
1997*SK	-0.44 (0.20)	0.65	0.44, 0.96	0.03
1998*SK	-0.32 (0.20)	0.73	0.49, 1.08	0.11
1999*SK	-0.27 (0.20)	0.76	0.52, 1.12	0.16
2000*SK	-0.11 (0.19)	0.89	0.61, 1.29	0.54
2001*SK	-0.29 (0.20)	0.75	0.51, 1.11	0.15
2002*SK	-0.02 (0.19)	0.98	0.68, 1.42	0.91
2003*SK	-0.19 (0.20)	0.82	0.56, 1.22	0.33
2004*SK	-0.10 (0.20)	0.91	0.62, 1.33	0.61
2005*SK	-0.30 (0.21)	0.74	0.49, 1.11	0.14
2006*SK	-0.38 (0.21)	0.68	0.45, 1.03	0.07

[1]Reference category: Canada (excluding SK), 2007

Evaluating these differences, examination of the gap in incidence between Saskatchewan and Canada was then undertaken across the years. Examining risk ratios for the interaction terms, it is apparent that all are less than one, indicating that elevations in Saskatchewan stillbirth risk above that of the rest of Canada were never greater than

in 2007, the reference year. As the relative risk values for the interactions compare the relative risk of late stillbirth in Saskatchewan to Canada for specific years against the corresponding relative risk in 2007, values that are close to one indicate a similar regional gap in incidence between years. Years with interaction values that are approximately 0.65 indicate that their specific relative risk value for regions has dropped to 65% of the reference year and have essentially no gap between regions (e.g. SK*1997: RR = 1.58*.65 = 1.03). Those years with interaction relative risk values less than 0.65 will have regional relative risk values less than 1, suggesting that Saskatchewan has a lower risk than the rest of Canada for that year. This result can be visualized in Figure 5.3.

FIGURE 5.3 Late stillbirth incidence 1987 to 2007, Saskatchewan and Canada



[1]Error bars for both Canada and SK represent 95% confidence intervals (CI)
[2]Canadian CI calculation assumes a normal distribution of the incidence while Saskatchewan assumes a Poisson distribution
[3]Canadian calculations do not include Saskatchewan

Interpreting this interaction another way, the effect of time on stillbirth incidence is not the same for both Saskatchewan and the rest of Canada. Although the model effect p-value of 0.26 suggests that time is not an important predictor over all, the interaction highlights the need to better assess its influence within each specific region; thus time was used to model incidence for Saskatchewan and Canada separately. When the data was stratified, the simple univariate relationship between stillbirth rate and individual year for the remainder of Canada was strongly significant (model effect p-value = <0.001), even if Bonferroni correction is applied to the significance cut-point to compensate for multiple testing in two groups (i.e. 0.05/2 = 0.025) As would be expected, values were statistically significantly higher in earlier years and not statistically different as the reference year approached, although a general decline in estimates could be appreciated across all years. Re-examined as a continuous variable, a relative risk of 0.984 (p-value <0.001) was determined, again suggesting an approximate annual decrease of 1.5%.

Looking at the Saskatchewan data, time in categorical form was not a statistically significant predictor overall (model effect p-value = 0.48), and although some of the individual years had incidence values that were statistically significantly different from the 2007 incidence, there was no discernable pattern among them. When considered as a continuous variable, time was again non-significant (p = 0.15) indicating no recognizable directional change in incidence over time. The detailed results of the stratified analysis are available in Appendix J.

5.1.2.2 Regional Incidence

5.1.2.2.1 Incidence by Census Division

To assess regional variation, incidence was further examined within the province's eighteen census divisions. As a great deal of variability due to low cases numbers was seen within certain year-division combinations, five year incidence was assessed rather than annual incidence and is presented in Table 5.6. Stillbirth counts per five year period ranged from 0 to 70 per census division and their values, as well as those of the corresponding live births used in incidence calculations, can be found in Appendix K. The overall twenty year incidence was also mapped in Figure 5.4 with approximate total number of stillbirths indicated to provide context for these values. Presented in Table 5.7, Poisson regression suggested that a statistically significant difference in this incidence exists between census divisions 9, 10, 15, 16, and the reference census division, 11. Differences of borderline significance were also seen for divisions 6 and 17. Five year period again was not a statistically significant predictor although a number of regions did experience isolated changes of 25% or more over the two decades as also indicated in Figure 5.4. The significance values for tests of overall model effect for division and time period were 0.008 and 0.29 respectively.

TABLE 5.6 Late stillbirth incidence per 1000 births by census division and five year period

Division	1987-91	95%CI	1992-96	95%CI	1997-01	95%CI	2002-06	95%CI	Overall	95%CI
1	**2.96**	1.19, 6.09	**5.03**	2.51, 9.00	**4.15**	1.79, 8.17	**4.52**	1.95, 8.91	**4.12**	2.87, 5.73
2	**2.59**	0.70, 6.63	**4.80**	1.76, 12.28	**3.66**	1.19, 8.54	**3.83**	1.04, 9.81	**3.65**	2.16, 5.77
3	**1.66**	0.34, 4.85	**1.12**	0.03, 6.23	**5.87**	1.90, 13.68	**3.27**	0.67, 9.54	**2.65**	1.22, 5.04
4	**1.09**	0.03, 6.08	**1.33**	0.03, 7.40	**4.83**	1.31, 12.36	**0.00**	0.00, 5.58	**1.77**	0.57, 4.12
5	**2.12**	0.69, 4.95	**4.23**	1.82, 8.34	**6.35**	3.05, 11.68	**5.32**	2.29, 10.49	**4.23**	2.86, 6.05
6	**3.85**	3.02, 4.89	**4.45**	3.495.69	**3.79**	2.81, 5.00	**2.87**	2.00, 3.99	**3.78**	3.31, 4.32
7	**1.33**	0.43, 3.10	**3.92**	2.03, 6.87	**3.54**	1.62, 6.72	**2.98**	1.20, 6.14	**2.82**	1.93, 3.98
8	**3.10**	1.24, 6.38	**1.71**	0.35, 5.00	**3.69**	1.35, 9.45	**3.26**	1.06, 7.60	**2.93**	1.81, 4.48
9	**3.76**	1.80, 6.91	**5.34**	2.67, 9.56	**4.36**	1.88, 8.60	**9.70**	5.75, 15.33	**5.59**	4.11, 7.43
10	**6.31**	2.89, 11.98	**2.64**	0.54, 7.70	**3.92**	1.07, 10.03	**8.23**	3.55, 16.21	**5.27**	3.38, 7.85
11	**2.79**	2.13, 3.65	**3.54**	2.73, 4.61	**3.30**	2.45, 4.35	**2.87**	0.21, 3.87	**3.12**	2.71, 3.59
12	**4.40**	1.90, 8.66	**5.64**	2.4311.1	**1.44**	0.30, 4.21	**4.15**	1.34, 9.67	**3.95**	2.50, 5.92
13	**3.58**	1.54, 7.06	**4.15**	1.678.56	**3.28**	1.06, 7.63	**2.98**	0.81, 7.62	**3.53**	2.27, 5.27
14	**5.53**	3.22, 8.85	**2.75**	1.10, 5.67	**1.74**	0.47, 4.45	**2.83**	1.04 7.26	**3.39**	2.36, 4.71
15	**2.63**	1.56, 4.16	**4.35**	2.84, 6.40	**4.17**	2.64, 6.26	**5.52**	3.67, 8.01	**4.06**	3.30, 4.99
16	**5.04**	2.88, 8.16	**3.94**	1.97, 7.06	**4.61**	2.45, 7.88	**4.74**	2.52, 8.10	**4.60**	3.44, 6.07
17	**5.12**	3.17, 7.83	**3.69**	2.02, 6.21	**4.49**	2.62, 7.19	**3.39**	1.80, 5.80	**4.19**	3.26, 5.41
18	**2.07**	0.99, 3.80	**3.25**	1.82, 5.37	**2.16**	0.99, 4.11	**3.77**	2.16, 6.11	**2.80**	2.08, 3.70

FIGURE 5.4 Saskatchewan late stillbirth incidence by census division, 1987 to 2006

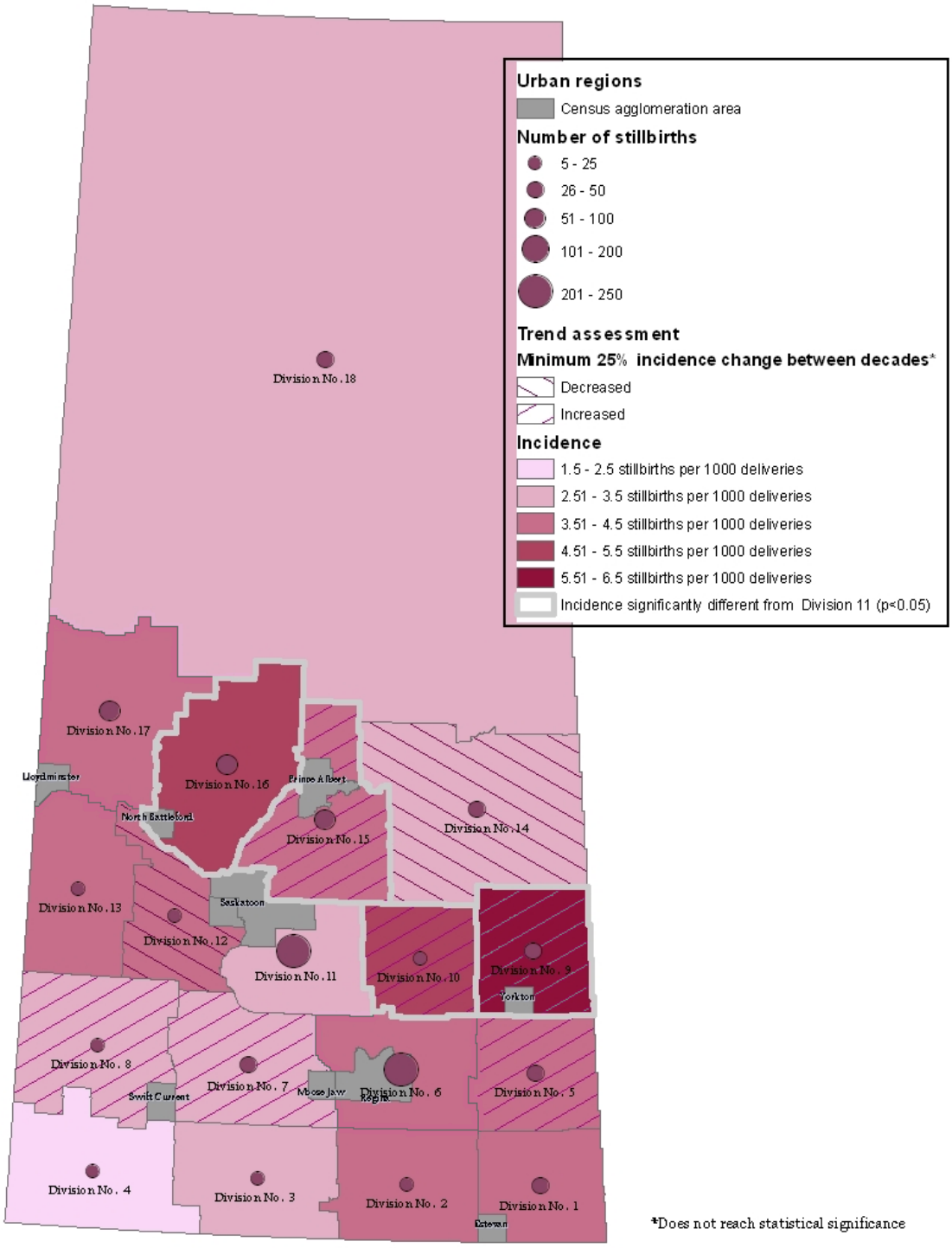


TABLE 5.7 Parameter estimates for Poisson regression of census division on late stillbirth incidence, 1987 to 2006

Division	Lambda [s.e.(Lambda)] $\hat{\lambda}[s.e(\hat{\lambda})]$	RR	95% CI	p-value
1	0.28 (0.20)	1.32	0.90, 1.95	0.16
2	0.16 (0.26)	1.17	0.70, 1.96	0.55
3	-0.16 (0.36)	0.85	0.42, 1.74	0.66
4	-0.57 (0.48)	0.57	0.22, 1.46	0.24
5	0.31 (0.21)	1.36	0.91, 2.03	0.14
6	0.19 (0.10)	1.21	0.99, 1.48	0.06
7	-0.10 (0.20)	0.90	0.61, 1.34	0.62
8	-0.06 (0.24)	0.94	0.58, 1.52	0.80
9	0.58 (0.17)	**1.79**	**1.28, 2.51**	**0.00**
10	0.52 (0.23)	**1.69**	**1.08, 2.65**	**0.02**
12	0.24 (0.23)	1.27	0.80, 2.00	0.31
13	0.13 (0.23)	1.13	0.72, 1.78	0.58
14	0.08 (0.20)	1.09	0.74, 1.60	0.67
15	0.26 (0.13)	**1.30**	**1.01, 1.69**	**0.045**
16	0.39 (0.16)	**1.47**	**1.07, 2.03**	**0.02**
17	0.30 (0.15)	1.34	1.00, 1.81	0.051
18	-0.11 (0.17)	0.90	0.65, 1.25	0.52
11	**Reference**			

Attempts to examine possible interaction between five year period and census division were unsuccessful as the model failed to converge, potentially due to data sparseness. Subsequently, five year time periods and delivery outcome (stillbirth or live birth) were examined by cross tabulation within each census division to determine if time was significant within some regions and not others. Linear-by-linear associations were suggested within Census Division 9 (Chi square p = 0.05, linear-by-linear association p = 0.02), Division 14 (Chi square p = 0.09, linear-by-linear association p = 0.05), and Division 15 (Chi square p = 0.10, linear-by-linear association p = 0.02) but did not meet

the corrected significance level (p = 0.003). Spearman coefficients suggest an increasing direction in Divisions 9 and 15, and a decreasing one in Division 14.

5.1.2.2.2 Incidence by Modified Beale Code

To further assess the effects of remoteness and local community size, the individual census divisions were aggregated by Modified Beale Code (MBC) as described in Chapter 3 and again assessed by Poisson regression. Results are presented in Table 5.8.

TABLE 5.8: Parameter estimates for Poisson regression of Modified Beale Codes on late stillbirth incidence, 1987 to 2006

Code	Lambda [s.e.(Lambda)] [$\hat{\lambda}[s.e(\hat{\lambda})]$	RR	95% CI	p-value
10	-0.20 (0.17)	0.82	0.59, 1.14	0.24
9	0.40 (0.21)	**1.50**	0.98, 2.28	**0.06**
8	-0.66 (0.51)	0.52	0.19, 1.41	0.20
7	0.17 (0.09)	**1.18**	0.99, 1.41	**0.06**
6	0.15 (0.13)	1.16	0.90, 1.48	0.26
4	0.06 (0.11)	1.07	0.85, 1.33	0.58
3	Reference			

Of interest is the borderline significance seen between increased stillbirth risk and residence in areas coded as 7 and 9, both categories indicating relative remoteness from census divisions containing a CMA (Code 3 areas). Areas adjacent to a census division containing a CMA (Codes 4, 6, and 8) as well as the far northern area (Code 10) had no suggestion of statistical difference from Code 3 areas.

Although time was not a statistically significant main effect overall, evaluation of the influence of time on individual MBC's required cross tabulation and Chi-square testing of MBC's and delivery outcome during the individual time periods. Only Code 4

(divisions containing an urban area and adjacent to a CMA-containing division) showed a statistically significant relationship between stillbirth incidence and time (Chi-squared p = 0.021, linear by linear association p = 0.007, Spearman's correlation co-efficient = 0.015, p =0.006); examining the standardized residuals, the majority of this effect appears to be due to a statistically significant increase in late stillbirth incidence occurring between the first two time periods.

5.2 Objective 2

As outlined in Chapter 3, log linear modeling was used to examine potential associations between variables. Although a more simplistic Chi-square analysis was attempted in the context of Objective 1 relating time period and region to various stillbirth characteristics, the second objective sought to explore associations between other characteristics in more depth, adjusting for other additional factors.

5.2.1 Log-linear Model Building

As examination of all possible two factor combinations was the first step in model building, all thirty-six possible pairings that could be created were individually assessed. Each pair was examined in their respective three term models containing both the main effects of interest and their interaction. The statistically significant interactions are reported in Table 5.9 and all two factor interactions assessments can be found in Appendix L. A number of interesting, statistically significant associations can be seen among interactions that could not be further included in the model building process due to sample size inadequacy. These included associations between male losses and both older maternal age (OR = 1.55) and high parity (OR = 1.44); a tendency for losses involving a multiple pregnancy to occur preterm (OR = 2.82) and possibly more

frequently in women who have had a previous stillbirth (OR = 5.65), but less so in non-Aboriginal women (OR = 0.44); and a predominance of preterm losses among women who have had at least one prior stillbirth (OR = 2.77).

TABLE 5.9 Statistically significant interactions (p value <0.05) for two factor combinations of late stillbirth characteristics

Interaction	$\hat{\lambda}$	**OR**	**95% CI**	**p-value**
Maternal Age ≥ 35 years*low parity	-0.66	**0.51**	0.32, 0.83	**0.006**
Maternal Age ≥ 35 years*high parity	0.84	**2.30**	1.54, 3.45	**<0.001**
Maternal Age ≥ 35 years*Aboriginal	-0.46	**0.63**	0.41, 0.97	**0.04**
Maternal Age ≥ 35 years*male fetus	0.44	**1.55**	1.08, 2.22	**0.02**
High parity*Aboriginal	1.32	**3.75**	2.68, 5.25	**<0.001**
High parity*RBC 5	0.64	**1.90**	1.30, 2.79	**0.001**
High parity*RBC 4	0.67	**1.96**	1.27, 3.01	**0.002**
High parity*Male fetus	0.36	**1.44**	1.05, 1.97	**0.02**
Aboriginal*RBC 5	1.20	**3.30**	2.34, 4.67	**<0.001**
Aboriginal*RBC 4	0.93	**2.52**	1.71, 3.72	**<0.001**
Aboriginal*LGA	0.75	**2.13**	1.37, 3.28	**0.001**
Aboriginal*multiple pregnancy	-0.82	**0.44**	0.23, 0.85	**0.01**
Previous stillbirth*preterm loss	1.02	**2.77**	1.53, 5.01	**0.001**
Previous stillbirth*multiple pregnancy[1]	1.73	**5.65**	3.03, 10.54	**<0.001**
RBC 5*SGA	-0.33	**0.72**	0.54, 0.96	**0.03**
RBC 5*multiple pregnancy	-0.86	**0.42**	0.23, 0.78	**0.006**
RBC 4*multiple pregnancy	-0.76	**0.47**	0.24, 0.92	**0.03**
Preterm loss*SGA	0.86	**2.36**	1.83, 3.05	**<.001**
Preterm loss*multiple pregnancy	1.03	**2.82**	1.64, 4.85	**<.001**

[1]More than 20% of cells in this cross classification have expected values < 5. The significance for this interaction is unreliable.

As described in Chapter 4, further cross-classification yielded six combinations of main effects; models built within these groups of variables together with their generating classes and statistically significant interactions are indicated in Table 5.10.

TABLE 5.10 Statistically significant associations between late stillbirth risk factors[1] (odds ratios with 95% confidence intervals)

	Model 1 Parity*Ethnicity Age*Ethnicity Age*Parity	**Model 2** RBC*Ethnicity Age*Ethnicity	**Model 3** RBC*Ethnicity Parity*Ethnicity RBC*Parity	**Model 4** Parity*Ethnicity Fetal size*Ethnicity	**Model 5** Fetal size*Ethnicity* Age	**Model 6** Fetal size*Ethnicity RBC*Ethnicity
Goodness of fit (p-value, Likelihood Ratio Test):	0.38	0.61	0.16	0.47	Saturated model	0.19
Model term:						
Aboriginal† * ≥ 3 prior deliveries‡	**4.25 (3.00-6.02)**		**3.27 (2.27-4.72)**	**3.75 (2.68-5.25)**		
Aboriginal† * No prior deliveries‡	0.97 (0.70-1.35)		0.99 (0.69-1.41)	1.01 (0.73-1.40)		
≥ 35 years§ * ≥ 3 prior deliveries‡	**2.95 (1.93-4.53)**					
≥ 35 years§ * No prior deliveries‡	**0.51 (0.32-0.83)**					
Aboriginal† * ≥ 35 years§	**0.41 (0.26-0.66)**	**0.56 (0.35-0.91)**				
Aboriginal† * Code 5††		**3.30 (2.34-4.67)**	**2.99 (2.10-4.26)**			**3.31 (2.34-4.67)**
Aboriginal† * Code 4††		**2.52 (1.71-3.72)**	**2.28(1.53-3.39)**			**2.52 (1.71-3.72)**
≥ 3 prior deliveries‡ * Code 5††			**1.47 (0.99-2.19)**			
≥ 3 prior deliveries‡ * Code 4††			**1.63 (1.04-2.54)**			
No prior deliveries‡ * Code 5††			0.81 (0.59-1.12)			
No prior deliveries‡ * Code 4††			1.00 (0.70-1.42)			
Aboriginal† * Small for gestation‡‡				0.84 (0.63-1.12)		0.80 (0.59-1.08)
Aboriginal† * Large for gestation‡‡				**2.13 (1.37-3.28)**		**2.21 (1.40-3.49)**
≥ 35 years§ * Small for gestation‡‡ * Aboriginal†					1.26 (0.44-3.60)	
≥ 35 years§ * Large for gestation‡‡ * Aboriginal†					**4.32 (1.20-15.6)**	

Reference categories: † Non-Aboriginal, ‡1-2 prior deliveries, § <35 years of age, ††Code 3, ‡‡Appropriate size for gestation

5.2.2 Log-linear Model Results

5.2.2.1 Two-way Interaction

Several characteristics examined in this work appear in conjunction with other specified variables more or less often than expected. From Table 5.10, it appears that comparing Aboriginal women to non-Aboriginal women, Aboriginal women who experience a late stillbirth are 3 - 4 times more likely to be of high parity rather than moderate parity prior to late stillbirth, regardless of and adjusting for the effects of age, place of residence, or fetal size. Aboriginal stillbirths versus non-Aboriginal stillbirths are also approximately 2.3 to 2.5 times and 3.0 to 3.3 times more likely to have occurred in Beale Code 4 areas and Beale Code 5 areas respectively as compared to Code 3 areas, again similarly addressing the characteristics of maternal age, parity, or fetal size.

