Modeling the Risk of Hip Fracture among Residents in the Long Term Care Facilities in British Columbia, Canada: Impact of Misspecification of the Correlation Structure on the Parameter Estimates

A Thesis Submitted to the
College of Graduate Studies and Research
in Partial Fulfillment of the Requirements
for the degree of Master of Biostatistics
in the School of Public Health
University of Saskatchewan
Saskatoon

By
Mehdi Rostamiforooshani

Permission to Use

In presenting this thesis in partial fulfilment of the requirements for a Postgraduate degree from the University of Saskatchewan, I agree that the Libraries of this University may make it freely available for inspection. I further agree that permission for copying of this thesis in any manner, in whole or in part, for scholarly purposes may be granted by the professor or professors who supervised my thesis work or, in their absence, by the Head of the Department or the Dean of the College in which my thesis work was done. It is understood that any copying or publication or use of this thesis or parts thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of Saskatchewan in any scholarly use which may be made of any material in my thesis.

Requests for permission to copy or to make other use of material in this thesis in whole or part should be addressed to:

Head of the School of Public Health

104 Clinic Place

University of Saskatchewan

Saskatoon, Saskatchewan

Canada

S7N 2Z4

Abstract

In practice, survival data are often grouped into clusters, such as clinical sites, geographical regions and so on. This clustering imposes correlation among individuals within each cluster, which is known as within cluster correlation. For instance, in our motivating example, within each long term care facility (LTCF), the elderly are likely from nearby areas with similar quality of life and having access to similar health care. As such, individual sharing the same hidden features may correlate with each other. The shared frailty model is therefore often used to take into account the correlation among individuals from the same cluster. In some applications, when the survival data are collected over geographical regions, random effects corresponding to geographical regions in closer proximately to each other might also be similar in magnitude, due to underlying environmental characteristics. Therefore, shared spatial frailty model can be adopted to model the spatial correlation among the clusters, which are often implemented using Bayesian Markov Chain Monte Carlo method. This method comes at the price of slow mixing rates and heavy computational cost, which may reader it impractical for data intensive application.

In this thesis, motivated by the computational challenges encountered in modelling spatial correlation in a real application involving large scale survival data, we used simulations to assess the efficiency loss in parameter estimates if residual spatial correlation is present but using a spatially uncorrelated random effect term in the model. Our simulation study indicates that the share frailty model with only the spatially correlated random effect term may not be sufficient to govern the total residual variation, whereas the simpler model with only the spatially uncorrelated random effect term performs surprisingly well in estimating

the model parameters compared with the true model with both the spatially correlated and uncorrelated random effect terms. As such, using the shared frailty model with independent frailty term should be reliable for estimating the effects of covariates, especially when the percentage of censoring is not high and the number of clusters is large. Also, such model is advantageous, since it can be easily and efficiently implemented in a standard statistical software. This is not to say that the shared frailty model with independent frailty term should be preferred over the spatial frailty model in all cases. Indeed, when the primary goal of inference is predicting the hazard for specific covariates group, additional care needs to be given due to the bias in the scale parameter associated with the Weibull distribution, when the correlation structure is misspecified.

Acknowledgements

Firstly, I would like to express my sincere gratitude to my supervisor Dr. Cindy Xin Feng, and my co-supervisor Dr. Susan Whiting for their guidance, encouragements, patience and continuous support during my M.Sc. study. I offer my sincere appreciation for the learning opportunities provided by my supervisors. This thesis could not have been written without their invaluable advice and patient guidance.

I would also like to thank the rest of my thesis committee: Dr. Longhai Li, Dr. Michael Szafron and my external examiner, Dr. Xulin Guo for their valuable comments.

My especial thanks go, as well, to Dr. Mohammad Owais Suria, a physician, also a master's student at the University of Saskatchewan. I had the opportunity and honor to work with him on several projects. His enthusiasm and motivation to do research and his admirable confidence have always inspired me. His encouragements, advice and guidance in last two years have been invaluable to me and have opened a new horizon in my academic life.

My sincere thanks also goes to Dr. Catherine Trask for offering me the summer internship opportunity. I also would like to thank Dr. Hassan Vatanparast for the opportunities working on the research projects using various statistical methods.

Finally, I would especially like to thank my wife, Najmeh Eshghi, and my parents and siblings for their love, support and constant encouragement over the years. You are the salt of the earth, and I undoubtedly could not have done this without you.

I dedicate this thesis to my patient wife, Najmeh.

Contents

List of Tables

List of Figures

List of Abbreviations

SCUBA	Self Contained Underwater Breathing Apparatus
LOF	List of Figures
LOT	List of Tables

Chapter 1

Introduction

1.1 Background and Motivation

Hip fracture is a fracture of the proximal femur, either through the femoral cervix or through the trochanteric region 1.1. In Canada, up to 28% and 37% of men and women, respectively, die in the first year following hip fracture, mostly as a result of serious underlying medical conditions [1]. Survivors, on the other hand, will barely regain the level of function they had prior to the hip fracture as 44% of people discharge from hospital for a hip fracture return home; of the rest, 10% go to another hospital, 27% go to rehabilitation care, and 17% go to long-term care facilities (LTCFs) [1]. As well, one third of survivors re-fracture within one year and half of them re-fracture within five years after the primary event of hip fracture. Hip fracture incidence increases with age in elderly people over 65 such that more than 80% of people who experience hip fracture are over 50 years of age. In Canada, around 30,000 people experience hip fracture which is more than incidence frequency of heart attack, stroke and breast cancer combined, while currently only 14% of Canada's population are over 65 [2]. Consequently, each hip fracture costs the health care system $21,285 in the first year after hospitalization, and $44,156 if the patient is institutionalized [3]. The total health care budget spent on hip fracture is $1.2 billion. It is estimated that the elderly population will

increase up to 24% in Canada's population and hip fracture expenditure alone on health care will cost $2.4 billion in 2041 [3].