Adjusting for ethnicity, Table 5.10 also indicates that stillbirths occurring in women thirty-five years and older were half as likely to be the end result of a first delivery than those occurring in women younger than thirty-five; similarly stillbirths occurring in the prior group are approximately three times more likely to be a fourth or subsequent pregnancy compared to those occurring among their younger counterparts. High levels of parity, rather than moderate levels of parity, were also associated with stillbirths occurring in areas moderately removed from a metropolitan area (OR = 1.63) or substantially removed from a metropolitan area (OR = 1.47), again adjusting for ethnicity. The lack of additional interaction between these two-way terms and ethnicity (i.e. a three-way interaction) indicate that these associations are the same for both Aboriginal and non-Aboriginal stillbirths.

Two statistically significant two-way associations were intentionally not highlighted above as they overlap a three-way interaction in Model 5. As it is inappropriate to consider these characteristics without the third important variable, they will be discussed in the following section.

5.2.2.2 *Three-Way Interaction*

In building Model 5, this model was of marginal adequacy in its fit compared to the saturated model after all possible two-way interactions were added (Goodness-of-fit testing p-value = 0.065), suggesting that the three-way interaction term would substantially improve the model. The addition of this interaction, which generated a saturated model, produced a statistically significant term representing the combination of maternal age ≥ 35 years, Aboriginal ethnicity, and large for gestational age (OR 4.32, 95% CI 1.20-15.61, p-value = 0.03). This interaction indicates that the tendency for Aboriginal stillbirths to be large for gestational age compared to non-Aboriginal women is not consistent; among older women it is approximately four times greater than among younger women. Interpreted another way, the odds that an older mother who experiences a stillbirth has an excessively large baby, relative to a younger mother, depends on whether or not she is Aboriginal. Again, the measure of association between increased maternal age and LGA is four times larger if the stillbirth was Aboriginal rather than non-Aboriginal. Thirdly, this interaction communicates that the association between Aboriginality and increased maternal age depends on fetal size and is four times stronger in LGA versus AGA fetuses.

Although it is apparent from the above that the noted associations differ according to the presence of other noted characteristics by a factor four, the statistical

output does not indicate the strength of the associations within each subgroup. To determine these values, six logit differences with their 95% confidence intervals were calculated for each of the three interpretations above. A sample calculation is provided in Appendix M and results are presented in Table 5.11.

TABLE 5.11 Odds ratios and 95% confidence intervals for variables in the three-way interaction Aboriginal * Maternal age * LGA

Associated Variables	OR	95% CI
LGA * Aboriginal, among women ≥ 35 years	**7.66**	**(2.32, 25.32)**
LGA * Aboriginal, among women <35 years	**1.77**	**(1.10, 2.86)**
≥ 35 years * LGA, among Aboriginal women	**4.64**	**(1.71, 12.61)**
≥ 35 years * LGA, among non-Aboriginal women	1.07	(0.48, 2.40)
Aboriginal * ≥ 35 years, among women with LGA loss	1.79	(0.64, 4.95)
Aboriginal * ≥ 35 years, among women with AGA loss	**0.41**	**(0.19, 0.90)**

The above table, based on the three-way interaction in Model 5, indicates substantial differences in three of the parameter estimates when stratified on other characteristics. Although Models 1 and 2 indicate that Aboriginal women who experienced a late stillbirth were approximately half as likely as non-Aboriginal women to be older (OR 0.41-0.56), the interaction indicates that this was only true if the stillbirth was appropriate for gestational age; if the stillbirth was LGA, a difference was not convincingly seen. Aboriginal stillbirths compared to non-Aboriginal stillbirths were also on average twice as likely to be LGA based on Models 4 and 6 (OR 2.13, 2.21). This association was much stronger, however, if the women were thirty-five years and older, with Aboriginal stillbirths approximately seven times more likely to be LGA than non-Aboriginal losses. The association between Aboriginality and LGA was also present, albeit weaker, among younger losses (OR 1.77, 95% CI 1.10-2.86). The

association between increased maternal age and LGA also differed by Aboriginality, finding stillbirths in Aboriginal women thirty-five years and older four times more likely to be large when compared to Aboriginal women under 35 years. A difference in stillbirth size across age categories was not seen for non-Aboriginal late stillbirths.

5.3 Objective 3

5.3.1 Preliminary Area-level Model

Objective 3 required an attempt to model late stillbirth incidence for census divisions using area-level data. Most of these variables, as outlined in Chapter 3, were initially continuous in nature, but univariate analysis of quartile estimates did not show a relatively consistent increase or decrease in estimates across categories and corresponding confidence intervals also often showed substantial overlap. These observations suggested that for many of these variables the categorical form would be more appropriate than the continuous form (233). As such many of the variables were utilized in categorical form and their complete univariate estimates are in Appendix N

Given the similar nature of many variables, concerns about correlation between them were immediate at the outset of the analysis. Pearson's and Spearman's correlation coefficients was used to assess the degree of correlation; variables with values of 0.7 or higher were assessed together in a simple two-factor model, with the stronger variable retained if collinearity was suggested. A correlation table is presented in Appendix O and variables used in the analysis are presented in Table 5.12 in order of their entrance into the model.

TABLE 5.12: Variables used for area-level model building in order of introduction, univariate associations shown

Variable	Categories	RR (95%CI)	p-values
Population density (per km^2)	≥2.3	1.30 (1.01, 1.67)	0.045
	1.7-2.2	1.68 (1.24, 2.28)	0.001
	1.2-1.6	1.37 (1.01, 1.85)	0.04
	≤1.1	Reference	
Proportion of reproductive age women who are immigrant	≥3.0%	0.96 (0.81, 1.13)	0.58
	2-2.9%	1.35 (1.11, 1.64)	0.003
	<2%	Reference	
Ratio of children 0-12 years to reproductive age women	≥ 1.10	1.11 (0.95, 1.29)	0.21
	1.04-1.09	1.42 (1.11, 1.84)	0.01
	<1.04	Reference	
Proportion of reproductive age women who are ≥35 years	≥35%	1.25 (1.06, 1.47)	0.01
	<35%	Reference	
Proportion of total adult population with no diploma	≥36%	1.09 (0.91, 1.31)	0.35
	29-35.9%	1.27 (1.05, 1.53)	0.02
	<29%	Reference	
Proportion of land area sprayed with fungicide	≥ 3.5%	0.84 (0.71, 0.98)	0.03
	<3.5%	Reference	
Estimated average age (years)	≥39.5	1.29 (1.02, 1.63)	0.04
	35.6-39.4	0.94 (0.80,1.10)	0.45
	≤ 35.5	Reference	
Median household income	> $45000	0.82 (0.69, 0.99)	0.04
	≤ $45000	Reference	
Population change between census years (%)	Declining 6% or more	1.15 (0.99, 1.35)	0.07
	Not declining 6% or more	Reference	
Community size	Rural	1.13 (0.73, 1.75)	0.58
	Town	1.16 (0.97, 1.40)	0.09
	City	1.23 (0.97, 1.56)	0.09
	Metropolitan area	Reference	
Proportion of reproductive age women in primary production work	≥5.5/1000	1.01 (0.78, 1.30)	0.95
	2-5.4/1000	0.86 (0.72, 1.03)	0.093
	<2/1000	Reference	

Proportion of land area sprayed with herbicide	≥48%	1.05 (0.83, 1.34)	0.67
	42-47.9%	1.14 (0.87, 1.49)	0.36
	33-40.9%	1.27 (0.95, 1.72)	0.11
	<33%	Reference	
Median family income	≥ $52000	0.87 (0.73, 1.034)	0.11
	$47000-51999	1.12 (.092, 1.37)	0.26
	< $47000	Reference	
Proportion of land area sprayed with herbicide	≥48%	1.05 (0.83, 1.34)	0.67
	42-47.9%	1.14 (0.87, 1.49)	0.36
	33-40.9%	1.27 (0.95, 1.72)	0.11
	<33%	Reference	
Proportion of total population with graduate degree as highest level of education	≥36%	1.09 (0.87, 1.38)	0.45
	29-35.9%	1.25 (0.93, 1.67)	0.15
	<29%	Reference	
Revised Beale Code	5	1.14 (0.95, 1.37)	0.16
	4	1.15 (0.94, 1.41)	0.17
	3	Reference	
Proportion of reproductive age males with undergraduate-level degree or certificate as highest education	≥33%	1.01 (0.82, 1.24)	0.93
	30-32.9%	1.17 (0.94, 1.47)	0.17
	<30%	Reference	
Proportion of total population with undergraduate-level degree or certificate as highest education	≥28%	1.07 (0.83, 1.38)	0.61
	23-27.9%	1.19 (0.82, 1.54)	0.18
	<23%	Reference	
Proportion of children age 0-4 years who are Aboriginal	>35%	1.13 (0.94, 1.35)	0.19
	≤35%	Reference	
Proportion of families with lone female parent	Linear	0.988 (0.969, 1.007)	0.22
Proportion of total population who are immigrant	Linear	0.98 (0.94, 1.01)	0.21
Proportion of reproductive age males with no degree	≥50%	0.85 (0.66, 1.10)	0.23
	<50%	Reference	

Following the model building strategy described in Chapter 4, the initial main effects model consisted of the parameters as described in Table 5.13. Proportion of Aboriginal children 0 to 4 years of age was retained although the p-value was of borderline significance because of its relevance to the Saskatchewan population. Interactions were assessed between all main effects in the model as well as between the main effects and those that were removed from the model. Several interactions were noted to be significant, but on examining these cross-classifications all were found to have expected counts less than 5 in more than 20% of the cells. Due to the subsequent potential for bias, these terms were not retained in the model per se although two interactions with increased counts and strongly significant p-values (0.007) were noted (Areas with a moderate proportion of reproductive age women in primary production work*High ratio of children 0 to 12 years to reproductive age women; Moderate proportion of reproductive age females in primary production work*RBC 4).

The model was then assessed for the need to include additional terms as confounders. Seven variables (Proportion of reproductive age women who are ≥35 years, ratio of children 0 - 12 years to reproductive age women, proportion of land area sprayed with herbicide, proportion of land area sprayed with fungicide, Revised Beale Code, population change between census years, largest community size) when added individually changed the estimates of the significant main effects by more than 20%. When all seven were added to the model together, however, the overall effect was largely non-significance of both the main effects and the confounders. Thus only those variables in Table 5.14 that showed significance or borderline significance (<0.10) after this major adjustment were retained, resulting in significant revision of the model.

TABLE 5.13 Preliminary area-level main effects model

Parameter		Lambda [s.e.(Lambda)] [$\hat{\lambda}[s.e(\hat{\lambda})]$	R.R.	95% CI	p-values
Intercept		-5.90 (0.12)	0.00	0.0022, 0.0035	<0.001
Population density (per km^2)	≥2.3	0.41 (0.11)	1.50	1.21, 1.86	<0.001
	1.7-2.2	0.59 (0.13)	1.80	1.39, 2.33	<0.001
	1.2-1.6	0.39 (0.13)	1.48	1.15, 1.90	0.002
	≤1.1	Ref.			
Estimated average age (years)	≥39.5	0.35 (0.100)	1.41	1.15, 1.73	0.001
	35.6-39.4	0.05 (0.080)	1.05	0.90, 1.22	0.54
	≤ 35.5	Ref.			
Median household income	> $45000	-0.20 (0.086)	0.82	0.69, 0.97	0.018
	≤ $45000	Ref.			
Proportion of reproductive age women in primary production work	≥5.5/1000	-0.17 (0.12)	0.85	0.67, 1.06	0.15
	2-5.4/1000	-0.16 (0.070)	0.85	0.74, 0.98	0.023
	<2/1000	Ref.			
Proportion of children age 0-4 years who are Aboriginal	>35%	0.15 (0.076)	1.16	1.00, 1.35	0.053
	≤35%	Ref.			

TABLE 5.14: Preliminary model with potential confounders included

Variable	Categories	Lambda [s.e.(Lambda)] [$\hat{\lambda}[s.e(\hat{\lambda})]$	RR	95% CI	p-values
Intercept		-6.118 (0.27)	0.00	0.00,0.00	0.00
Population density per km^2	≥2.3	0.10 (0.31)	1.11	0.61, 2.02	0.74
	1.7-2.2	0.38 (0.24)	1.47	0.91, 2.36	0.12
	1.2-1.6	0.10 (0.28)	1.10	0.64, 1.90	0.72
	≤1.1	Reference			
Estimated average age (years)	≥39.5	0.30 (0.21)	1.35	0.90, 2.04	0.15
	35.6-39.4	0.07 (0.16)	1.07	0.78, 1.47	0.69
	≤ 35.5	Reference			

Median household income	> $45000	-0.12 (0.13)	0.89	0.69, 1.14	0.35
	≤ $45000	Reference			
Proportion of reproductive age women in primary production work	≥5.5/1000	-0.010 (0.13)	0.99	0.76, 1.29	0.94
	2-5.4/1000	-0.043 (0.09)	0.96	0.80, 1.15	0.64
	<2/1000	Reference			
Proportion of children age 0-4 years who are Aboriginal	>35%	0.59 (0.21)	1.80	1.20, 2.71	**0.004**
	≤35%	Reference			
Proportion of reproductive age women who are ≥35 years	≥35%	0.051 (0.14)	1.05	0.80, 1.38	0.71
	<35%	Reference			
Proportion of land area sprayed with herbicide	≥48%	0.44 (0.25)	1.55	0.95, 2.52	**0.08**
	42-47.9%	0.45 (0.21)	1.57	1.05, 2.35	**0.03**
	33-40.9%	0.56 (0.28)	1.75	1.02, 3.00	**0.04**
	<33%	Reference			
Revised Beale Code	5	-0.49 (0.61)	0.61	0.32, 1.16	0.13
	4	-0.52 (0.27)	0.60	0.35, 1.00	**0.05**
	3	Reference			
Proportion of land area sprayed with fungicide	≥ 3.5%	-0.21 (0.12)	0.81	0.64, 1.01	**0.07**
	<3.5%	Reference			
Ratio of children 0-12 years to reproductive age women	≥ 1.10	-0.011 (0.23)	0.99	0.63, 1.54	0.96
	1.04-1.09	0.063 (0.21)	1.07	0.71, 1.61	0.76
	<1.04	Reference			
Population change between census years (%)	Decline ≥ 6%	0.23 (0.15)	1.26	0.94, 1.69	0.11
	Not declining 6% or more	Reference			
Community size	Rural	0.04 (0.37)	1.04	0.50, 2.17	0.91
	Town	0.19 (0.30)	1.21	0.67, 2.18	0.52
	City	0.00	1	.	.
	Metro area	Reference			

5.3.2 Final Area-level Model

The final model outlined in Table 5.15 is the product of an attempt to adjust for confounding as described Section 5.3.1. Revised Beale Code lost its significance when removed from the fully adjusted model but remains in the new model as it confounds the estimates for herbicide exposure. In the new model, the two uppermost quartiles for herbicide application were collapsed as the estimates were virtually identical.

TABLE 5.15: Final area-level model

Parameter	**Categories**	**Lambda [s.e.(Lambda)]** $[\hat{\lambda}[s.e(\hat{\lambda})]$	**RR**	**95% CI**	**p-value**
Intercept		-6.02 (0.14)	0.002	0.002, 0.003	<0.001
Proportion of children age 0-4 years who are Aboriginal	>35% ≤35%	0.43 (0.13) Reference	**1.53**	1.19, 1.97	**0.001**
Proportion of land area sprayed with herbicide	≥42% 33-41.9% <33%	0.44 (0.13) 0.62 (0.16) Reference	**1.55** **1.86**	1.21, 1.98 1.40, 2.56	**<0.001** **<0.001**
Proportion of land area sprayed with fungicide	≥ 3.5% <3.5%	-0.17 (0.079) Reference	**0.85**	0.73, 0.99	**0.04**
Revised Beale Code	5 4 3	0.14 (0.11) -0.09 (0.13) Reference	1.15 0.92	0.92, 1.43 0.71, 1.18	0.23 0.50

Interactions were again assessed as terms in this model were quite different than in the preliminary version. A statistically significant interaction was noted between areas with a moderate proportion of land area sprayed with herbicide and Revised Beale Code, raising the possibility that the association between moderate amounts of herbicide

application and increased late stillbirth incidence is stronger in more remote areas (p-value 0.013). It must be noted, again, however, that more than 20% of cells when cross-classified on these variables had expected counts less than 5. An additional interaction of interest also appeared between the proportion of children 0 to 4 years who were Aboriginal and population density. This interaction suggests that the association between high proportions of Aboriginal people and late stillbirth incidence is weaker at moderately high, and to a lesser degree, high levels of population density rather than at low ones. Although the interaction involving moderately high levels of population density is more likely to be truly significant given its very small p-value of 0.003, it too lacks adequate expected cell counts to convey a confident result. Thus it also was not included in the final model but these estimates are displayed in Table 5.16.

TABLE 5.16 Interaction estimates for proportion of children age 0-4 years who are Aboriginal with population density

Parameter	**Lambda [s.e.(Lambda)]** $[\hat{\lambda}[s.e(\hat{\lambda})]$	**RR**	**95% CI**	**p-values**
High proportion of children age 0-4 years are Aboriginal*High population density	-0.62 (0.32)	0.54	0.29, 1.01	0.053
High proportion of children age 0-4 years are Aboriginal* Moderately high population density	-0.71 (0.24)	0.49	0.31, 0.79	0.003
Low proportion of children age 0-4 years are Aboriginal*Low population density	Reference			

The main effects model in Table 5.15 indicates that overall, late stillbirth incidence is 1.53 times higher in areas where more than 35% of children age 0 to 4 years are Aboriginal. It is also 1.86 and 1.55 times higher respectively in areas where more than 33% and 42% of land area has been sprayed with herbicide compared to areas of lower exposure. Questionably, stillbirth incidence appears to be slightly lower in census divisions where more than 3.5% of the land area has been sprayed with fungicide. These associations have been adjusted for the other variables in the model and as fungicide and herbicide estimates changed less than 20% between the fully adjusted model in Table 5.16 and the final model, they also do not appear significantly confounded by the previously considered variables. The estimate pertaining to the proportion of Aboriginal children, however, did decrease by 27% in the final model when compared to the estimate in the fully adjusted model. This difference suggests that a small degree of negative confounding is present in regard to this variable and that the association between high proportions of Aboriginal children and increased stillbirth incidence may be slightly higher than indicated in the final model.

CHAPTER 6:

6.0 DISCUSSION

The analysis reported in Chapter 5 presents some interesting findings. These results, however, require careful consideration as to their actual interpretation. This chapter will critically examine the associations noted in this work.

6.1 Objective 1

6.1.1 Late Stillbirth Characteristics

6.1.1.1 Descriptions

The characteristics of cases in this work can only legitimately be considered descriptive as corresponding data on live births that would allow definite statistical comparison of their proportions as possible risk factors was not obtained. Of interest is the observation that nearly all individual risk factors occurred in relatively small proportions of the cases (e.g. although age is a known risk factor, only a minority of women who experienced a stillbirth are thirty-five years or older). This recognition highlights that basic descriptive statistics alone do not allow the development of a characteristic stillbirth profile.

6.1.1.2 Characteristics in Relation to Time and Region

Several late stillbirth characteristics showed statistically significant associations with time. The increased proportion of losses that are Aboriginal over time periods is

not completely unexpected given the growth of Saskatchewan's Aboriginal population. More Aboriginal pregnancies would be expected to translate into a larger proportion of Aboriginal stillbirths, particularly against the corresponding decline seen in the non-Aboriginal Saskatchewan population (236). A tendency towards increasing fetal size among stillbirths over time may also be in part due to an increasing proportion of Aboriginal pregnancies as First Nations babies show a tendency to be heavier than non-First Nations babies (237,238). It must be recognized, however, that other more generalized factors such as increasing obesity among pregnant women and earlier intervention for SGA fetuses that would otherwise have resulted in SGA stillbirths, may also contribute in the trend towards larger stillbirths. The noted increase in maternal age over time may also be a reflection of increased maternal age at time of pregnancy, a dynamic recognized in other parts of the developed world as well as Saskatchewan, rather than the result of a true change in risk for older women (31,239). It is also interesting to note the increasing linear-by-linear relationship between RBC and 5 year period. As it is recognized that many of Saskatchewan's rural populations are aging and in decline, the expectation would be of fewer pregnancies and fewer stillbirths. This raises the possibility that late stillbirth risk in these areas may be increasing although the effect of the previously mention Aboriginal population growth in more rural and remote areas cannot be ruled out. This result could also be due to fewer urban stillbirths over time. It should be noted that although these last two associations had p-values <0.05, they did not meet the corrected significance level and cannot be considered definitive. Associations between stillbirth characteristics, including RBC's will be further evaluated in Objective 2.

An additional variable that showed an interesting but non-significant relationship to time was that of pregnancy duration. The isolated decrease in post-term late stillbirths between the 1987-1991 and 1992 -1996 is suspected to reflect the introduction of labor induction between 41 and 42 completed weeks of gestation as part of typical prenatal care.

A number of characteristics showed changes over Revised Beale Codes and, as would be expected, for the extreme ends of the Modified Beale Codes as well. A linear association between RBC's and Aboriginality among stillbirths possibly reflects the larger proportions of people who are Registered Indian among more remote Saskatchewan populations. Increasing parity noted with remote stillbirths may parallel the higher levels of fertility associated with rural women in general, which may again be related to higher proportions of Aboriginal women with higher fertility rates (240,241). A tendency towards fewer stillbirths involving multiple pregnancies with increasing remoteness may reflect factors predisposing to singleton pregnancies such as younger maternal age or decreased access to assisted reproductive technologies.

Without assessment of these characteristics in the general pregnant population of Saskatchewan during these twenty-one years, it is not possible to know if late stillbirth risk associated with these characteristics actually varies by period and place. It does seem, however, that their differing proportions among stillbirths could simply be a reflection of differences in pregnant population characteristics at different times and locations.

6.1.1.3 Cause of Death

In Chi-square testing, it was clear that considering all categories, the proportions for causes of death were not consistent over time. Examination of the residuals indicated that this was mainly due to a very large drop in the proportion of stillbirths with no stated cause of death between the second and third five-year periods. This change was accompanied by increased proportions of losses attributed to all of the other categories but most substantially to the percentage of placenta, cord, and membrane related losses. The reason for this sharp change in proportions is unknown. As for the category of other causes, it should be noted that this large grouping includes specific maternal conditions such as pre-existing hypertension, diabetes, or trauma that may have been documented as the cause of death. Although these conditions are generally considered antecedent to the more primary cause of death categories described, it is worthwhile to recognize that maternal conditions make up 36% of the "other cause" group; further improvements in prenatal care may decrease risk for this category of loss.

When these causes where not considered in the relative terms of proportionate mortality but as specific outcomes with their own cause-specific incidence, only the risk of stillbirth from non-specified causes appeared to have a consistent, significant, directional change over time. It is somewhat surprising that an overall decline in congenital anomalies and maternal complications was not noted in spite of advances in early detection of malformations, folic acid supplementation, and evolving prenatal care. Overall, given the high peak in stillbirths without cause of death provided during 1992-1996 and its subsequent drop in the following five year period, it is very possible that trend assessment might have had different findings were the causes behind these cases

available. Even so, it appears that further attention needs to be paid to decreasing losses related to cord, placenta, and membrane problems; improving diagnostic capabilities for losses of unspecified causes; and examining other causes of stillbirth outside of those indicated by the broad categories of this classification.

A markedly limiting factor in the assessment of cause of death overall is that of correct assessment. In many cases, cause of death will likely be assigned based on patient history and clinical findings without the assistance of an autopsy given limited pathology resources and potential unacceptability to parents. Although published Saskatchewan statistics are not readily available as to what proportion of stillbirths in the province do receive an autopsy, Alberta reported that only 48.8% of its stillbirths received an autopsy in 2004, even after the introduction of stillbirth investigation guidelines (242). As highlighted in the literature review, autopsy has been recognized to change or add to the presumptive cause of death in up to 50% of cases. Therefore, given the assumed relative lack of pathological examinations, it must be acknowledged that the results in this study in terms of cause of late stillbirth may be subject to significant inaccuracy.

6.1.2 Incidence

6.1.2.1 National and Provincial Incidence

In examining provincial and regional stillbirth rates, it is evident that Saskatchewan has not seen a statistically significant decline in late stillbirth incidence, which is apparent in other parts of Canada. As would be expected, the gap between Saskatchewan and the rest of Canada is generally wider in the second half of the twenty-one years under study. It is interesting to note that the earliest years actually saw lower

incidence values for Saskatchewan when compared to the rest of Canada. Reasons for this difference are not readily apparent and would require a comparative examination of maternal, pregnancy, and prenatal care characteristics among Saskatchewan and other Canadian women over the past two decades.

6.1.2.2 Regional Incidence

6.1.2.2.1 Incidence by Census Division

Intra-provincial regional differences in risk were also detected. Compared to Saskatoon's Census Division 11 where the largest proportion of pregnant women resided, divisions 9, 10, 15, and 16 and showed significantly higher values. Of surprise was the borderline higher incidence seen in Division 6 which contains the census metropolitan area of Regina ($p = 0.058$), but closer examination of its values suggests this difference was largely isolated to the first five-year time period. The non-significance of Division 18 was also unexpected, particularly with increased risk noted for other northern areas. Possible explanations for the latter include a true protective effect, prevention of stillbirth by the transport of remote-residence women with complicated pregnancies to larger centers, and under-reporting of such losses in the far north.

The possible lack of recognized association with Division 18 appears to be of genuine concern and may create distortion even among the reported cases in this study. Sixty-five cases (5.8%) had no place of residence supplied[1] and of them, 69.2% (45

[1] Twenty-four cases (36.9%) with no CD provided had a place of residence that mapped to two CDs.

cases) indicated Registered Indian Status, a marked overrepresentation compared to 26.8% among late stillbirths generally. Census data from 1996, the midpoint of the time period under investigation, indicates that 23% of the North American Indian population in Saskatchewan lived in Division 18 (185). Thus it could be reasonably expected that at least 10 additional cases (45*0.23 = 10.3) were resident in Division 18 and would thereby increase this region's twenty year incidence to from 2.8 to 3.4 per 1000 births, a value now higher than the 3.2 per 1000 births calculated in Division 11 if a similar adjustment is applied. If cases truly are under-reported from Division 18, this will also likely also result in an underrepresentation of descriptive characteristics that are often associated with Aboriginal losses in this area.

Divisions 9 and 15 are of particular interest as there is suggestion of increasing late stillbirth incidence in these regions. From a statistical perspective, however, caution must be applied in interpreting these trends as definite given that repeatedly evaluating the role of time in eighteen census divisions at a significance level of 0.05 has a strong possibility of generating at least one false positive. Applying a Bonferroni correction to the significance level of 0.05/18 = 0.002 as compensation for multiple testing would leave the linear-by-linear associations in all census divisions non-significant. Further assessment within these areas should be undertaken.

6.1.2.2.2 Incidence by Modified Beale Code

Given their borderline significance (p = 0.06), areas that are far from a metropolitan center by Modified Beale Code (MBC 7, 9) are suspected to have higher stillbirth risks than those containing CMA's. This association was not convincingly seen for closer regions (Codes 4, 6, and 8). Decreasing community size does not appear to

substantially increase stillbirth incidence among those close to a metropolitan area (Codes 4, 6, and 8); the small estimate value for Code 8 areas (rural and adjacent to a CMA) raises the possibility that this particular situation may even be protective although this association is not statistically significant. In settings that are farther away from a metropolitan area, estimates show greater difference according to community size although the fact that Saskatchewan does not have a city far from a metropolitan area limits this observation. Re-assignment of the reference group did not indicate a statistically significant difference between Codes 7 and 9. Again Code 10, representing Division 18 may reflect under-reporting. This model provides unadjusted associations and although they indicate that more remote women are potentially at increased risk of late stillbirth, they do not indicate why.

6.2 Objective 2

The purpose of log-linear modeling in this study was to allow descriptive insight into characteristics that are associated among stillbirths. It answers questions such as, "Compared to non-remote areas, are stillbirths in remote areas more likely to involve younger women?" or "Do SGA stillbirths more frequently occur in women with high parity rather than moderate parity?" Higher-than-anticipated counts for these combinations may then suggest individuals who are at greater risk for the outcome than anticipated by both factors simply exerting their influence (interaction). The assessment of interactions is of particular interest in the area of stillbirth research as it appears infrequently undertaken. If meaningful associations could be determined, many of the recognized risk factors could be addressed more effectively in individuals where they have the greatest potential influence.

The preliminary two-factor assessment in Section 5.2.1 highlighted some previously recognized associations. The tendency for earlier losses in multiple pregnancies is documented in the literature (83,84). The curiously positive and statistically significant associations seen between male losses and older mothers has also been seen among pregnancies generally (243) as has some suggestion of increase in twinning among women with a previous stillbirth (244); among the stillbirths examined these associations appeared somewhat stronger than in live birth outcomes. Associations between lower levels of multiple pregnancy losses and Aboriginal women could reflect a truly protective combination, but it is also possible that Aboriginal women carry a multiple pregnancy less often than non-Aboriginal women. Information on the latter could not be located.

The associations denoted in the six models developed also highlight certain associations that may act as "red flags" for potentially increased stillbirth risk. They indicate that Aboriginal stillbirths are more often of higher parity than non-Aboriginal stillbirths, raising the possibility that the risk introduced by higher parity is magnified if the mother is Aboriginal, or considered conversely, that risk associated with Aboriginality is compounded by higher parity. Similarly, Aboriginal stillbirths are more likely to occur in Revised Beale Codes 4 and 5 than non-Aboriginal stillbirths, proposing that Aboriginal women are at greater risk than non-Aboriginal women of late losses more remotely. Aboriginal women are less likely to be 35 years of age and over compared to non-Aboriginal women, suggesting that Aboriginal women may not have the same susceptibility to losses with advanced age compared to non-Aboriginal women. The association between LGA and Aboriginality suggests that Aboriginal women

carrying an LGA fetus are more likely to experience a loss than non-Aboriginal women with an LGA fetus, especially in older mothers as indicated by the three-way interaction. Similarly older Aboriginal women who are carrying an LGA fetus may be more likely to experience a loss than younger Aboriginal women with an LGA fetus; among women with AGA fetuses, older Aboriginal women appear to be at decreased risk of loss compared to non-Aboriginal women. Continuing to take these results at face value, associations between age and parity would suppose that older pregnant women more successfully carried first pregnancies and that higher parity puts a woman at greater risk if she lives more remotely.

The above associations are, of course, clearly suspect in their role as risk factors. Again, a key understanding that would move the analysis from describing characteristics that occur together, and subsequent speculation as to their impact, to defining associations that may truly increase risk is knowledge of the distribution of these combinations in the pregnant population in general. For example, recognition that Aboriginal stillbirths occur disproportionately in the more remote Revised Beale Code areas is only meaningful as a risk factor if the number of Aboriginal pregnancies occurring in those locations can be identified. Were a large number of Aboriginal pregnancies to have occurred in those regions, a corresponding high number of Aboriginal stillbirths would also be expected, which then would not suggest Aboriginal women in more remote contexts to be increased risk in spite of high counts.

Pregnancy literature and vital statistics data can provide some insight into the above mentioned problem and additional data was sought to provide background associations between other characteristics in the pregnant population. Crude odds ratios

were calculated for these associated characteristics in the general pregnant or live birth populations as available and are compared to the odds ratios from the stillbirth data in Table 6.1. Not all associations or reasonably appropriate data for their calculations in the general pregnant population could be located. Examining Table 6.1, it does appear that the combination of Aboriginality and high parity occurs more frequently among late stillbirths than in the general pregnant population, suggesting that the combination of Aboriginality and high parity may be associated with a true increase in risk. Increases in counts among older women with high parity and among Aboriginal women removed from a major center resemble those of the pregnant population and do not appear to increase risk.

TABLE 6.1 Comparison of odds ratios for crude bivariable combinations among women experiencing a late stillbirth and women in the general pregnant populations

Variable combination	**Crude OR among stillbirths (95% CI)**	**Crude OR pregnant/ live birth population**
Aboriginality*High parity	**3.75 (2.68, 5.25)**	**2.63**
≥35 years*Low parity	0.51 (0.32, 0.83)	0.47
≥35 years *High parity	2.30 (1.54, 3.45)	2.25
Aboriginality*RBC 5	3.30 (2.34, 4.67)	3.03
Aboriginality*RBC 4	2.52 (1.71, 3.72)	1.71
High parity *RBC 5	1.90 (1.30, 2.79)	N/A
High parity*RBC 4	1.96 (1.27, 3.01)	N/A
Aboriginality*Fetal Size*Maternal Age:		
LGA * Aboriginal, among women ≥ 35 years	**7.66 (2.32, 25.32)**	**1.73**
LGA * Aboriginal, among women <35 years	1.77 (1.10, 2.86)	1.63
≥ 35 years * LGA, among Aboriginal women	**4.64 (1.71-12.61)**	**1.31**
≥ 35 years * LGA, among non-Aboriginal women	1.07 (0.48, 2.40)	1.24
Aboriginal * ≥ 35 years , among LGA births	**1.79 (0.64, 4.95)**	**0.44**
Aboriginal * ≥ 35 years, among AGA births	0.41 (0.19, 0.90)	0.41

Given the three way interaction noted, the other significant two-way interactions in the log-linear models had to be evaluated in the context of the third factor. It does appear that the number of LGA fetuses among older Aboriginal women who experience a loss is much larger than would be expected based on the number of LGA fetuses recognized in older pregnant Aboriginal women generally (OR 7.66 vs. 1.73). This may indicate a truly increased risk associated with being an older Aboriginal woman carrying a LGA fetus when compared to older non-Aboriginal women also with an LGA fetus. Among women 35 years of age and under, the higher number of LGA fetuses within Aboriginal stillbirths appears to be a reflection of more LGA fetuses in pregnant Aboriginal women in this age group generally, given that the odds ratios for a large fetus in both stillbirths and live births are similar (OR 1.77 vs. 1.63). Considering only Aboriginal pregnancies, the increased count seen among women who are over 35 years of age and carrying an LGA fetus does not appear to be strictly the result of more LGA fetuses in older Aboriginal women than younger ones (OR 4.64 vs. 1.31). Although the stillbirth counts for older Aboriginal women among the LGA losses were not statistically suspicious themselves, the relatively low presence of older, Aboriginal women carrying an LGA fetus in the pregnant population suggests that these counts do indicate risk (OR 1.79 vs. 0.44).

It should again be stated that these comparisons are more suggestive than definitive as the pregnant populations utilized may not perfectly represent the characteristics of Saskatchewan live births. To examine the occurrence of Aboriginality and parity together in the general pregnant population, Saskatchewan data was found in work by Dyck et al (245). Although the study focus was on gestational diabetes, total

numbers by parity were provided for all Aboriginal and general population pregnancies that attended the Royal University Hospital for delivery at approximately the midpoint of this study. From these values an odds ratio for an association between parity and Aboriginality among the subjects could be calculated. For maternal age and parity, Saskatchewan data could not be located and national level data was used for the approximate midpoint of the study (246). The number of Registered Indian live births within each census division was also not readily available although the number of children age 0-4 years of Aboriginal identity and the proportion of Aboriginal individuals with Registered Indian status within each census division was known (186, 192). These values allowed the calculation of a plausible substitutive odds ratio for Registered Indian births by Revised Beale Code. Data on pregnant women by age, Aboriginality, and fetal size combined was somewhat challenging to locate although published British Columbia vital statistic data providing raw provincial counts for these combinations was used, encompassing all live births that occurred between 1981 and 2000 (247).

6.3 Objective 3

6.3.1 Area-level Predictor Variables

The area-level analysis resulted in surprisingly few risk factors of significance after confounding was considered. Although the preliminary model does contain several characteristics that may serve as indicators of areas with higher stillbirth risk, their lack of significance after adjustment suggests that they are not the cause of it. The two strongest predictors in the final model are the proportion of Aboriginal children less than five years of age and the proportion of land sprayed with herbicide.

Aboriginal children of this age group were included in this analysis as a reasonable reflection of the proportion of pregnancies in the past five years that were Aboriginal. This variable makes an attempt to at least capture the proportion of Aboriginal pregnancies rather than simply the proportion of Aboriginal people. Although it is an improvement over the latter, it still does not assess actual pregnancy outcome in clear relation to Aboriginality (i.e. individual level associations) and may be biased by migration of Aboriginal infants and preschoolers.

Although it is surprising that Aboriginal ethnicity retained such strong significance after adjustment for so many variables, one must be careful not to perceive Aboriginality as a cause itself. In recent years as the determinants of health have come into focus as the root causes behind many health problems, it is clear that there are multiple determinant that have not been considered in this study (248). Although income, education, and to a lesser degree, work environment and culture have been included, there are gaps in the assessment of personal health behaviors (e.g. smoking, alcohol, nutritional adequacy, physical activity), health services (e.g. the availability of prenatal care), biology (e.g. obesity, high blood pressure, diabetes), and social environments (e.g. stress levels, domestic violence). It is very plausible that adjustment for these aspects, which are certainly not exclusive to Aboriginal people, may have rendered the association between Aboriginality and increased stillbirth incidence non-significant. A better understanding of this association may lie in the possible interaction between relatively higher levels of population density and high proportions of Aboriginal children. These relatively higher densities are associated with lower stillbirth incidence,

possibly due to improvements in some of the social determinants considered above (e.g. access to prenatal care, social supports).

Similarly the association between herbicide application and late stillbirth incidence may be subject to residual confounding although potential confounders associated with both high applications of herbicide and increased stillbirth incidence are more difficult to postulate. It may be that other exposures of farm life (e.g. less access to prenatal care, more physical labor, other toxic exposure, financial inadequacy) may contribute to the increase. There is some suggestion from the interaction term that the association between herbicide levels and stillbirth incidence may differ by distance from a major center. It is quite possible that the application of herbicide is not uniform across the province in the type of chemical or method, concentration, and frequency of application; this information was not available for this analysis. The harmful effect of herbicide may also be blunted by other factors not considered in this study that decrease with increasing distance from a major center, such as prenatal care.

It is interesting that areas with higher proportions of land areas sprayed with fungicide were at lower risk of stillbirth. It is not likely that exposure to fungicide is actually beneficial to pregnancy and suggests that some form of residual confounding is likely present for this particular variable. Its unexpected significance is a reminder that all associations at the area-level, including the more convincing ones of Aboriginality and herbicide exposure, are subject to the following limitations and are tenuous at best.

6.3.2 Area-level Limitations

Although increased risk associated with these main exposures does show some alignment with other studies, it is important to keep the limitations that are inherent to

the ecological method and to the use of census data in mind (233,249,250). Most importantly it must be recognized that individual level information is not available and without knowing whether or not the individuals who experienced a stillbirth were Aboriginal or truly exposed to herbicide, the association is speculative and risks ecological fallacy. This may be of particular concern where areas are relatively large, such as in this study, as exposures levels assumed for the entire area may actually only be pocketed within certain subregions away from the individuals who are assumed to be exposed. Additionally, ecological analysis is plagued with great potential for ecological bias due to unaccounted for individual level confounding, confounding by group, and effect modification (234). These biases can be severe and difficult to compensate for in area-level work (234).

The use of census data may have some unique problems (250). Census data is subject to random rounding which may create over or underestimation of exposure proportions, particularly in small samples. Unlike individual-level analysis, non-differential exposure misclassification within ecological studies has the potential to overestimate estimates (249). Non-response may be an issue, particularly for the "long" census form questions in Division 18 where the global non-response rate to questions may be has high as 25%. This will be problematic if individuals who did not respond differ from responders on a particular characteristic of interest. Sampling error is also possible as for all census divisions other than 18 as results are extrapolated from a 20% sample of the population.

It should also be recalled from Chapter 4 that a repeated measures methodology could not be determined that would assess the within-subject variation given the specifics

of this dataset. Although failure to do this would be expected to create Type 1 errors due to overdispersion of the data, this effect is anticipated to be minimized by the scale parameter that is applied. The lambda estimates themselves may be also be biased, however, as the total sample size itself is relatively small (n=54). Simulation studies suggest that in samples with n<100, the maximum likelihood approach tends to exaggerate estimates in multivariable models (251,252). Thus the associations in this area-level model may be overstated.

6.4 Conclusions

6.4.1 Objective 1

- Individual previously-recognized stillbirth risk factors in this study occur relatively infrequently within Saskatchewan women who experience a late stillbirth.
- Characteristics of late stillbirths have not been uniform over time. More recent stillbirths are more often Aboriginal and larger for their gestational age. There is also suggestion that the proportion of losses with older mothers and resident in remote places may be increasing. Similarly Aboriginality, higher parity, singleton pregnancy, and fetal size among late stillbirths show increase across remoteness. Such changes may be the result of truly elevated relative risk but could also simply reflect changes in pregnancy characteristics.
- Causes of death among late stillbirths have not been entirely static. The largest change has been a marked drop in the proportion of cases with no stated cause of death. This change was accompanied by increases in proportions of all other stated causes of death, particularly losses related to problems of the

cord, placenta, or membranes. There is only strong evidence of a cause-specific trend for increasing risk of unspecified losses. .

- Over the past two decades, the difference in late stillbirth incidence has varied quite substantially between Saskatchewan and the rest of Canada, although Saskatchewan has generally had the higher incidence. A statistically significant decline can be seen for non-Saskatchewan stillbirths but not within Saskatchewan.
- Census divisions 9, 10, 15, and 16 on average have had a significantly higher incidence of late stillbirths than Census Division 11 where the largest proportion of women giving birth reside. There is suggestion of increase over time for Divisions 9 and 15 although statistical significance cannot be definitely stated. When considered by Modified Beale Code, areas that were far from a major metropolitan center, including those with communities of up to 20 000 people, were suspected to have an increased stillbirth risk. Areas that were near metropolitan centers were not convincingly different from areas containing metropolitan centers. The association of remoteness and stillbirth risk is not clearly applicable to the most northern area of the province (Census Division 18).

6.4.2 Objective 2:

- Perceived risk factors for late stillbirth frequently present together among cases. It was difficult in this study to evaluate these associations as risk factors without taking into consideration the occurrence of these

characteristics among live birth outcomes. Efforts to approximate this information led to the following tentative conclusions:

1. The combination of Aboriginality and high parity increases risk beyond what is expected from these two factors.
2. Large for gestational age fetuses in Aboriginal women are at increased risk if the women are thirty-five years or older
3. Women thirty-five years and older carrying a large fetus are at increased risk if they are Aboriginal
4. Aboriginal women thirty-five years and older are at increased risk of loss if they are carrying large for gestational age fetuses.
5. Male losses may be at increased risk in both women thirty-five years and older and women who have had at least three previous pregnancies. These latter observations were not compared against birth data, but such associations are not known or are suggested to be lower in the general pregnant population.

- An association of higher parity levels and remoteness was seen but could not be evaluated for the pregnant population to allow comparison. It, together with all associations noted as possible interactions, need to be revisited and comparison undertaken with characteristics of Saskatchewan live births during the same time period.

6.4.3 Objective 3:

- A number of factors at the area-level appear to have crude associations with increased stillbirth incidence including higher population density, a moderate

proportion of immigrant women in the female reproductive age population, a moderate ratio of children to reproductive age women, a large proportion of reproductive age women thirty-five year of age and older, a moderate proportion of adults without a high school education, a high average age for the total population, and a median annual household income of $45 000 or less. The presence of these factors can identify regions with higher late stillbirth risk but they cannot explain it.

- Areas deemed to have a high proportion of Aboriginal births and a large proportion of hectares sprayed with herbicide appear to have strong associations with stillbirth once multiple confounding factors have been considered. Although it is possible that these factors truly are causal, the ecological nature of the area-level analysis, the relatively small sample size, and the potential for residual confounding, particularly for the association of Aboriginality, make individual-level associations impossible to draw.

6.5 Comparison to Other Stillbirth Research

6.5.1 Descriptive Statistics and Incidence

General descriptive statistics about stillborn deliveries are relatively difficult to locate in the research literature and vary in nature and format. To provide some comparison between stillbirth characteristics in Saskatchewan and elsewhere, results from four other studies using national registries as presented in Table 6.2. It should be noted that not all characteristics were available from each study and some were not comparable due to differences in categorization. Additionally, all four comparison studies include both early and late stillbirths. Overall, however, their results are not

strikingly different from this work with the exception of a higher Aboriginal proportion and differences in distribution by geography.

TABLE 6.2: Comparison of late stillbirth maternal and pregnancy characteristics, thesis results and other published studies

Stillbirth risk factor	Thesis	MacDorman et al.[1]	Sutan et al.[2]	Mohsin et al.[3]	Froen et al.[4]
Maternal age ≥ 35 y	12.8%	17.8%	16.9%	21.8%	15.4%
Parity					
zero	36.1%		39.6%		
≥ 3	21.0%		15.5%		
Registered Indian	26.8%			4.1%	
Previous stillbirth	5.6%		3.0%		2.6%
Modified Beale Code[5]					
3	40.5%		41.4%		
4	12.0%		29.8%		
6	9.1%		9.7%		
7	24.6%		3.4%		
8	<1%		10.8%		
9	2.9%		4.9%		
10	4.7%				
Unknown	5.8%				
Male fetus	52.1%	52.1%	52.8%	52.7%	51.8%
Fetal Size					
SGA[6]	44.6%				
LGA	9.2%				
Plurality	6.8%	9.2%		9.5%	

[1]Data from: National Center for Health Statistics, USA, 2003 (253)

[2]Data from: Information and Statistics Division of the National Health Service in Scotland, 1994-2003 (unexplained antepartum losses only) (254)

[3]Data from: NSW Midwives Data Collection, Australia, 1998-2002 (20)

[4]Data from: Medical Birth Registry of Norway, 1986-1995 (57)

[5]Sutan et al did not use Modified Beale Codes but employed a similar system combining settlement size and driving distance.

[6]Although fetal size for gestation was not described in these studies, SGA has been described to occur in 41% and 48% of stillbirths in two other studies using an ultrasound derived growth standard (90,91)

Thesis findings indicate Saskatchewan stillbirths have increasingly become more Aboriginal and are generally bigger for gestational age than previously. There is also suggestion of increasing maternal age. Although no other work appears to have been undertaken in Saskatchewan to examine temporal directions in these characteristics among stillbirths per se, the results do align with the overall population growth of Aboriginal people recognized in Saskatchewan and the increased LGA/decreasing SGA outcomes in births generally that was seen in Canada during the 1990's (215,255). The possible increase in maternal age among stillbirth over time is also in keeping with the general increase in maternal age noted in Canada (216). Some caution should be exercised, however, in assuming that the increasing proportion of Aboriginal stillbirths is solely a reflection of changes in the population; Luo et al found that among Aboriginal women in Quebec, stillbirth risk itself actually increased between the 1980's and the 1990's (35).

Additional work by Luo et al also in Quebec suggests that women giving birth who live far from a metropolitan center are more likely to be Aboriginal, of higher parity, and younger (43). In this thesis, stillbirth characteristics across Revised Beale Codes align with the first two of these characteristics although maternal age among stillbirths did not change with remoteness. If it is true that pregnant Saskatchewan women who live farther away are also younger than their urban counterparts, it raises the possibility that older women farther from a metropolitan center are at greater risk than those living more proximally.

Proportions of specific causes of death were not remarkably different in comparison. The percentages for specific causes of death in Table 5.3 include losses

with other or unstated causes of death; losses in these categories are not included in the Perinatal Surveillance System reports. To make the proportions comparable, the number of cases in these additional categories were removed from the denominator values and percentages for Saskatchewan were recalculated. The largest proportions during 2002 - 2006 were attributed to membrane, cord, and placental complications (50.8%), followed by losses stated as unspecified (31.2%) and congenital anomalies (10.6%). Canadian Perinatal Surveillance Report 2008 data indicates that causes of stillbirth proportions during 2003 for all stillbirths in Canada, were quite similar (membrane, cord, and placental complications: 42.8%, losses stated as unspecified: 30.8%, congenital anomalies: 14.3%) (215). Looking at the three earlier periods in a similar fashion, there is little consistency or directionality in the differences for these characteristics between Saskatchewan and Canada (256).

Again comparing incidence rates in the 2003 and 2008 surveillance reports for cause-specific stillbirth risks, there appears to be a substantial decline from 1985 to 1999 in the Canadian risk of cord, placenta, and membrane related losses which was not appreciated in this analysis for Saskatchewan. This not completely surprising, however, as Saskatchewan has been recognized to have a statistically higher incidence of placental abruption than Canada as a whole (257). The increased risk of unspecified loss suggested among Saskatchewan women was not apparent for Canada overall. The Saskatchewan risk within these categories also does not align with work in Northern England that saw statistically significant declines in congenital anomalies, antepartum hemorrhage, pre-eclampsia, intrapartum causes, and no substantial change in unexplained rates (164). Recent American work has actually indicated a decline in the latter (165).

The finding of a lack of clear decline in late stillbirth incidence differs from the statistically significant trend that has been calculated for stillbirth in other parts of the developed world. In the United States the decline in stillbirth incidence, largely attributed to fewer late losses, is similar to that seen in this work for the rest of Canada at 1.5% annually (253). The United Kingdom is also experiencing a decline in stillbirth incidence overall evident since 2004 (258). Little information on trend in late stillbirth incidence appears readily available for comparison either within Canada or otherwise.

6.5.2 Log-linear Associations

Associations in the log-linear analysis of stillbirth characteristics yielded some interesting results. An increased number of stillbirths with both high parity and male gender noted in the preliminary model building steps could not be compared among live birth outcomes and the similar association between increased maternal age and male gender also noted was indicated in one study of live births (243). Data from this study indicates an odds ratio for male fetus among older women compared to younger women at 1.24. This is lower than 1.55 in this analysis and raises the question as to whether males carried by an older mother are at greater risk of late pregnancy demise.

The technique of log-linear modeling is aimed at providing information on interactions, an important analytical aspect in stillbirth research where recognized individual risk factors tend to have relatively weak associations on their own. Of particular interest is the finding of suggested increased stillbirth risk in older, Aboriginal women carrying a large for gestational age fetus. As noted in the literature review section, increased maternal age and Aboriginality have been well documented individually but a combined impact has not been indicated in the literature, perhaps due

its dependence on the third factor of fetal size. It is interesting that LGA markedly increases this association, a characteristic which is otherwise generally not considered a risk factor for fetal death. In a recent British Columbia study LGA status has even been seen as protective against stillbirth in Aboriginal women (246). Given the connection diabetes has with Aboriginality, maternal age, fetal macrosomia, and stillbirth, evaluation of its occurrence as a confounder in the current association must be undertaken (259, 260).

6.5.3 Area-level Associations

The area-level analysis suggests that areas with high proportions of Aboriginal children, assumed to be reflective of high proportions of Aboriginal pregnancies, have higher late stillbirth incidence values. This again is in keeping with the individual level associations documented between Aboriginality and stillbirth outcome (33-35). The association of large areas of herbicides application in relation to stillbirth incidence is not frequently seen in the research literature although increased stillbirth has been associated with insecticide exposures or more general pesticide exposure (46,47,50). White et al. did note an association between second trimester area-level exposure to agricultural chemicals, largely herbicides, and increased stillbirth outcomes as did this investigation, but this has not been seen in other studies (53,259). Herbicide exposure appears to be more typically linked to fetal losses occurring prior to twenty weeks gestation (261,262).

6.6 Further Research Directions

Much additional work should be undertaken to better understand the characteristics of Saskatchewan women who experience a late stillbirth. Further examination of the stillbirth characteristics in this study needs to be made in comparison

to live Saskatchewan births during the same time period. Recognizing the variation in stillbirth characteristics over time as noted in this analysis, additional attention needs to be paid to how their role as risk factors may have changed. Given the lack of decline in Saskatchewan late stillbirth incidence particularly in comparison to a declining trend in Canada overall, it would also be valuable to determine how late stillbirths, and pregnancy in general, differ between Saskatchewan and Canada.

As risk of loss from complications of cord, placenta, and membranes does not appear to have declined in Saskatchewan as it has for Canada and presents the highest cause-specific incidence in the province, a more detailed examination of deaths in this category is warranted. As risk of stillbirth from the category of "non-specific" causes is rising, diagnostic methods need to improve. Given the primary importance of autopsy to correct determination of cause of death, additional research needs to uncover what could be done to improve the uptake of this investigation. Recent work from Scotland suggests that better educated health care providers, the involvement of senior staff, clearly outlined care protocols, regular prenatal pathology meetings, and easier access to pathology services may impact this (263). Within the United Kingdom, the lack of a perinatal pathologist, parental anxiety, and a sense that the procedure is unnecessary have been identified as limiting factors to neonatal autopsy (264,265). No work appears to have been undertaken in Canada to understand barriers to autopsy in the situation of fetal loss.

Given the associations noted in the log-linear portion of this work, further investigation of the possible risk introduced by combinations of characteristics, particularly Aboriginality with high parity and Aboriginality with older maternal age and

LGA status, needs to be assessed. This will again require corresponding live birth data as a control group. Particularly for the latter combination, the role of diabetes needs to be evaluated.

Aboriginality itself remains poorly understood as a risk factor for stillbirth outcomes in the literature. Work to date, including this analysis, has relied on birth registries (e.g. vital statistics data) or other non-specific collection methods to examine this variable, missing important characteristics such as maternal factors/conditions, obstetrical complications, and past obstetrical history that could shed further light on what underlies this association. Collecting more detailed data on this relatively infrequent and often heart-breaking event is difficult. One feasible and non-threatening avenue might be the development of a standard electronic provincial prenatal form that could be released (with permission) in de-identified form for investigative purposes. Such a resource province-wide could benefit the understanding of birth outcomes for all Saskatchewan women.

The association of regional herbicide application and late stillbirth is somewhat surprising given its limited presence in the research literature. As this finding was ecological in nature with relatively large units of analysis, a next step would be to reassess this association within smaller geographic areas. The broad herbicide category should also be re-evaluated to identify more specific chemical agents of interest. Individual levels information measuring personal exposure, although challenging to collect, would ultimately be required to support or disprove this association.

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APPENDIX A: Definitions

Abruption: the separation of the placenta from its site of implantation before delivery (212)

Antenatal: before birth (266)

Antepartum: Occurring before the onset of labour (266)

Asphyxia: a life-threatening condition in which oxygen is prevented from reaching the tissues by obstruction of or damage to any part of the respiratory system (266)

Beale codes: An American classification system that has been adapted for Canadian non-metropolitan analysis ("modified Beale codes") that considers both population size/density and settlement context (214)

Blishen Index: a Canadian-based scale for ranking the socioeconomic status of occupations by assigning codes based on education and income levels for each occupational category (267)

Body Mass Index: weight in kilograms divided by height in squared meters

Census agglomeration: one or more adjacent municipalities centered on an urban core with a minimum population of 10 000 living in the core (268)

Census division: the general term for provincially legislated areas or their equivalents. Census divisions are intermediate geographic areas between the province/territory level and the municipality (census subdivision) (268)

Census metropolitan area: one or more adjacent municipalities centered on an urban core with a total population of at least 100,000, of which at least 50,000 live in the urban core (268)

Congenital anomaly: an abnormality present at birth. (266)

Customized growth curves: computer-generated antenatal growth charts derived from ultrasound based intrauterine weights and adjusted for individual maternal/fetal characteristics (94)

Early neonatal death: Death of a child under one week of age (0 to 6 days) (269)

Eclampsia: Seizures that cannot be attributed to other causes in a woman with pre-eclampsia (212)

Gestational diabetes: Diabetes that is induced or possibly unmasked by pregnancy (212)

Hydrops fetalis: the accumulation of fluid in fetal tissues or body cavities (266)

Intrapartum: occurring during labor or delivery (212)

Intrauterine growth restriction: failure of a fetus to achieve its growth potential, resulting in the birth of a baby whose birth weight is abnormally low in relation to its gestational age (266)

Isoimmunization: development of antibodies in response to isoantigens, antigens existing in more than one form in a species, thus inducing an immune response when one form is transferred to members of the species who lack it (e.g. maternal immune response to different fetal blood type when exposure occurs); typical isoantigens are the blood group antigens. (212)

Monochorionic: having a single chorion, the membrane surrounding the embryo, amniotic cavity, and amniotic sac and contributing to the fetal part of the placenta (212). Identical twins may share a common chorionic membrane

Multiparous: having completed two or more pregnancies to 20 weeks or more (270)

Multiple pregnancy: the presence of more than one fetus in the uterus at the same time (212)

Nulliparity: the state of never having completed a pregnancy beyond 20 weeks gestation. Nulliparous women may or may not have been pregnant or may have had a spontaneous or elective abortion(s) (270)

Parity: the number of pregnancies reaching 20 weeks gestation, whether delivered alive or dead (270)

Perinatal death: Death of a child under one week of age (0 to 6 days) or a stillbirth of 28 or more weeks of gestation (269)

Polymerase chain reaction testing: a technique of molecular genetics in which a particular sequence of DNA can be isolated and amplified sufficiently to enable genetic analysis. The technique may be utilized, for example, in the identification of viruses in tissue samples (266)

Population attributable risk proportion: the proportion of the total incidence in an exposed group that is attributable to the exposure (221)

Post term pregnancy: a pregnancy that has gone beyond 42 weeks gestation or 294 days from the first date of the last menstrual period (266)

Pre-eclampsia: gestational hypertension with proteinuria or typical end-organ dysfunction (212)

Pre-existing hypertension: hypertension that pre-dates pregnancy or appears before twenty weeks (271)

Pregnancy induced hypertension: Refers to increased blood pressure without proteinuria seen during pregnancy for the first time. This term has been relabeled and further specified as gestational hypertension (212,271)

Premature rupture of membranes: rupture of the amniotic sac prior to term (37 weeks gestation) (272)

Singleton: a pregnancy involving a single fetus

Small for Gestational Age: newborns whose birth weight is typically below the 10^{th} percentile for gestational age (212)

Stillbirth – "Fetal death (stillbirth) is death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. Only fetal deaths where the product of conception has a birth weight of 500 grams or more or the duration of pregnancy is 20 weeks or longer are registered in Canada (5)."

"Late fetal death refers to a fetal death (stillbirth) with a duration of pregnancy of 28 weeks or more (5)."

Term: anytime after 37 completed weeks of gestation and up until 42 weeks completed weeks of gestation (260 to 294 days) (212)

Thrombophilia: an inherited or acquired condition that predisposes individuals to thrombosis (clot formation) (266)

Umbilical cord knot: an actual knotting of the umbilical cord (true knot) due to fetal movement, opposed to false knots which have a similar appearance but result from kinking of the vessels and are benign (270)

APPENDIX B: Saskatchewan Stillbirth Registration Forms

V-7.1 REG 1 VITAL STATISTICS

Form V.S. 3
[Section 10]
Registration of Stillbirth

Formulaire V.S. 3
[Article 10]
Enregistrement de Mortinaissance

V.S. 3

Saskatchewan Health
Vital Statistics
Ministère de la Santé
de la Saskatchewan
Services de l'état civil

REGISTRATION OF
STILLBIRTH
ENREGISTREMENT DE
MORTINAISSANCE

Registration No. (*office use only*)
N° d'enregistrement (*à l'usage du bureau*)

This is a permanent legal document. Type or print in blue or black ink and complete all items.
Ceci est un document juridique définitif. Dactylographier ou écrire en lettres moulées à l'encre bleue ou noire. Remplir toutes les cases.

CHILD ENFANT

1. Surname / Nom de famille — 2. Sex / Sexe
Given Name(s) / Prénom(s)
3. Date of Stillbirth / Date de mortinaissance — Month / Mois, Day / Jour, Year / Année
4. Duration of pregnancy / Durée de la grossesse _____ (*weeks / semaines*)
5. Weight at stillbirth / Poids à la mortinaissance (*grams / grammes*)
6. Place of Stillbirth — Name of Hospital or exact address where stillbirth occurred
Lieu de mortinaissance — Nom de l'hôpital ou adresse exacte où a eu lieu la mortinaissance
City, town, village or other place. (*If rural, give section, township, range and meridian*)
Ville, village ou autre endroit. (*s'il s'agit d'une municipalité rurale, indiquer la section, le rang, le canton et le méridien*)
7. Kind of birth / Type de naissance — ☐ Single / Simple ☐ Twin / Jumeaux ☐ Triplet / Triplés ☐ other (*specify*) / autre (*préciser*) _____
8. Birth order, if multiple birth — Ordre de naissance, s'il s'agit d'une naissance multiple — ☐ 1st / 1er ☐ 2nd / 2e ☐ 3rd / 3e ☐ other (*specify*) / autre (*préciser*) _____
9. Total children born to this mother (*including this stillbirth*) — Nombre d'enfants nés de la mère (*y compris la présente mortinaissance*) — Liveborn / Nés vivants ☐☐ Stillborn / Mort-nés ☐☐
10. Name of attending physician (*or other attendant*) — Nom du médecin accoucheur (*ou autre personne qui a aidé à l'accouchement*)

MOTHER MÈRE

11. Current Surname / Nom de famille actuel — Maiden Surname / Nom de jeune fille — Given Name(s) / Prénom(s)
12. Place of Birth — city, town or village / Lieu de naissance — ville ou village — Province, state or country / Province, état ou pays
13. Date of Birth / Date de naissance — Month / Mois, Day / Jour, Year / Année
14. Usual Residence — street address (*if rural give section, township, range and meridian*) — Résidence habituelle — rue [adresse complète] (*s'il s'agit d'une municipalité rurale, indiquer la section, le rang, le canton et le méridien*)
City, town or village or other place / Ville ou village ou autre endroit — Province or country / Province ou pays — Postal code / Code postal
15. Complete mailing address (*if different from item 14*) / Adresse postale complète (*si elle diffère de 14*) — Postal code / Code postal
16. Marital status (*optional*) / Situation de famille (*facultatif*) — ☐ Never married / Célibataire ☐ Married / Mariée ☐ Widowed / Veuve ☐ Divorced / Divorcée
17. Saskatchewan Health Card Number / Numéro de carte de santé de la Saskatchewan
18. Are you (*optional*) / Statut (*facultatif*) — ☐ Indian / Indienne ☐ Métis / Métisse ☐ Inuit / Inuit
If registered under the *Indian Act*: / Si vous êtes enregistrée selon la *Loi sur les Indiens* : Name of Band / Nom de la bande — Registry Number / Numéro d'enregistrement
19. I certify this statement to be true and correct to the best of my knowledge and belief: / J'atteste qu'à ma connaissance, les renseignements donnés ci-dessus sont véridiques et exacts : — Signature of Mother / Signature de la mère X_____
20. Date signed / Date de signature — Month / Mois Day / Jour Year / Année

Father's particulars must not be shown unless his signature is present.
Renseignements à ne pas donner sans la signature du père.

FATHER PÈRE

21. Surname / Nom de famille — Given Name(s) / Prénom(s)
22. Place of Birth — city, town or village / Lieu de naissance — ville ou village — Province, state or country / Province, état ou pays
23. Date of Birth / Date de naissance — Month / Mois, Day / Jour, Year / Année
24. Complete mailing address / Adresse postale complète — Postal code / Code postal
25. Marital status (*optional*) / Situation de famille (*facultatif*) — ☐ Never married / Célibataire ☐ Married / Marié ☐ Widowed / Veuf ☐ Divorced / Divorcé
26. Saskatchewan Health Card Number / Numéro de carte de santé de la Saskatchewan
27. Are you (*optional*) / Statut (*facultatif*) — ☐ Indian / Indien ☐ Métis / Métis ☐ Inuit / Inuit
If registered under the *Indian Act*: / Si vous êtes enregistré selon la *Loi sur les Indiens* : Name of Band / Nom de la bande — Registry Number / Numéro d'enregistrement
28. I certify this statement to be true and correct to the best of my knowledge and belief: / J'atteste qu'à ma connaissance, les renseignements donnés ci-dessus sont véridiques et exacts : — Signature of Father / Signature du père X_____
29. Date signed / Date de signature — Month / Mois Day / Jour Year / Année

The statutory declaration on the back of this form must be completed if neither parent is capable of completing and signing this registration.
Si aucun des parents n'est capable de remplir et de signer l'enregistrement, remplir la déclaration solennelle au verso.

HEALTH / SANTÉ 2005

CERTIFICATION OF INFORMANT ATTESTATION DU DÉCLARANT

If neither parent is capable of completing and signing this registration, the person standing in place of the parents or any person who has knowledge of the stillbirth must sign and date the following:

Si aucun des parents n'est capable de remplir et de signer l'enregistrement, la personne qui remplace les parents de l'enfant ou toute personne qui a connaissance de la mortinaissance de l'enfant doit signer et dater la déclaration suivante :

30. I certify this statement to be true and correct to the best of my knowledge and belief:
J'atteste qu'à ma connaissance, les renseignements donnés ci-dessus sont véridiques et exacts :
Signature of Informant
Signature du déclarant X _____

31. Date signed / Date de signature
Month / Mois | Day / Jour | Year / Année

32. Complete mailing address / Adresse postale complète

Postal code / Code postal

If neither parent is capable of completing and signing this registration, the person standing in place of the parents or any person who has knowledge of the stillbirth must complete the statutory declaration below.

Si aucun des parents n'est capable de remplir et de signer l'enregistrement, la personne qui remplace les parents de l'enfant ou toute personne qui a connaissance de la mortinaissance doit remplir la déclaration solennelle qui suit.

STATUTORY DECLARATION DÉCLARATION SOLENNELLE

I, / Je soussigné(e) _____ do solemnly declare that: / déclare solennellement que :

- The mother is incapable because of:
  la mère est une incapable pour la raison suivante :
  ☐ death / décès ☐ illness / maladie ☐ absence from the province / absence de la province
  ☐ otherwise (if otherwise — state reason) / autre raison (Préciser la raison) _____
- The father is incapable because of:
  le père est un incapable pour la raison suivante :
  ☐ death / décès ☐ illness / maladie ☐ absence from the province / absence de la province
  ☐ otherwise (if otherwise — state reason) / autre raison (Préciser la raison) _____

I make this solemn declaration conscientiously believing it to be true and knowing it to be of the same force and effect as if made under oath, and by virtue of the *Canada Evidence Act*.

Je fais cette déclaration solennelle la croyant, en mon âme et conscience véridique et sachant qu'elle a la même force et le même effet que si elle avait été faite sous serment, et en vertu de la *Loi sur la preuve du Canada*.

Declared before me at
Déclaré devant moi à _____ , Saskatchewan,

this day of
ce _____ jour de _____ , 20_____

X _____
Signature of Declarant
Signature du déclarant

_____
Signature of Notary Public, Justice of the Peace or Commissioner for Oaths in and for Saskatchewan
Signature du notaire, juge de paix ou commissaire à l'assermentation en et pour la Saskatchewan

My appointment expires
Mon mandat expire le _____

FUNERAL DIRECTOR POUR L'ENTREPRENEUR DE POMPES FUNÈBRES

33. Burial, cremation or other disposition
Inhumation, crémation ou autre disposition

34. Date of burial or disposition
Date de l'inhumation ou autre disposition
Month / Mois | Day / Jour | Year / Année

35. Name and address of cemetery, crematorium or place of disposition
Nom et adresse du cimetière, du crématorium ou endroit proposé pour toute autre disposition du corps

36. Name and address of funeral director or person in charge of remains
Nom et adresse de l'entrepreneur de pompes funèbres ou de la personne responsable des restes

DO NOT WRITE BELOW THIS LINE—OFFICE USE ONLY NE RIEN ÉCRIRE CI-DESSOUS —À L'USAGE DU BUREAU

Notations / Remarques :

Registration Division / Division d'enregistrement

I certify this return was accepted by me on this date:
J'atteste avoir accepté le présent enregistrement à la date suivante :

_____ _____
Month / Mois, Day / Jour, Year / Année Signature of Division Registrar / Signature du registraire de division

Saskatchewan Health
Vital Statistics
Ministère de la Santé
de la Saskatchewan
Services de l'état civil

MEDICAL CERTIFICATE OF **STILLBIRTH** CERTIFICAT MÉDICAL DE **MORTINAISSANCE**

Registration No. *(office use only)*
N° d'enregistrement *(à l'usage du bureau)*

1. Surname / Nom de famille — 2. Sex / Sexe

Given Name(s) / Prénom(s)

3. Date of Stillbirth / Date de mortinaissance — Month / Mois | Day / Jour | Year / Année

4. Duration of pregnancy / Durée de la grossesse _____ *(weeks / semaines)*

5. Weight at stillbirth / Poids à la mortinaissance ☐☐☐☐ *(grams / grammes)*

6. Place of Stillbirth — Name of Hospital or exact address where birth occurred
Lieu de mortinaissance — Nom de l'hôpital ou adresse exacte où a eu lieu laccouchement

City, town, village or other place. *(If rural, give section, township, range and meridian)*
Ville, village ou autre endroit. *(s'il s'agit d'une municipalité rurale, indiquer la section, le rang, le canton et le méridien)*

SEE REVERSE FOR INSTRUCTIONS BEFORE COMPLETING
LIRE LES DIRECTIVES AU VERSO AVANT DE REMPLIR CE QUI SUIT

7. Cause of Death / Cause de décès

Check whether fetal or maternal: Cocher : Fetal / Foetus — Maternal / Mère

Part I / Partie I

I

Immediate cause—fetal disease or condition directly leading to stillbirth
Cause immédiate—Maladie ou état du foetus entraînant directementla mortinaissance
a) _____ due to, or as a consequence of / causé par ou en conséquence de ☐ ☐

Antecedent causes—Fetal and/or maternal conditions, if any, giving rise to the immediate cause (a) above, *stating the underlying cause last*
Causes antérieures—Affections du foetus ou de la mère, ou les deux à la fois, ayant, le cas échéant, provoqué la cause immédiate a). *Mentionner la cause initiale en dernier*
b) _____ due to, or as a consequence of / causé par ou en conséquence de ☐ ☐
c) _____ ☐ ☐

Part II / Partie II

II

Other significant conditions of fetus or mother which may have contributed to the stillbirth but were not causally related to the immediate cause (a) above
Autres affections importantes du foetus ou de la mère qui peuvent avoir contribué à la mortinaissance mais qui ne sont pas directement reliées à la cause immediate a)
_____ ☐ ☐
_____ ☐ ☐

8. Autopsy being held? / Y a-t-il autopsie? ☐ Yes / Oui ☐ No / Non

9. Does the cause of stillbirth take into account the autopsy findings? / La cause de la mortinaissance susmentionée tient-elle compte des résultats de l'autopsie? ☐ Yes / Oui ☐ No / Non

10. May further information relating to the cause of stillbirth be available later? / Y aura-t-il d'autres renseignements ultérieurs concernant la cause de la mortinaissance? ☐ Yes / Oui ☐ No / Non

11. Manipulative, instrumental or other operative procedure for delivery? / Y a-t-il eu manipulation, usage d'instrument ou autre intervention lors de l'accouchement? ☐ Yes (*specify*) / Oui (*préciser*) ☐ No / Non

Was fetus dead before such procedure? / Le foetus était-il mort avant cette intervention? ☐ Yes / Oui ☐ No / Non

12. Did death occur before labour? / La mort a-t-elle eu lieu avant le travail? ☐ Yes / Oui ☐ No / Non

During labour? / Pendant le travail? ☐ Yes / Oui ☐ No / Non

Labour induced? _____ A-t-elle été provoquée par le travail? ☐ Yes (*specify method*) / Oui (*préciser comment*) ☐ No / Non

13. Congenital malformation? / Malformation congénitale? ☐ Yes (*specify*) / Oui (*préciser*) ☐ No / Non

14. Birth injuries? / Traumatisme obstétrical? ☐ Yes (*specify*) / Oui (*préciser*) ☐ No / Non

15. Pregnancy complication? / Complication pendant la grossesse? ☐ Yes (*specify*) / Oui (*préciser*) ☐ No / Non

16. Name of physician or coroner (*print or type*)
Nom du médecin ou du coroner (*dactylographier ou écrire en lettres moulées*)

Address / Adresse

17. ☐ Attending physician / Médecin présent ☐ Physician attending after death / Médecin présent après le décès ☐ Coroner / Coroner

18. I certify that this medical certificate of stillbirth is true and correct to the best of my knowledge and belief:
J'atteste qu'à ma connaissance, ce certificat medicale de mortinaissance est véridique et exact :

_____
Signature (*attending physician, coroner*)
Signature (*médecin présent, coroner*)

_____
Month / Mois Day / Jour Year / Année
Date of signature / Date de signature

This is a permanent legal document. Type or print in blue or black ink and complete all items.
Ceci est un document juridique définitif. Dactylographier ou écrire en lettres moulées à l'encre bleue ou noire. Remplir toutes les cases.

Notes for the Certifying Physician or Coroner Regarding the Medical Certificate of Stillbirth

A "stillbirth" is defined under *The Vital Statistics Act, 1995*, of Saskatchewan, as follows:

> **"Stillbirth" means the complete expulsion or extraction from the mother after at least 20 weeks pregnancy, or after attaining a weight of at least 500 grams, of a product of conception in which, after the expulsion or extraction, there is no breathing, beating of the heart, pulsation of the umbilical cord or unmistakable movement of voluntary muscle.**

The cause of death section (point no. 7) consists of two parts. Part I is designed to facilitate reporting, in ascending causal order of sequence, the train of morbid events leading directly to death, or the circumstances of the accident, poisoning or violence which produced the fatal injury. The underlying cause of death is reported alone on the lowest used line of Part I and the conditions, if any, which arose as a consequence of this underlying cause will be entered above it, one condition to each line, in ascending order of causal sequence. Part II is for reporting other significant conditions that contributed to the death but are not part of the sequence reported in Part I.

Fetal or Maternal Diseases or Conditions

Conditions reported as Antecedent causes may relate to either the fetus or the mother. It is important to indicate whether the reported condition was a "fetal" or "maternal" condition by checking off (✔ *or* X) in the appropriate box.

Additional Information

Question 10—If you indicate that there will be further information available at a later date from autopsy or other findings, the Director of Vital Statistics will initiate a request for this information.

The following example illustrates the essential principles in completing the Medical Certificate of Stillbirth:

Remarques pour le médecin ou le coroner concernant le certificat médical de mortinaissance

Selon la *Loi de 1995 sur les services de l'état civil* de la Saskatchewan, une "mortinaissance" est définie comme suit:

> **« mortinaissance » L'expulsion ou l'extraction complète du corps de la mère d'un produit de la conception après 20 semaines au moins de grossesse ou qui pèse 500 grammes au moins, chez lequel, après cette expulsion ou extraction, il n'y a aucune respiration, aucun battement du coeur, aucune pulsation du cordon ombilical ou contraction nettement perceptible d'un muscle volontaire.**

La cause de décès (section 7) comporte deux parties. La Partie I est conçue pour faciliter la déclaration, par ordre croissant de l'enchaînement causal, de la séquence des événements morbides ayant conduit directement à la mort ou les circonstances de l'accident, de l'empoisonnement ou de la violence qui a produit le traumatisme mortel. La cause initiale de décès est déclarée seule sur la dernière ligne utilisée (c.-à-d. la plus basse) de la Partie I et, s'il y a lieu, les états morbides qui sont survenus comme conséquence de cette cause initale sont nscrits au-dessus de cette dernière, un état morbide par ligne, par ordre croissant de l'enchaînement causal. La Partie II sert à signaler d'autres états morbides importants qui ont contribué au décès, mais qui ne font pas partie de la séquence exposée dans la Partie I.

Maladies ou affections du foetus ou de la mère

Les affections mentionnées comme causes antérieures peuvent s'appliquer au foetus comme à la mère. Il est important de mentionner si la affections s'appliquait au "foetus" ou à la "mère" en cochant (✔ *or* X) la case appropriée.

Renseignements supplémentaires

Question 10—Si l'on mentionne qu'on est dans l'attente des résultats de l'autopsie, le directeur des services de l'état civil exigera ces résultats.

L'exemple suivant illustre les principes essentiels pour remplir le certificat médical de mortinaissance :

7. Cause of Death / Cause de décès

Check whether fetal or maternal: Cocher : Fetal Foetus / Maternal Mère

Part I / Partie I

Immediate cause—fetal disease or condition directly leading to stillbirth
Cause immédiate—Maladie ou état du foetus entraînant directement la mortinaissance

Antecedent causes—Fetal and/or maternal conditions, if any, giving rise to the immediate cause (a) above, *stating the underlying cause last*
Causes antérieures—Affections du foetus ou de la mère, ou les deux à la fois, ayant, le cas échéant, provoqué la cause immédiate a). *Mentionner la cause initiale en dernier*

I

a) *INTRAUTERINE ANOXIA*
ANOXIE INTRA-UTÉRINE — Fetal ☐ Maternal ☐
due to, or as a consequence of / causé par ou en conséquence de

b) *PLACENTAL INSUFFICIENCY*
INSUFFISANCE PLACENTAIRE — Fetal ☐ Maternal ☒
due to, or as a consequence of / causé par ou en conséquence de

c) *GESTATIONAL DIABETES*
DIABÈTE GESTATIONNEL — Fetal ☐ Maternal ☒

Part II / Partie II

Other significant conditions of fetus or mother which may have contributed to the stillbirth but were not causally related to the immediate cause (a) above
Autres affections importantes du foetus ou de la mère qui peuvent avoir contribué à la mortinaissance mais qui ne sont pas directement reliées à la cause immediate a)

II

POOR NUTRITION
MALNUTRITION — Fetal ☐ Maternal ☒

Fetal ☐ Maternal ☐

8. Autopsy being held? / Y a-t-il autopsie? ☐ Yes / Oui ☒ No / Non

9. Does the cause of stillbirth take into account the autopsy findings? / La cause de la mortinaissance susmentionée tient-elle compte des résultats de l'autopsie? ☐ Yes / Oui ☒ No / Non

10. May further information relating to the cause of stillbirth be available later? / Y aura-t-il d'autres renseignements ultérieurs concernant la cause de la mortinaissance? ☐ Yes / Oui ☒ No / Non

11. Manipulative, instrumental or other operative procedure for delivery? / Y-a-t-il eu manipulation, usage d'instrument ou autre intervention lors de l'accouchement? ☒ Yes (*specify*) / Oui (*préciser*) *LOW FORCEPS / FORCEPS À LA PARTIE BASSE* ☐ No / Non

Was fetus dead before such procedure? / Le foetus était-il mort avant cette intervention? ☐ Yes / Oui ☐ No / Non

12. Did death occur before labour? / La mort a-t-elle eu lieu avant le travail? ☒ Yes / Oui ☐ No / Non

During labour? / Pendant le travail? ☐ Yes / Oui ☒ No / Non

Labour induced? / A-t-elle été provoquée par le travail? ☐ Yes (*specify method*) / Oui (*préciser comment*) ☒ No / Non

13. Congenital malformation? / Malformation congénitale? ☐ Yes (*specify*) / Oui (*préciser*) ☒ No / Non

14. Birth injuries? / Traumatisme obstétrical? ☐ Yes (*specify*) / Oui (*préciser*) ☒ No / Non

15. Pregnancy complication? / Complication pendant la grossesse? ☒ Yes (*specify*) / Oui (*préciser*) *GESTATIONAL DIABETES / DIABÈTE GESTATIONNEL* ☐ No / Non

INSTRUCTIONS FOR REGISTRATION OF STILLBIRTH

1. "Stillbirth" means the complete expulsion or extraction from the mother of a fetus weighing 500 grams or more, if the fetus shows no sign of life at or after the birth. Within this definition, the stillbirth of every child in Saskatchewan must be registered within 15 days after the birth. If a stillbirth occurs in a hospital, hospital staff will require that the Registration of Stillbirth be completed before the mother leaves the hospital.
2. Registering the birth is the responsibility of:
   (a) the mother or the father of the child or both;
   (b) if both the mother and the father are incapable, the person standing in place of the parents; or
   (c) if there is no person to whom (a) or (b) applies, any person who has knowledge of the stillbirth.

   "Incapable" means unable to act because of death, illness, absence from the province or otherwise.
3. When completing the Registration of Stillbirth, the section pertaining to the father's particulars can be completed only if the father is able to sign the form. However, the father's surname can be given to the child without the father's signature. **THE FATHER'S PARTICULARS ARE NOT TO BE ENTERED IF HE IS UNABLE TO SIGN THE FORM.**
4. If the registration is completed by a person named in 2(b) or (c) above, the statutory declaration contained on the back of the Registration of Stillbirth form must be completed and signed. The statutory declaration must be witnessed and signed by a Commissioner for Oaths, Justice of the Peace or Notary Public. An example of a completed statutory declaration is as follows:

STATUTORY DECLARATION / **DÉCLARATION SOLENNELLE**

I, / Je soussigné(e) *JANE M. THOMAS* do solemnly declare that: / déclare solennellement que :

- The mother is incapable because of: / la mère est une incapable pour la raison suivante :
  ☐ death / décès ☒ illness / maladie ☐ absence from the province / absence de la province
  ☐ otherwise (if otherwise — state reason) / autre raison (Préciser la raison) _____
- The father is incapable because of: / le père est un incapable pour la raison suivante :
  ☐ death / décès ☐ illness / maladie ☒ absence from the province / absence de la province
  ☐ otherwise (if otherwise — state reason) / autre raison (Préciser la raison) _____

I make this solemn declaration conscientiously believing it to be true and knowing it to be of the same force and effect as if made under oath, and by virtue of the *Canada Evidence Act*.

Je fais cette déclaration solennelle la croyant, en mon âme et conscience véridique et sachant qu'elle a la même force et le même effet que si elle avait été faite sous serment, et en vertu de la *Loi sur la preuve du Canada*.

Declared before me at / Déclaré devant moi à *Regina*, Saskatchewan,

this / ce *1* day of / jour de *May*, 20 *04*

X *Jane M. Thomas*
Signature of Declarant / Signature du déclarant

Nancy Peters
Signature of Notary Public, Justice of the Peace or Commissioner for Oaths in and for Saskatchewan / Signature du notaire, juge de paix ou commissaire à l'assermentation en et pour la Saskatchewan

My appointment expires / Mon mandat expire le *March 31, 2008*

5. The child's name must be written entirely in characters of the Roman alphabet. If identifiers such as Junior, Jr, II or III are included in either the given name(s) or surname of the child, it will become part of their legal name. A child's surname can contain no more than two names hyphenated or combined. A child's surname can be any name chosen by the parent(s) and does not have to be the same name as that of either parent.

Options	Surnames	Result
(a) Parents have the same or different surnames and agree on their child's surname.	Child's surname will be as chosen by the parents regardless of the parents' surnames and can consist of a single surname or a hyphenated or combined surname.	Child and parents may or may not have the same surname.
(b) Parents have different surnames but do not agree on their child's surname.	Child's surname will consist of both parents' surnames hyphenated or combined in alphabetical order.	Child has a hyphenated or combined surname made up of the parents' surnames.
(c) Parents have the same surname but do not agree on their child's name.	Child's surname will be the parents' surname.	Child and parents have the same surname.
(d) One or both parents have a hyphenated or combined surname and want to give their child a hyphenated or combined surname.	Child's surname will consist of only one of the names from the surname of the mother which can be hyphenated or combined with only one of the names from the surname of the father.	Child has a hyphenated or combined surname made up of the parents' surnames.
(e) Where only one parent completes and signs the Registration of Stillbirth.	The child's surname will be the surname chosen by that parent and can consist of a single surname or a hyphenated or a combined surname.	Child and parent may or may not have the same surname.
(f) If a person who is not the child's parent completes and signs the the Registration of Stillbirth.	The child's surname will be the parents' surname, if they have the same surname. If the parents have different surnames. the child's surname will consist of both parents' surnames hyphenated or combined in alphabetical order. If only one parent is known, the child's surname will be that parent's surname.	Child has a hyphenated or combined surname or the child's surname will be the same as the parent's(s') surname.

PLEASE CHOOSE THE CHILD'S NAME CAREFULLY.

6. If a pregnancy results in the stillbirth of more than one child, a Registration of Stillbirth must be completed for each child.
7. Where a Registration of Stillbirth cannot be obtained prior to the mother leaving the hospital, the operator of the hospital shall report the stillbirth to the Director of Vital Statistics within 24 hours using Form V.S. 6

ANY INQUIRIES REGARDING THE REGISTRATION OF STILLBIRTH MAY BE DIRECTED TO THE OFFICE OF VITAL STATISTICS, REGINA, SASKATCHEWAN.

DIRECTIVES POUR L'ENREGISTREMENT D'UNE MORTINAISSANCE

1. *Mortinaissence* : Expulsion ou extraction complète hors du corps de la mère d'un foetus qui pèse au moins 500 grammes et qui, au moment de la naissance ou après, ne montre aucun signe de vie. Selon cette définition, la mortinaissance de tout enfant mort-né en Saskatchewan doit être enregistrée dans les 15 jours qui suivent la naissance. Si la mortinaissance a lieu dans un hôpital, l'administration de l'hôpital est tenue de faire remplir l'enregistrement de mortinaissance avant que la mère ne quitte l'hôpital.
2. L'enregistrement de la mortinaissance incombe :
   a) à la mère ou au père de l'enfant, ou aux deux parents;
   b) à la personne qui tient lieu des parents de l'enfant, si la mère et le père sont tous deux des incapables;
   c) à toute personne qui a connaissance de la mortinaissance de l'enfant, si les alinéas a) et b) ne s'appliquent à personne.
   «incapable» veut dire empêché d'agir pour cause de décès, de maladie ou d'absence de la province, ou autre raison.
3. La partie se rapportant aux renseignements sur le père ne peut être remplie que si le père est capable de signer la déclaration. Cependant, on peut donner le nom de famille du père à l'enfant sans la signature du père. **NE PAS INSCRIRE LES ENSEIGNEMENTS SUR LE PÈRE S'IL EST INCAPABLE DE SIGNER.**
4. Si l'enregistrement est rempli par une personne mentionnée à l'alinéa 2 b) ou c), la déclaration solennelle qui se trouve au verso de l'enregistrement de naissance doit être obligatoirement remplie et signée. Cette déclaration solennelle doit être attestée et signée par un commissaire à l'assermentation, un juge de paix ou un notaire. Se référer à l'exemple qui suit :

STATUTORY DECLARATION — DÉCLARATION SOLENNELLE

I, / Je soussigné(e) JANE M THOMAS do solemnly declare that: / déclare solennellement que :

- The mother is incapable because of:
  la mère est une incapable pour la raison suivante :
  ☐ death / décès ☒ illness / maladie ☐ absence from the province / absence de la province
  ☐ otherwise (if otherwise — state reason) / autre raison (Préciser la raison) _____
- The father is incapable because of:
  le père est un incapable pour la raison suivante :
  ☐ death / décès ☐ illness / maladie ☒ absence from the province / absence de la province
  ☐ otherwise (if otherwise — state reason) / autre raison (Préciser la raison) _____

I make this solemn declaration conscientiously believing it to be true and knowing it to be of the same force and effect as if made under oath, and by virtue of the *Canada Evidence Act*.

Je fais cette déclaration solennelle la croyant, en mon âme et conscience véridique et sachant qu'elle a la même force et le même effet que si elle avait été faite sous serment, et en vertu de la *Loi sur la preuve du Canada*.

Declared before me at / Déclaré devant moi à Regina, Saskatchewan,

this / ce 1 day of / jour de May, 20 04

X Jane M. Thomas
Signature of Declarant / Signature du déclarant

Nancy Peters
Signature of Notary Public, Justice of the Peace or Commissioner for Oaths in and for Saskatchewan / Signature du notaire, juge de paix ou commissaire à l'assermentation en et pour la Saskatchewan

My appointment expires / Mon mandat expire le March 31, 2008

5. Le nom de l'enfant doit être écrit entièrement en caractères romains. Si on inclut des termes comme fils, II, ou III, dans le(s) prénom(s) ou nom de famille de l'enfant, ils feront partie de son nom légal. Le nom de famille de l'enfant ne peut comporter plus de deux noms de famille unis par un trait d'union ou accolés. Le nom de famille de l'enfant peut être n'importe quel nom choisi par le(s) parent(s) et N'EST PAS obligatoirement le même nom que celui de l'un ou de l'autre parent.

Options	Nom de famille	Résultat
a) Les parents ont le même nom de famille ou des noms de famille différents et s'entendent sur le nom de famille de leur enfant.	L'enfant peut recevoir un seul nom de famille, ou le nom de famille des deux parents, unis par un trait d'union ou accolés.	L'enfant et les parents peuvent porter le même nom de famille ou des noms de famille différents.
b) Les parents ont des noms de famille différents mais ne **s'entendent pas** sur le nom de famille de leur enfant.	L'enfant reçoit les noms de famille des deux parents, unis par un trait d'union ou accolés, par ordre alphabétique.	L'enfant porte un nom de famille formé des noms de famille des parents, unis par un trait d'union ou accolés.
c) Les parents ont le même nom de famille mais **ne s'entendent pas** sur le nom de famille de leur enfant.	L'enfant reçoit le nom de famille des parents.	L'enfant et les parents portent le même nom de famille.
d) Un parent, ou les deux, ont deux noms de famille, unis par un trait d'union ou accolés, et veulent donner à leur enfant deux noms de famille, unis ou accolés.	L'enfant reçoit deux noms de famille, unis par un trait d'union ou accolés, dont un seul des noms compris dans les noms de famille du père et un seul compris dans les noms de famille de la mère.	L'enfant porte un nom de famille formé des noms de famille des parents, unis par un trait d'union ou accolés.
e) Un seul parent remplit et signe l'enregistrement de mortinaissance.	Le parent choisit le nom de famille de l'enfant. L'enfant peut recevoir un seul nom de famille ou deux noms de famille, unis par un trait d'union ou accolés.	L'enfant et le parent peuvent porter le même nom de famille ou des noms de famille différents.
f) Une personne qui tient lieu des père et mère remplit et signe l'enregistrement de mortinaissance.	L'enfant reçoit le nom de famille des parents, s'ils portent le même nom de famille. S'ils ont des noms de famille différents, l'enfant reçoit les noms de famille des deux parents, unis par un trait d'union ou accolés, par ordre alphabétique. Si un seul parent est connu, l'enfant reçoit le nom de famille de ce parent.	L'enfant porte une nom de famille formé des noms de famille des parents, unis par un trait d'union ou accolés, ou porte le même nom de famille que le parent.

VEUILLEZ CHOISIR SOIGNEUSEMENT LE NOM DE FAMILLE DE L'ENFANT.

6. Si une grossesse se termine par la mortinaissance de plusieurs enfants, une enregistrement doit être rempli pour chaque enfant.
7. Si on ne peut obtenir un enregistrement de mortinaissance avant que la mère ne quitte l'hôpital, l'administration de l'hôpital est tenue de déclarer la mortinaissance au directeur des services de l'état civil dans les 24 heures suivant la mortinaissance à l'aide du formulaire V.S. 6 des services de l'état civil.

POUR TOUTE DEMANDE DE RENSEIGNEMENTS SUR L'ENREGISTREMENT D'UNE MORTINAISSANCE, S'ADRESSER AU BUREAU DES SERVICES DE L'ÉTAT CIVIL, REGINA, SASKATCHEWAN.

APPENDIX C: Certificate of Ethical Approval

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Punam Pahwa	Community Health and Epidemiology	10-27

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
University of Saskatchewan
Saskatoon SK

STUDENT RESEARCHERS
Rhonda Bryce

SPONSORING AGENCIES
Canadian Centre for Health and Safety in Agriculture (CCHSA)

TITLE
: Demographic Risk Factors for Late Pregnancy Stillbirth in Saskatchewan Women

ORIGINAL REVIEW DATE	APPROVED ON	APPROVAL OF	EXPIRY DATE
12-Feb-2010	23-Feb-2010	Review of medical Charts/Health Records (08-Feb-2010) Acknowledgement of: Certificate of Completion of the McMaster University Chart Review Tutorial: Rhonda Bryce	16-Feb-2011

Delegated Review: ☒ Full Board Meeting: ☐

CERTIFICATION
The study is acceptable on scientific and ethical grounds. The Bio-REB considered the requirements of section 29 under the Health Information Protection Act (HIPA) and is satisfied that this study meets the privacy considerations outlined therein. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board has been approved by the Minister of Health, Province of Saskatchewan, to serve as a Research Ethics Board (REB) for research projects involving human subjects under section 29 of The Health Information Protection Act (HIPA).

Gordon McKay, Ph.D., Vice-Chair
University of Saskatchewan
Biomedical Research Ethics Board

Please send all correspondence to:

Research Ethics Office
University of Saskatchewan
Box 5000 RPO University
1607 – 110 Gymnasium Place
Saskatoon, SK Canada S7N 4J8

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval
Study Amendment

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Punam Pahwa	Community Health and Epidemiology	10-27

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
University of Saskatchewan
Saskatoon SK

STUDENT RESEARCHER(S)
Rhonda Bryce

SPONSORING AGENCIES
Canadian Centre for Health and Safety in Agriculture (CCHSA)

TITLE
: Demographic Risk Factors for Late Pregnancy Stillbirth in Saskatchewan Women

APPROVAL OF	APPROVED ON	CURRENT EXPIRY DATE
Amendment to Application: -Cause of death classification -Proposed ICD-Based Classification -Canadian Perinatal Surveillance System Classification -Data file/storage	12-Jan-2011	16-Feb-2012

Delegated Review: ☒ Full Board Meeting: ☐

CERTIFICATION
The study is acceptable on scientific and ethical grounds. The Bio-REB considered the requirements of section 29 under the Health Information Protection Act (HIPA) and is satisfied that this study meets the privacy considerations outlined therein. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

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REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This approval and the views of this REB have been documented in writing.

Gordon McKay, Ph.D., Vice-Chair
University of Saskatchewan
Biomedical Research Ethics Board

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Saskatoon SK S7N 4J8

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Re-Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Punam Pahwa	Community Health and Epidemiology	10-27

INSTITUTION (S) WHERE RESEARCH WILL BE CARRIED OUT

University of Saskatchewan
Saskatoon SK

STUDENT RESEARCHER(S)

Rhonda Bryce

SPONSORING AGENCIES

Canadian Centre for Health and Safety in Agriculture (CCHSA)

TITLE:

Demographic Risk Factors for Late Pregnancy Stillbirth in Saskatchewan Women

RE-APPROVED ON	EXPIRY DATE
11-Jan-2011	16-Feb-2012

Full Board Meeting ☐

Delegated Review ☑

CERTIFICATION

The study is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This re-approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This re-approval and the views of this REB have been documented in writing.

Michel Desautels, Ph.D., Chair
University of Saskatchewan
Biomedical Research Ethics Board

Please send all correspondence to:

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Saskatoon, SK S7N 4J8
Phone: (306) 966-2975 Fax: (306) 966-2069

APPENDIX D: Fetal Weight Standards

I. Intrauterine fetal weight standard

Table 1
In Utero Fetal Weight Standards at US

Menstrual Week	Percentiles (g)				
	3rd	10th	50th	90th	97th
28	908	1,004	1,210	1,416	1,513
29	1,034	1,145	1,379	1,613	1,724
30	1,169	1,294	1,559	1,824	1,649
31	1,313	1,453	1,751	2,049	2,189
32	1,465	1,621	1,953	2,285	2,441
33	1,622	1,794	2,162	2,530	2,703
34	1,783	1,973	2,377	2,781	2,971
35	1,946	2,154	2,595	3,036	3,244
36	2,110	2,335	2,813	3,291	3,516
37	2,271	2,513	3,028	3,543	3,785
38	2,427	2,686	3,236	3,786	4,045
39	2,576	2,851	3,435	4,019	4,294
40	2,714	3,004	3,619	4,234	4,524

Table reproduced/adapted from: Hadlock et al. (209)

II. Canadian birth weight standard (sex-specific)

TABLE 1. Birth Weight (g) for Gestational Age, Canadian Male Singletons Born Between 1994 and 1996, Corrected and Smoothed

Gestational Age	n*	3rd Percentile	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile	97th Percentile	Mean	SD
41	54 139	2926	3025	3179	3733	4328	4512	4631	3745	459
42	8791	2960	3070	3233	3815	4433	4631	4773	3800	485
43	276	2954	3081	3249	3864	4528	4747	4941	3793	527

* Sample size at each gestational age after exclusions.

TABLE 2. Birth Weight (g) for Gestational Age, Canadian Female Singletons Born Between 1994 and 1996, Corrected and Smoothed

Gestational Age	n*	3rd Percentile	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile	97th Percentile	Mean	SD
41	52 063	2809	2906	3051	3576	4154	4330	4444	3588	439
42	7970	2849	2954	3114	3655	4251	4423	4554	3656	448
43	277	2862	2975	3159	3717	4333	4495	4685	3693	459

* Sample size at each gestational age after exclusions.

Tables reproduced/adapted from: Kramer et al. (211)

APPENDIX E: Saskatchewan Census Divisions by Modified (Ehrensaft's) Beale Codes and Revised Beale Codes (213)

Census division (CD)	Modified Beale Codes	Revised Beale Codes
1	7	5
2	7	5
3	7,9[1]	5
4	8	4
5	7	5
6	3	3
7	4	4
8	6	4
9	7	5
10	9	5
11	3	3
12	6	4
13	7	5
14	7	5
15	4	4
16	6	4
17	7	5
18	10	5

[1]Due to decline in population numbers Census Division 3 changed from Modified Beale Code 7 to 9 at the 2001 census.

APPENDIX F: International Classification of Diseases, 10th Revision[1] (184)

I. Major causes/mechanisms of fetal death with relevant subcategories (P00-P96, Q00-99)

ICD-10 code	"Certain conditions originating in the perinatal period"
P00-P04	**Fetus and newborn affected by maternal factors and by complications of pregnancy, labour and delivery**
P00	Fetus and newborn affected by maternal conditions that may be unrelated to present pregnancy
P00.0	*Maternal hypertensive disorders*
P00.1	*Maternal renal and urinary tract diseases*
P00.2	*Maternal infectious and parasitic diseases*
P00.3	*Maternal circulatory and respiratory diseases*
P00.4	*Maternal nutritional disorders*
P00.5	*Maternal injury*
P00.6	*Surgical procedure on mother*
P00.7	*Other medical procedures on mother, not elsewhere classified*
P00.8	*Other maternal conditions*
P00.9	*Unspecified maternal condition*
P01	Fetus and newborn affected by maternal complications of pregnancy[2]
P01.1	*Premature rupture of membranes*
P01.5	*Multiple pregnancy*
P01.6	*Maternal death*
P01.8	*Other maternal complications of pregnancy*
P01.9	*Maternal complication of pregnancy, unspecified*
P02	Fetus and newborn affected by complications of placenta, cord and membranes[2]
P02.1	*Placenta praevia*
P02.2	*Placental separation and haemorrhage*
P02.3	*Placental abnormalities, unspecified morphological/functional*
P02.4	*Placental transfusion syndrome*
P02.5	*Prolapsed cord*
P02.6	*Cord compression (tight nuchal, entanglement, true knot)*
P02.7	*Unspecified cord conditions*
P02.8	*Other membrane abnormalities*
P02.9	*Membrane abnormalities, unspecified*
P03	Fetus and newborn affected by other complications of labour and delivery
P04	Fetus and newborn affected by noxious influences transmitted via placenta or breast milk

P05-P08	**Disorders related to length of gestation and fetal growth**
P05	Slow fetal growth and fetal malnutrition
P07	Disorders related to short gestation and low birth weight, not elsewhere classified
P08	Disorders related to long gestation and high birth weight
P10-P15	**Birth Trauma**
P20-P29	**Respiratory and cardiovascular disorders specific to the perinatal period**
P20	Intrauterine hypoxia[2]
P20.0	*Intrauterine hypoxia first noted before onset of labour*
P20.1	*Intrauterine hypoxia first noted during labour and delivery*
P20.9	*Intrauterine hypoxia, unspecified*
P21	Birth asphyxia[2]
P21.0	*Severe birth asphyxia*
P21.1	*Mild and moderate birth asphyxia*
P21.9	*Birth asphyxia, unspecified*
P35-P39	**Infections specific to the perinatal period**
P35	Congenital viral disease
P37	Other congenital infectious and parasitic diseases
P39	Other infections specific to the perinatal period (includes intra-amniotic infection of fetus, not elsewhere classified)
P50-P61	**Haemorrhagic and haematological disorders of fetus and newborn**
P50	Fetal blood loss
P50.0	*From vasa praevia*
P50.1	*From ruptured cord*
P50.2	*From placenta*
P50.3	*Haemorrhage into co-twin*
P50.4	*Haemorrhage into maternal circulation*
P50.5	*Fetal blood loss from cut end of co-twin's cord*
P50.6	*Other fetal blood loss*
P50.7	*Fetal blood loss, unspecified*
P52	Intracranial nontraumatic haemorrhage of fetus and newborn
P56	Hydrops fetalis due to haemolytic disease
P61	Other perinatal haematological disorders
P70-P74	**Transitory endocrine and metabolic disorders specific to fetus and newborn**
P70	Transitory disorders of carbohydrate metabolism specific to fetus and newborn (includes Syndrome of infant of a diabetic mother)

P75-P78	**Digestive system disorders of fetus and newborn**
P75	Meconium ileus
P77	Necrotizing enterocolitis of fetus and newborn
P78	Other perinatal digestive system disorders
P80-P83	**Conditions involving the integument and temperature regulation of fetus and newborn**
P83	Other conditions of integument specific to fetus and newborn (includes hydrops fetalis not due to haemolytic disease)
P90-P96	**Other disorders originating in the perinatal period**
P95	Fetal death of unspecified cause[2]
P96	Other conditions originating in the perinatal period (includes complications of intrauterine procedures not elsewhere classified)
P96.9	*Conditions originating in the perinatal period, unspecified*[2]
Q00-Q99	**Congenital malformations, deformations and chromosomal abnormalities**[2]
Q00-Q07	Congenital malformations of the nervous system
Q10-Q18	Congenital malformations for the eye, ear, face and neck
Q20-Q28	Congenital malformations of the circulatory system
Q30-Q34	Congenital malformations of the respiratory system
Q35-Q37	Cleft lip and cleft palate
Q38-Q45	Other congenital malformations of the digestive system
Q50-Q56	Congenital malformations of the genital organs
Q60-Q64	Congenital malformations of the urinary system
Q65-Q79	Congenital malformations and deformations of the musculoskeletal system
Q80-Q89	Other congenital malformations
Q90-Q99	Chromosomal abnormalities, not elsewhere classified

[1]Subcategories applying to newborns only not shown

[2]Indicates category used by the Perinatal Surveillance System for cause of death comparisons

APPENDIX G - Tabular Values of 95 Percent Confidence Limit Factors for Estimates of a Poisson-distributed Variable[1] (223)

Observed number on which estimate is based	Lower Limit Factor	Upper Limit Factor	Observed number on which estimate is based	Lower Limit Factor	Upper Limit Factor	Observed number on which estimate is based	Lower Limit Factor	Upper Limit Factor
1	0.0253	5.57	21	0.619	1.53	120	0.833	1.2
2	0.121	3.61	22	0.627	1.51	140	0.844	1.184
3	0.206	2.92	23	0.634	1.50	160	0.854	1.171
4	0.272	2.56	24	0.641	1.49	180	0.862	1.16
5	0.324	2.33	25	0.647	1.48	200	0.868	1.151
6	0.367	2.18	26	0.653	1.47	250	0.882	1.134
7	0.401	2.06	27	0.659	1.46	300	0.892	1.121
8	0.431	1.97	28	0.665	1.45	350	0.899	1.112
9	0.458	1.90	29	0.67	1.44	400	0.906	1.104
10	0.48	1.84	30	0.675	1.43	450	0.911	1.098
11	0.499	1.79	35	0.697	1.39	500	0.915	1.092
12	0.517	1.75	40	0.714	1.36	600	0.922	1.084
13	0.532	1.71	45	0.729	1.34	700	0.928	1.078
14	0.546	1.68	50	0.742	1.32	800	0.932	1.072
15	0.56	1.65	60	0.77	1.30	900	0.936	1.068
16	0.572	1.62	70	0.785	1.27	1000	0.939	1.064
17	0.583	1.6	80	0.798	1.25			
18	0.593	1.58	90	0.809	1.24			
19	0.602	1.56	100	0.818	1.22			
20	0.611	1.54						

[1]To use, find the number of observed cases in the sample. Note the corresponding upper and lower values and multiply both by numerator of the estimated incidence in the desired standardized form (e.g. per 1000). These new values are the numerator values for the upper and lower 95% confidence limits in the desired standardized form (e.g. per 1000).

APPENDIX H: Proportionate Mortality by Census Division, Saskatchewan Late Pregnancy Stillbirths, 1987 to 2007[1]

CD		Congenital anomalies	Maternal complications	Complications of placenta cord or membranes	Intrauterine hypoxia and birth asphyxia	Indicated as unspecified	Other cause of death indicated	No cause of death indicated	All causes
1	Count	X	X	9	X	11	5	6	37
	% within CD	X	X	24.3%	X	29.7%	13.5%	16.2%	100.0%
2	Count	X	X	8	X	7	X	X	18
	% within CD	X	X	44.4%	X	38.9%	X	5.6%	100.0%
3	Count	X	X	5	X	X	X	X	9
	% within CD	X	X	55.6%	X	X	X	X	100.0%
4	Count	X	X	X	X	X	X	X	5
	% within CD	X	X	X	X	X	X	X	100.0%
5	Count	X	X	11	X	X	8	X	31
	% within CD	X	X	35.5%	X	X	25.8%	X	100.0%
6	Count	15	12	75	12	43	32	45	234
	% within CD	6.4%	5.1%	32.1%	5.1%	18.4%	13.7%	19.2%	100.0%
7	Count	X	X	13	X	X	X	9	34
	% within CD	X	X	38.2%	X	X	X	26.5%	100.0%
8	Count	X	X	8	X	5	7	X	23
	% within CD	X	X	34.8%	X	21.7%	30.4%	X	100.0%
9	Count	X	X	25	6	X	9	8	50
	% within CD	X	X	50.0%	12.0%	X	18.0%	16.0%	100.0%
10	Count	X	X	11	X	X	8	X	26
	% within CD	X	X	42.3%	X	X	30.8%	X	100.0%
11	Count	17	6	78	9	41	30	37	218
	% within CD	7.8%	2.8%	35.8%	4.1%	18.8%	13.8%	17.0%	100.0%

12	Count	X	X	11	X	X	X	8	24
	% within CD	X	X	45.8%	X	X	X	33.3%	100.0%
13	Count	X	X	11	X	7	X	5	27
	% within CD	X	X	40.7%	X	25.9%	X	18.5%	100.0%
14	Count	X	X	13	X	5	13	X	40
	% within CD	X	X	32.5%	X	12.5%	32.5%	X	100.0%
15	Count	5	X	35	8	21	13	14	X
	% within CD	5.0%	X	35.0%	8.0%	21.0%	13.0%	14.0%	100.0%
16	Count	X	X	13	X	15	12	9	55
	% within CD	X	X	23.6%	X	27.3%	21.8%	16.4%	100.0%
17	Count	7	X	26	X	18	6	9	69
	% within CD	10.1%	X	37.7%	X	26.1%	8.7%	13.0%	100.0%
18	Count	8	X	17	X	9	9	10	53
	% within CD	15.1%	X	32.1%	X	17.0%	17.0%	18.9%	100.0%

[1]X = data suppressed as total cases for the cell <5

APPENDIX I: Annual Number of Late Stillbirths and Total Births for Saskatchewan and Canada, 1987 to 2007[1]

Year	**Cases** SK	**Total births** SK	**Cases** Canada	**Total births** Canada
1987	66	17 527	1 584	371 326
1988	53	16 657	1 435	378 230
1989	58	16 830	1 593	394 254
1990	61	16 560	1 559	407 045
1991	63	15 718	1 396	403 929
1992	61	15 238	1 512	400 149
1993	56	14 687	1 419	389 805
1994	65	14 133	1 371	386 479
1995	58	13 853	1 323	379 336
1996	39	13 431	1 246	367 444
1997	45	13 159	1 174	349 761
1998	46	12 757	1 079	343 481
1999	49	12 726	1 087	338 310
2000	57	12 581	1 060	328 923
2001	47	12 131	1 097	334 817
2002	58	12 054	1 028	329 799
2003	47	11 841	1 027	336 194
2004	50	12 171	972	338 008
2005	41	11 956	1 012	343 131
2006	39	11 964	1 078	355 650
2007	60	11 978	1 172	368 978
Overall	**1 119**	**289 952**	**26 224**	**7 645 049**

[1]Canadian data does not include Saskatchewan

APPENDIX J: Parameter Estimates for Poisson Regression of Year, Categorical and Continuous, on Late Stillbirth Incidence, 1987 to 2007, Canada and Saskatchewan[1]

Canada

Categorical Year	**Lambda [s.e.(Lambda)]** [$\hat{\lambda}[s.e(\hat{\lambda})]$	**RR**	**95% CI**	**p-values**
1987	0.29 (0.039)	1.34	1.25, 1.45	<0.001
1988	0.18 (0.039)	1.19	1.11, 1.29	<0.001
1989	0.24 (0.038)	1.27	1.18, 1.37	<0.001
1990	0.19 (0.039)	1.21	1.12, 1.30	<0.001
1991	0.084 (0.040)	1.09	1.01, 1.18	0.033
1992	0.17 (0.039)	1.19	1.10, 1.28	<0.001
1993	0.14 (0.039)	1.15	1.06, 1.24	<0.001
1994	0.11 (0.040)	1.12	1.03, 1.21	0.006
1995	0.094 (0.040)	1.10	1.01, 1.19	0.020
1996	0.065 (0.041)	1.07	0.99, 1.16	0.11
1997	0.055 (0.041)	1.06	0.97, 1.15	0.18
1998	-0.011 (0.042)	0.99	0.91, 1.07	0.79
1999	0.011 (0.042)	1.01	0.93, 1.10	0.79
2000	0.014 (0.042)	1.02	0.93, 1.10	0.73
2001	0.031 (0.042)	1.03	0.95, 1.12	0.46
2002	-0.019 (0.043)	0.98	0.90, 1.07	0.66
2003	-0.039 (0.043)	0.96	0.88, 1.05	0.36
2004	-0.099 (0.043)	0.91	0.83, 0.99	0.02
2005	-0.074 (0.043)	0.93	0.85, 1.01	0.08
2006	-0.047 (0.042)	0.95	0.88, 1.04	0.27
2007	Reference			
Continuous Year	-0.016 (0.0015)	0.984	0.981, 0.987	<0.001

Saskatchewan

Categorical Year	**Lambda [s.e.(Lambda)]** $[\hat{\lambda}[s.e(\hat{\lambda})]$	**RR**	**95% CI**	**p-values**
1987	-0.29 (0.18)	0.75	0.53, 1.07	0.11
1988	-0.45 (0.19)	0.64	0.44, 0.92	0.02
1989	-0.37 (0.18)	0.69	0.48, 0.99	0.04
1990	-0.31 (0.18)	0.74	0.51, 1.05	0.09
1991	-0.22 (0.18)	0.80	0.56, 1.14	0.22
1992	-0.22 (0.18)	0.80	0.56, 1.14	0.22
1993	-0.27 (0.19)	0.76	0.531.10	0.14
1994	-0.09 (0.18)	0.92	0.65, 1.30	0.63
1995	-0.18 (0.18)	0.84	0.58, 1.20	0.33
1996	-0.55 (0.21)	0.58	0.39, 0.87	0.008
1997	-0.38 (0.20)	0.68	0.46, 1.00	0.05
1998	-0.33 (0.20)	0.72	0.49, 1.06	0.09
1999	-0.26 (0.19)	0.77	0.53, 1.12	0.17
2000	-0.10 (0.18)	0.90	0.63, 1.30	0.59
2001	-0.26 (0.19)	0.77	0.53, 1.13	0.19
2002	-0.04 (0.18)	0.96	0.67, 1.38	0.83
2003	-0.23 (0.19)	0.79	0.54, 1.16	0.23
2004	-0.20 (0.19)	0.82	0.56, 1.19	0.30
2005	-0.38 (0.20)	0.68	0.46, 1.02	0.06
2006	-0.43 (0.21)	0.65	0.43, 0.97	0.04
2007	Reference			
Continuous Year	0.0068 (0.0047)	1.007	0.998, 1.016	0.15

[1]Canadian data does not include Saskatchewan data

APPENDIX K: Late Stillbirth and Live Birth Counts for Five Year Periods by Census Division, 1987 - 2006

Division	1987-91		1992-96		1997-01		2002-06		Total	
	Cases	Live Births[1]	Cases	Live Births[1]	Cases	Live Births[1]	Cases	Live Births[1]	Cases	Total Live Births[1]
1	7	2361.5	11	2176	8	1921.5	8	1761.5	**34**	**8220.5**
2	x	x	6	1245	x	x	x	x	**18**	**4913**
3	x	x	x	x	x	x	x	x	**9**	**3382**
4	x	x	x	x	x	x	x	x	**5**	**2823**
5	5	2349.5	8	1882.5	10	1566	8	1495	**31**	**7293**
6	70	18106	68	15227.5	50	13144	36	12517	**224**	**58994.5**
7	5	3747.5	12	3046.5	9	2535	7	2340.5	**33**	**11669.5**
8	7	2251.5	x	x	6	1619.5	x	x	**21**	**7146.5**
9	10	2652	11	2048.5	8	1825.5	18	1837	**47**	**8363**
10	9	1418	x	x	x	x	8	964.5	**24**	**4533**
11	54	19315.5	61	17154	50	15119.5	42	14615	**207**	**66204**
12	8	1811.5	8	1410	x	x	x	x	**23**	**5806**
13	8	2225.5	7	1678.5	x	x	x	x	**24**	**6765.5**
14	17	3057	7	2537.5	x	x	x	x	**34**	**10002.5**
15	18	6820	26	5948.5	23	5492	28	5042.5	**95**	**23303**
16	16	3160	11	2779	13	2806.5	13	2730	**53**	**11475.5**
17	21	4084.5	14	3775.5	17	3765	13	3819	**65**	**15444**
18	10	4832	15	4596	9	4153.5	16	4223.5	**50**	**17805**
All Divisions	**265**	**81849**	**265**	**70031.5**	**203**	**62551**	**197**	**59712**	**997**	**274143.5**
All Cases[2]									**1120**	**274640**

[1]Annual births, summed for each five year period, determined by averaging midpoint estimates for two consecutive years. See Chapter 3 for further details.

[2]Includes cases without known census division and those occurring in 2007.

[3]Value suppressed due to small numbers of cases (<5).

APPENDIX L: Two Factor Interaction Assessments for Late Stillbirth Characteristics

	λ	OR	95% CI	p-value
Maternal Age ≥ 35 y*low parity	-0.664	**0.51**	0.32, 0.83	**0.006**
Maternal Age ≥ 35 y*high parity	0.835	**2.30**	1.54, 3.45	**<0.001**
Maternal Age ≥ 35 y*Aboriginal	-0.463	**0.63**	0.41, 0.97	**0.04**
Maternal Age ≥ 35 y*previous stillbirth	0.507	1.66	0.86, 3.19	0.13
Maternal Age ≥ 35 y*RBC 5	-0.258	0.77	0.51, 1.17	0.22
Maternal Age ≥ 35 y*RBC 4	-0.223	0.80	0.50, 1.28	0.35
Maternal Age ≥ 35 y*male fetus	0.437	**1.55**	1.08, 2.22	**0.02**
Maternal Age ≥ 35 y*post term pregnancy	0.639	1.89	0.61, 5.93	0.27
Maternal Age ≥ 35 y*preterm pregnancy	-0.077	0.93	0.65, 1.32	0.67
Maternal Age ≥ 35 y*SGA	0.239	1.27	0.87, 1.85	0.21
Maternal Age ≥ 35 y*LGA	0.534	1.71	0.96, 3.04	0.07
Maternal Age ≥ 35 y*multiple pregnancy	0.035	1.04	0.52, 2.06	0.92
Low parity*Aboriginal	0.01	1.01	0.73, 1.40	0.95
High parity*Aboriginal	1.322	3.75	2.68, 5.25	**<.001**
Low parity*previous stillbirth	-18.242	<.001	<.001, N/A	0.99
High parity*previous stillbirth	0.512	1.67	0.99, 2.82	0.06
Low parity*RBC 5	-0.209	0.81	0.59, 1.11	0.19
High parity*RBC 5	0.642	**1.90**	1.30, 2.79	**0.001**
Low parity*RBC 4	-0.001	1.00	0.70, 1.42	0.997
High parity*RBC 4	0.671	**1.96**	1.27, 3.01	**0.002**
Low parity*Male fetus	-0.096	0.91	0.70, 1.19	0.48
High parity*Male fetus	0.363	**1.44**	1.05, 1.97	**0.02**
Low parity*post term pregnancy	0.322	1.38	0.46, 4.18	0.57
High parity*post term pregnancy	0.544	1.72	0.51, 5.78	0.98
Low parity*preterm pregnancy	0.003	1.00	0.77, 1.31	0.38

High parity*preterm pregnancy	0.057	1.06	0.77, 1.45	0.73
Low parity*SGA	0.17	1.19	0.90, 1.47	0.23
Low parity*LGA	-0.136	0.87	0.53, 1.43	0.59
High parity*SGA	0.098	1.10	0.79, 1.53	0.56
High parity*LGA	0.133	1.14	0.67, 1.96	0.63
Low parity*multiple pregnancy	-1.341	0.26	0.13, 0.53	<.001
High parity*multiple pregnancy	0.14	1.15	0.68, 1.95	0.60
Aboriginal *previous stillbirth	0.253	1.29	0.74, 2.23	0.37
Aboriginal*RBC 5	1.195	**3.30**	2.34, 4.67	**<.001**
Aboriginal*RBC 4	0.926	**2.52**	1.71, 3.72	**<.001**
Aboriginal*male fetus	0.072	1.07	0.82, 1.40	0.59
Aboriginal*post term pregnancy	0.501	1.65	0.63, 4.34	0.31
Aboriginal*preterm pregnancy	-0.11	0.90	0.00, 1.17	0.42
Aboriginal*SGA	-0.176	0.84	0.63, 1.12	0.23
Aboriginal*LGA	0.754	**2.13**	1.37, 3.28	**0.001**
Aboriginal*multiple pregnancy	-0.819	**0.44**	0.23, 0.85	**0.01**
Previous stillbirth*RBC 5	-0.351	0.70	0.37, 1.32	0.28
Previous stillbirth*RBC 4	0.005	1.01	0.53, 1.92	0.99
Previous stillbirth*male fetus	-0.059	0.94	0.57, 1.57	0.82
Previous stillbirth*post term pregnancy	-14.195	<.001	<.001, N/A	0.99
Previous stillbirth*preterm pregnancy	1.018	**2.77**	1.53, 5.01	**0.001**
Previous stillbirth*SGA	0.306	1.36	0.79, 2.35	0.27
Previous stillbirth*LGA	0.546	1.73	0.75, 3.96	0.20
Previous stillbirth*multiple pregnancy[2]	1.731	**5.65**	3.03, 10.54	**<.001**
RBC 5*male fetus	0.027	1.03	0.78, 1.36	0.85
RBC 4*male fetus	0.046	1.05	0.77, 1.43	0.77

RBC 5*post term pregnancy	0.382	1.47	0.44, 4.89	0.53
RBC 5*preterm pregnancy	-0.062	0.94	0.71, 1.24	0.67
RBC 4*post term pregnancy	0.708	2.03	0.57, 7.18	0.27
RBC 4*preterm pregnancy	0.122	1.13	0.82, 1.55	0.45
RBC 5*SGA	-0.332	**0.72**	0.54, 0.96	**0.03**
RBC 5*LGA	-0.029	0.97	0.59, 1.59	0.91
RBC 4*SGA	-0.318	0.73	0.52, 1.01	0.06
RBC 4*LGA	-0.228	0.80	0.44, 1.43	0.44
RBC 5*multiple pregnancy	-0.857	**0.42**	0.23, 0.78	**0.006**
RBC 4*multiple pregnancy	-0.762	**0.47**	0.24, 0.92	**0.03**
Male fetus*post term pregnancy	-0.121	0.89	0.35, 2.27	0.80
Male fetus*preterm pregnancy	-0.058	0.94	0.74, 6.06	0.63
Male fetus*SGA	0.026	1.03	0.80, 1.31	0.84
Male fetus*LGA	0.327	1.39	0.90, 2.13	0.14
Male fetus*multiple pregnancy	0.019	1.02	0.64, 1.62	0.94
Post term pregnancy*SGA	-0.367	0.69	0.24, 2.00	0.50
Post term pregnancy*LGA	-1.01	0.36	0.05, 2.85	0.34
Preterm pregnancy*SGA	0.859	**2.36**	1.83, 3.05	**<.001**
Preterm pregnancy*LGA	-0.287	0.75	0.49, 1.16	0.20
Post term pregnancy*multiple pregnancy	-14.384	<.001	<.001, N/A	0.99
Preterm pregnancy*multiple pregnancy	1.037	**2.82**	1.64, 4.85	**<.001**
SGA*multiple pregnancy	1.766	5.85	3.11, 11.00	<.001
LGA*multiple pregnancy	0.231	1.26	0.35, 4.54	0.72

[1]y = years,

[2]More than 20% of cells in this cross classification have expected values less than 5. The significance for this interaction is unreliable.

APPENDIX M: Log-linear Modeling Logit Difference Sample Calculation (lambda estimate, odds ratio, and 95% confidence interval) for LGA * Maternal Age in Aboriginal Stillbirths (Model 5).

Aboriginal stillbirths (sb):

Odds (OR) of LGA vs. AGA in older mother sb = count of LGA in older, Aboriginal sb / count of AGA in older, Aboriginal sb

Odds of LGA vs. AGA in younger mother sb = count of LGA in younger, Aboriginal sb / count of AGA in younger, Aboriginal sb

Odds ratio for LGA in older mother sb and LGA in younger mother sb:

$$\frac{\dfrac{\text{count of LGA in older, Aboriginal sb}}{\text{count of AGA in older, Aboriginal}}}{\dfrac{\text{count of LGA in younger, Aboriginal sb}}{\text{count of AGA in younger, Aboriginal sb}}}$$

Substituting model terms:

$$OR_{LGA*Older\ mother} = EXP(\lambda_{LGA*Older\ mother}) =$$

$$\frac{\lambda_{LGA} + \lambda_{Older\ mother} + \lambda_{Aboriginal} + \lambda_{LGA*Older\ mother} + \lambda_{LGA*Aboriginal} + \lambda_{Older\ mother*Aboriginal} + \lambda_{Older\ mother*Aboriginal*LGA}}{\lambda_{AGA} + \lambda_{Older\ mother} + \lambda_{Aboriginal} + \lambda_{AGA*Older\ mother} + \lambda_{AGA*Aboriginal} + \lambda_{Older\ mother*Aboriginal} + \lambda_{Older\ mother*Aboriginal*AGA}}$$

$$\frac{\lambda_{LGA} + \lambda_{Younger\ mother} + \lambda_{Aboriginal} + \lambda_{LGA*Younger\ mother} + \lambda_{LGA*Aboriginal} + \lambda_{Younger\ mother*Aboriginal} + \lambda_{Older\ mother*Aboriginal*LGA}}{\lambda_{AGA} + \lambda_{Younger\ mother} + \lambda_{Aboriginal} + \lambda_{AGA*Younger\ mother} + \lambda_{AGA*Aboriginal} + \lambda_{Younger\ mother*Aboriginal} + \lambda_{Younger\ mother*Aboriginal*AGA}}$$

Cancelling like terms across the numerator and denominator, removing reference terms ($\lambda = 0$), and substituting estimates from Model 5, the equation reduces to the following:

$$OR_{LGA*Older\ mother,\ Aboriginal} = EXP(\lambda_{LGA*Older\ mother,\ Aboriginal}) = EXP(\lambda_{LGA*Older\ mother} + \lambda_{Older\ mother*Aboriginal*LGA}) = EXP(0.072 + 1.464) = EXP(\mathbf{1.535}) = \mathbf{4.64.}$$

In generic format, standard error (s.e.) = √[Variance X + Variance Y + 2(Covariance of X,Y)]

For current calculation, s.e. = √[Variance($\lambda_{LGA*Older\ mother)}$ + Variance ($\lambda_{Older\ mother*Aboriginal*LGA)}$ + 2Covariance ($\lambda_{LGA*Older\ mother,}$ $\lambda_{Older\ mother*Aboriginal*LGA}$)]

Utilizing estimate covariance and s.e's from Model 5 output (i.e. variance = $s.e.^2$),

s.e. = $\sqrt{[0.410^2 + 0.656^2 + 2(-0.168)}$ = √0.262436 = **0.51**

Including the calculated standard error in the confidence interval calculation,

95% CI = EXP[1.535 +/- 1.96(0.51)] = EXP[0.5354, 2.5346] = **[1.71, 12.61]**

Note: EXP indicates application of the following term as a power of the base e (e = 2.718281828)

APPENDIX N: Univariate Associations between Area-Level Characteristics and Late Stillbirth Incidence

Variables	Category	Lambda [s.e.(Lambda)] $[\hat{\lambda}[s.e(\hat{\lambda})]$	RR (95% CI)	p-value
Income				
Median household income	> $45000	-0.19 (0.095)	0.82 (0.69,0.99)	0.04
	≤ $45000	Ref.		
Median family income	≥ $52000	-0.139 (0.088)	0.87 (0.73,1.034)	0.11
	$47000-51999	0.11 (0.10)	1.12 (.092,1.37)	0.26
	< $47000	Ref.		
Education level				
Proportion of reproductive age females with no degree	≥36%	0.008 (0.094)	1.01 (0.84,1.21)	0.93
	30-35.9%	0.036 (0.13)	1.04 (0.81,1.32)	0.78
	0-29.9%	Ref.		
Proportion of reproductive age males with no degree	≥50%	-0.16 (0.13)	0.85 (0.66,1.10)	0.23
	<50%	Ref.		
Proportion of total adult population with no degree	≥36%	0.087 (0.092)	1.09 (0.91,1.31)	0.35
	29-35.9%	0.24 (0.097)	1.27 (1.05,1.53)	0.02
	<29%	Ref.		
Proportion of reproductive age females with high school diploma or equivalent as highest education	>23.8%	0.037 (0.12)	1.04 (0.82,1.31)	0.76
	21.9-23.8%	0.077 (0.15)	1.08 (0.81,1.44)	0.61
	<21.8%	Ref.		
Proportion of reproductive age males with high school diploma or equivalent as highest education	>28.5%	-0.057 (0.11)	0.95 (0.76,1.17)	0.61
	24-28.5%	-0.34 (0.098)	0.97 (0.80,1.17)	0.73
	<24%	Ref.		
Proportion of total adult population with high school diploma or equivalent as highest education	>19.38%	0.046 (0.13)	1.05 (0.81,1.35)	0.72
	14.61-19.38%	0.07 (0.12)	1.07 (0.85,1.36)	0.56
	13-14.60%	0.14 (0.14)	1.15 (0.87,1.52)	0.33
	<13%	Ref.		
Proportion of reproductive age females with undergraduate-level degree or certificate as highest education	≥41.55%	-0.066 (0.12)	0.94 (0.74,1.18)	0.58
	35.81-41.54%	0.031 (0.12)	1.03 (0.82,1.30)	0.79
	≤35.80%	Ref.		

Proportion of reproductive age males with undergraduate-level degree or certificate as highest education	≥33%	0.010 (0.10)	1.01 (0.82,1.24)	0.93
	30-32.9%	0.16 (0.12)	1.17 (0.94,1.47)	0.17
	<30%	Ref.		
Proportion of total population with undergraduate-level degree or certificate as highest education	≥28%	0.066 (0.13)	1.07 (0.83,1.38)	0.61
	23-27.9%	0.18 (0.13)	1.19 (0.82,1.54)	0.18
	<23%	Ref.		
Proportion of reproductive age females with graduate degree as highest level of education	>15/1000	-0.038 (0.12)	0.96 (0.77,1.21)	0.75
	10.1-15/1000	0.11 (0.14)	1.12 (0.86,1.46)	0.40
	7-10/1000	0.094 (0.15)	1.10 (0.82,1.47)	0.53
	<7/1000	Ref.		
Proportion of reproductive age males with graduate degree as highest level of education	≥13/1000	0.074 (0.11)	1.08 (0.86,1.35)	0.52
	5-12.9/1000	0.23 (0.12)	1.26 (0.99,1.60)	0.06
	<5/1000	Ref.		
Proportion of total population with graduate degree as highest level of education	≥13.9/1000	0.090 (0.12)	1.09 (0.87,1.38)	0.45
	8.1-13.9/1000	0.22 (0.15)	1.25 (0.93,1.67)	0.15
	≤8/1000	Ref.		
Ethnicity				
Proportion of the population who are Aboriginal	≥19%	0.19 (0.16)	1.20 (0.87,1.67)	0.26
	8.5-18.99%	0.053 (0.16)	1.05 (0.77,1.44)	0.74
	4.1- 8.49%	0.19 (0.16)	1.21(0.87,1.67)	0.25
	<4%	Ref.		
Proportion of children age 0-4 years who are Aboriginal	>35%	0.12 (0.19)	1.13 (0.94,1.35)	0.19
	≤35%	Ref.		
Proportion of reproductive age women who are immigrant	≥3.0%	-0.046 (0.084)	0.96 (0.81,1.13)	0.58
	2-2.9%	0.30 (0.10)	1.35 (1.11,1.64)	0.003
	<2%	Ref.		
Proportion of total population who are immigrant	Linear	-0.022 (0.018)	0.98 (0.94,1.01)	0.21
Proportion of reproductive age women who are black	>4.2/1000	-0.075 (0.11)	0.93 (0.75,1.15)	0.49
	1.2-4.2/1000	0.089 (0.12)	1.09 (0.87,1.37)	0.45
	<1.2/1000	Ref.		

Occupation				
Proportion of reproductive age women in primary production work	≥5.5/1000	0.0089 (0.13)	1.01 (0.78,1.30)	0.95
	2-5.4/1000	-0.15 (0.0910	0.86 (0.72,1.03)	0.093
	<2/1000	Ref.		
Proportion of reproductive age men in primary production work	>3.7%	0.064 (0.13)	1.07 (0.83,1.37)	0.62
	3.7-2.40	0.00039 (0.13)	1.00 (0.78,1.28)	0.998
	2.39-1.49%	-0.039 (0.10)	0.96 (0.71,0.96)	0.71
	<1.49%	Ref.		
Proportion of the total population involved in primary production work	>10/1000	0.070 (0.13)	1.07 (0.84,1.37)	0.58
	6.5-10/1000	0.019 (0.12)	1.46 (0.81,1.28)	0.87
	4.5-6.49/1000	-0.039 (0.11)	0.79 (0.78,1.19)	0.72
	<4.5/1000	Ref.		
Proportion of reproductive age women working in agriculture	≥5.4%	0.26 (0.11)	1.03 (0.83,1.26)	0.81
	3.3-5.39%	0.21 (0.097)	1.23 (1.02,1.49)	0.032
	≤3.29%	Ref.		
Proportion of reproductive age men working in agriculture	≥22%	-0.12 (0.17)	0.89 (0.63,1.24)	0.49
	15.5-21.9%	0.12 (0.11)	1.12 (0.90,1.41)	0.31
	10-15.4%	0.19 (0.11)	1.21 (0.98,1.50)	0.070
	<10%	Ref.		
Proportion of the total population working in agriculture	≥11%	0.014 (0.10)	1.01 (0.83,1.24)	0.89
	7.5-10.9%	0.26 (0.096)	1.3 (1.08,1.57)	0.01
	<7.5%	Ref.		
Proportion of adult female population who are farm operators	≥7.5%	-0.047 (0.13)	0.96 (0.74,1.23)	0.72
	6.5-7.4%	-0.070 (0.19)	0.93 (0.64,1.36)	0.72
	5-6.4%	0.25 (0.11)	1.28 (1.04,1.58)	0.02
	<5%	Ref.		
Proportion of the adult male population who are farm operators	≥24%	0.052 (0.11)	1.05 (0.85,0.97)	0.63
	17-23.9%	0.18 (0.10)	1.20 (0.97,1.47)	0.09
	<17%	Ref.		
Proportion of the total adult population who are farm operators	≥ 12%	0.0075 (0.11)	1.00 (0.81,1.01)	0.95
	8-11.9%	0.20 (0.095)	1.22 (1.01,1.47)	0.04
	<8%	Ref.		

General census division characteristics

Population density (per km^2)	≥2.3	0.26 (0.13)	1.30 (1.01,1.67)	0.045
	1.7-2.2	0.52 (0.15)	1.68 (1.24,2.28)	0.001
	1.2-1.6	0.31 (0.15)	1.37 (1.01,1.85)	0.04
	≤1.1	Ref.		
Community size	Rural	0.13 (0.22)	1.13 (0.73,1.75)	0.58
	Town	0.15 (0.092)	1.16 (0.97,1.40)	0.09
	City	0.21 (0.12)	1.23 (0.97,1.56)	0.09
	Metropolitan area	Ref.		
Population change between census years (%)	Declining 6% or more	0.14 (0.079)	1.15 (0.99,1.35)	0.07
	Not declining 6% or more	Ref.		
Estimated average age (years)	≥39.5	0.25 (0.12)	1.29 (1.02,1.63)	0.04
	35.6-39.4	-0.063 (0.082)	0.94 (0.80,1.10)	0.45
	≤ 35.5	Ref.		
Proportion of reproductive age women who are ≥35 years	≥35%	0.23 (0.083)	1.25 (1.06,1.47)	0.01
	<35%	Ref.		
Ratio of children 0-12 years to reproductive age women	≥ 1.10	0.10 (0.080)	1.11 (0.95,1.29)	0.21
	1.04-1.09	0.36 (0.13)	1.42 (1.11,1.84)	0.01
	<1.04	Ref.		
Proportion of families with lone female parent	Linear	-0.012 (0.009)	0.988 (0.969,1.007)	0.22
Proportion of land area sprayed with pesticide	>4.28%	-0.11 (0.12)	0.90 (0.71,1.14)	0.38
	1.47-4.28%	-0.06 (0.12)	0.94 (0.74,1.21)	0.64
	<1.47%	Ref.		
Proportion of land area sprayed with herbicide	≥48%	0.05 (0.12)	1.05 (0.83,1.34)	0.67
	42-47.9%	0.13 (0.14)	1.14 (0.87,1.49)	0.36
	33-40.9%	0.24 (0.15)	1.27 (0.95,1.72)	0.11
	<33%	Ref.		
Proportion of land area sprayed with fungicide	≥ 3.5%	-0.18 (0.083)	0.84 (0.71,0.98)	0.03
	<3.5%	Ref.		

Modified Beale Code	10	-0.13 (0.18)	0.88 (0.62,1.25)	0.48
	9	0.31 (0.24)	1.36 (0.85,2.19)	0.20
	8	-0.52 (0.54)	0.60 (0.21,1.72)	0.34
	7	0.18 (0.10)	1.19 (0.98,1.45)	0.08
	6	0.092 (0.15)	1.10 (0.82,1.46)	0.52
	4	0.21 (0.12)	1.23 (0.97,1.56)	0.09
	3	Ref.		
Revised Beale Code	5	0.13 (0.093)	1.14 (0.95,1.37)	0.16
	4	0.14 (0.10)	1.15 (0.94,1.41)	0.17
	3	Ref.		

APPENDIX O: Spearman Correlation Coefficients for Area-Level Variables[1]

	Median household income	Median family income	Proportion of reproductive age males with no degree	Proportion of total adult population with no degree	Proportion of reproductive age males with undergraduate-level degree or certificate as highest education	Proportion of total population with undergraduate-level degree or certificate as highest education	Proportion of reproductive age males with graduate degree as highest level of education	Proportion of total population with graduate degree as highest level of education
Median household income	1	0.47	-0.17	-0.52	0.22	0.35	0.16	0.24
Median family income	0.47	1	-0.26	-0.64	0.35	0.54	0.30	0.60
Proportion of reproductive age males with no degree	-0.17	-0.26	1	0.48	-0.46	-0.58	-0.45	-0.45
Proportion of total adult population with no degree	-0.52	-0.64	0.48	1	-0.55	-0.74	-0.55	-0.74
Proportion of reproductive age males with undergraduate-level degree or certificate as highest education	0.22	0.35	-0.46	-0.55	1	0.64	0.69	0.51
Proportion of total population with undergraduate-level degree or certificate as highest education	0.35	0.54	-0.58	-0.74	0.64	1	0.54	0.67
Proportion of reproductive age males with graduate degree as highest level of education	0.16	0.30	-0.45	-0.55	0.69	0.54	1	0.49
Proportion of total population with graduate degree as highest level of education	0.24	0.60	-0.45	-0.74	0.51	0.67	0.49	1
Proportion of children age 0-4 y who are Aboriginal	-0.11	-0.29	0.38	0.14	-0.31	-0.32	-0.24	-0.13
Proportion of reproductive age women who are immigrant	0.22	0.41	-0.36	-0.57	0.51	0.62	0.60	0.42
Proportion of total population who are immigrant	0.05	0.17	-0.18	-0.29	0.45	0.32	0.66	0.34
Proportion of reproductive age women in primary production work	0.15	0.11	-0.08	-0.08	-0.22	0.07	-0.20	-0.05

[1] Shaded areas indicated values ≥ 0.70

	Median household income	Median family income	Proportion of reproductive age males with no degree	Proportion of total adult population with no degree	Proportion of reproductive age males with undergraduate-level degree or certificate as highest education	Proportion of total population with undergraduate-level degree or certificate as highest education	Proportion of reproductive age males with graduate degree as highest level of education	Proportion of total population with graduate degree as highest level of education
Proportion of reproductive age women working in agriculture	-0.36	-0.27	-0.06	0.34	-0.24	-0.16	-0.23	-0.12
Proportion of reproductive age men working in agriculture	-0.33	-0.26	-0.05	0.36	-0.28	-0.16	-0.23	-0.18
Proportion of the total population working in agriculture	-0.19	-0.13	-0.14	0.31	-0.37	-0.13	-0.28	-0.20
Proportion of adult female population who are farm operators	-0.09	-0.02	0.08	0.26	-0.39	-0.18	-0.47	-0.23
Proportion of the adult male population who are farm operators	-0.17	-0.16	0.13	0.44	-0.47	-0.26	-0.51	-0.32
Proportion of the total adult population who are farm operators	-0.15	-0.17	0.12	0.43	-0.46	-0.24	-0.54	-0.29
Population density (per km^2)	0.15	0.12	-0.37	-0.32	0.55	0.33	0.55	0.26
Largest community size								
Population change between census years (%)	-0.13	0.05	-0.25	0.01	-0.18	-0.01	-0.08	0.07
Estimated average age	0.06	0.21	-0.38	-0.15	0.07	0.31	0.04	0.15
Proportion of reproductive age women who are ≥35 y	-0.23	-0.01	-0.37	0.05	0.04	0.11	0.14	0.07
Ratio of children 0-12 years to reproductive age women	-0.35	-0.41	0.31	0.47	-0.61	-0.42	-0.60	-0.36
Proportion of families with lone female parent	0.13	0.17	0.18	-0.25	0.14	0.07	0.11	0.24
Proportion of families with lone female parent	0.29	0.39	-0.26	-0.34	0.31	0.38	0.33	0.30
Proportion of families with lone female parent	0.28	0.38	0.05	-0.10	0.11	0.17	0.08	0.13
Herbicide	0.29	0.40	-0.26	-0.42	0.31	0.38	0.32	0.40
Fungicide	0.28	0.40	0.05	-0.21	0.11	0.17	0.08	0.24
Modified Beale Code	-0.22	-0.33	0.40	0.56	-0.57	-0.48	-0.71	-0.66
Revised Beale Code	-0.14	-0.29	0.18	0.52	-0.44	-0.37	-0.63	-0.65

	Proportion of children age 0-4 y who are Aboriginal	Proportion of reproductive age women who are immigrant	Proportion of total population who are immigrant	Proportion of reproductive age women in primary production work	Proportion of reproductive age women working in agriculture	Proportion of reproductive age men working in agriculture	Proportion of the total population working in agriculture	Proportion of adult female population who are farm operators	Proportion of the adult male population who are farm operators
Median household income	-0.11	0.22	0.05	0.15	-0.36	-0.33	-0.19	-0.09	-0.17
Median family income	-0.29	0.41	0.17	0.11	-0.24	-0.26	-0.13	-0.02	-0.16
Proportion of reproductive age males with no degree	0.38	-0.36	-0.18	-0.08	-0.06	-0.05	-0.14	0.08	0.13
Proportion of total adult population with no degree	0.14	-0.57	-0.29	-0.08	0.34	0.36	0.31	0.26	0.44
Proportion of reproductive age males with undergraduate-level degree or certificate as highest education	-0.31	0.51	0.45	-0.22	-0.24	-0.28	-0.37	-0.39	-0.47
Proportion of total population with undergraduate-level degree or certificate as highest education	-0.32	0.62	0.32	0.07	-0.16	-0.16	-0.13	-0.18	-0.26
Proportion of reproductive age males with graduate degree as highest level of education	-0.24	0.60	0.66	-0.20	-0.23	-0.23	-0.28	-0.47	-0.51
Proportion of total population with graduate degree as highest level of education	-0.13	0.42	0.34	-0.05	-0.12	-0.18	-0.20	-0.23	-0.32
Proportion of children age 0-4 y who are Aboriginal	1	-0.40	-0.41	0.00	-0.41	-0.45	-0.47	-0.33	-0.34
Proportion of reproductive age women who are immigrant	-0.40	1	0.64	-0.07	-0.09	-0.08	-0.10	-0.12	-0.24
Proportion of total population who are immigrant	0.43	0.64	1	-0.23	0.00	0.00	-0.12	-0.34	-0.30
Proportion of reproductive age women in primary production work	0.00	-0.07	-0.23	1	-0.15	-0.09	0.15	0.01	-0.01

	Proportion of children age 0-4 y who are Aboriginal	Proportion of reproductive age women who are immigrant	Proportion of total population who are immigrant	Proportion of reproductive age women in primary production work	Proportion of reproductive age women working in agriculture	Proportion of reproductive age men working in agriculture	Proportion of the total population working in agriculture	Proportion of adult female population who are farm operators	Proportion of the adult male population who are farm operators
Proportion of reproductive age women working in agriculture	-0.41	-0.09	0.00	-0.15	1	0.95	0.79	0.75	0.73
Proportion of reproductive age men working in agriculture	-0.45	-0.08	0.00	-0.09	0.95	1	0.86	0.83	0.83
Proportion of the total population working in agriculture	-0.47	-0.10	-0.12	0.15	0.79	0.86	1	0.86	0.84
Proportion of adult female population who are farm operators	-0.33	-0.12	-0.34	0.01	0.75	0.83	0.86	1	0.85
Proportion of the adult male population who are farm operators	-0.34	-0.24	-0.30	-0.01	0.73	0.83	0.84	0.85	1
Proportion of the total adult population who are farm operators	-0.29	-0.22	-0.38	0.04	0.75	0.84	0.87	0.88	0.93
Population density (per km^2)	-0.01	0.27	0.44	0.04	-0.49	-0.56	-0.56	-0.80	-0.71
Largest community size	-0.06	-0.40	-0.51	0.03	0.71	0.75	0.74	0.77	0.75
Population change between census years (%)	-0.39	-0.06	-0.06	0.06	0.60	0.60	0.59	0.50	0.48
Estimated average age	-0.44	0.08	-0.01	0.08	0.37	0.40	0.39	0.28	0.38
Proportion of reproductive age women who are ≥35 y	-0.45	0.10	0.12	0.00	0.48	0.51	0.55	0.36	0.40
Ratio of children 0-12 years to reproductive age women	0.42	-0.48	-0.57	0.04	0.31	0.32	0.33	0.40	0.45
Proportion of families with lone female parent	0.60	-0.03	0.77[2]	-0.03	-0.72	-0.79	-0.83	-0.69	-0.76
Proportion of land area sprayed with herbicide	-0.17	0.29	0.14	-0.01	-0.30	-0.23	-0.16	-0.04	-0.12
Proportion of land area sprayed with fungicide	-0.01	0.25	0.06	0.06	-0.32	-0.32	-0.25	-0.18	-0.28
Modified Beale Code	0.08	-0.42	-0.63	0.03	0.37	0.41	0.43	0.67	0.71
Revised Beale Code	0.04	-0.42	-0.65	0.23	0.21	0.25	0.39	0.42	0.53

[2] As both variables are continuous, Pearson correlation coefficient shown as it was much higher then the Spearman value (0.24).

	Population density (per km^2)	Largest community size	Population change between census years (%)	Estimated average age (years)	Proportion of reproductive age women who are ≥35 y	Ratio of children 0-12 years to reproductive age women	Proportion of families with lone female parent	Proportion of land area sprayed with herbicide	Proportion of land area sprayed with fungicide	Modified Beale Code	Revised Beale Code
Median household income	0.15	-0.24	-0.13	0.06	-0.23	-0.35	0.13	0.29	0.28	-0.22	-0.14
Median family income	0.12	-0.32	0.05	0.21	-0.01	-0.41	0.17	0.39	0.38	-0.33	-0.29
Proportion of reproductive age males with no degree	-0.37	0.25	-0.25	-0.38	-0.37	0.31	0.18	-0.26	0.05	0.40	0.18
Proportion of total adult population with no degree	-0.32	0.50	0.01	-0.15	0.05	0.47	-0.25	-0.34	-0.10	0.56	0.52
Proportion of reproductive age males with undergraduate-level degree or certificate as highest education	0.55	-0.55	-0.18	0.07	0.04	-0.61	0.14	0.31	0.11	-0.57	-0.44
Proportion of total population with undergraduate-level degree or certificate as highest education	0.33	-0.40	-0.01	0.31	0.11	-0.42	0.07	0.38	0.17	-0.48	-0.37
Proportion of reproductive age males with graduate degree as highest level of education	0.55	-0.64	-0.08	0.04	0.14	-0.60	0.11	0.33	0.08	-0.71	-0.63
Proportion of total population with graduate degree as highest level of education	0.26	-0.59	0.07	0.15	0.07	-0.36	0.24	0.30	0.13	-0.66	-0.65
Proportion of children age 0-4 y who are Aboriginal	-0.01	-0.06	-0.39	-0.44	-0.45	0.42	0.60	-0.17	-0.01	0.08	0.04
Proportion of reproductive age women who are immigrant	0.27	-0.40	-0.06	0.08	0.10	-0.48	-0.03	0.29	0.25	-0.42	-0.42
Proportion of total population who are immigrant	0.44	-0.51	-0.06	-0.01	0.12	-0.57	0.03	0.14	0.06	-0.63	-0.65
Proportion of reproductive age women in primary production work	0.04	0.03	0.06	0.08	0.00	0.04	-0.03	-0.01	0.06	0.03	0.23

	Population density (per km^2)	Largest community size	Population change between census years (%)	Estimated average age (years)	Proportion of reproductive age women who are ≥35 y	Ratio of children 0-12 years to reproductive age women	Proportion of families with lone female parent	Proportion of land area sprayed with herbicide	Proportion of land area sprayed with fungicide	Modified Beale Code	Revised Beale Code
Proportion of reproductive age women working in agriculture	-0.49	0.71	0.60	0.37	0.48	0.31	-0.72	-0.30	-0.32	0.37	0.21
Proportion of reproductive age men working in agriculture	-0.56	0.75	0.60	0.40	0.51	0.32	-0.79	-0.23	-0.32	0.41	0.25
Proportion of the total population working in agriculture	-0.56	0.74	0.59	0.39	0.55	0.33	-0.83	-0.16	-0.25	0.43	0.39
Proportion of adult female population who are farm operators	-0.80	0.77	0.50	0.28	0.36	0.40	-0.69	-0.04	-0.18	0.67	0.42
Proportion of the adult male population who are farm operators	-0.71	0.75	0.48	0.38	0.40	0.45	-0.76	-0.12	-0.28	0.71	0.53
Proportion of the total adult population who are farm operators	-0.76	0.77	0.44	0.30	0.38	0.53	-0.75	-0.15	-0.26	0.70	0.52
Population density (per km^2)	1	-0.76	-0.25	-0.11	-0.02	-0.50	0.39	0.41	0.13	-0.68	-0.39
Largest community size	-0.76	1	0.46	0.40	0.29	0.53	-0.83	-0.34	-0.34	0.92	0.58
Population change between census years (%)	-0.25	0.46	1	0.63	0.68	0.09	-0.52	-0.09	-0.08	0.12	0.15
Estimated average age	-0.11	0.40	0.63	1	0.43	-0.19	-0.38	0.00	0.09	0.22	0.23
Proportion of reproductive age women who are ≥35 y	-0.02	0.29	0.68	0.43	1	0.02	-0.55	0.05	-0.23	-0.01	0.09
Ratio of children 0-12 years to reproductive age women	-0.50	0.53	0.09	-0.19	0.02	1	-0.17	-0.27	-0.34	0.52	0.44
Proportion of families with lone female parent	0.39	-0.83	-0.52	-0.38	-0.55	-0.17	1	0.27	0.32	-0.38	-0.41
Proportion of land area sprayed with herbicide	0.41	-0.89	-0.09	0.00	0.05	-0.27	0.27	1	0.28	-0.32	-0.25
Proportion of land area sprayed with fungicide	0.13	-0.34	-0.08	0.09	-0.23	-0.34	0.32	0.28	1	-0.15	-0.14
Modified Beale Code	-0.68	0.92	0.12	0.22	-0.01	0.52	-0.38	-0.32	-0.15	1	0.78
Revised Beale Code	-0.39	0.58	0.15	0.23	0.09	0.44	-0.41	-0.25	0.78	0.78	1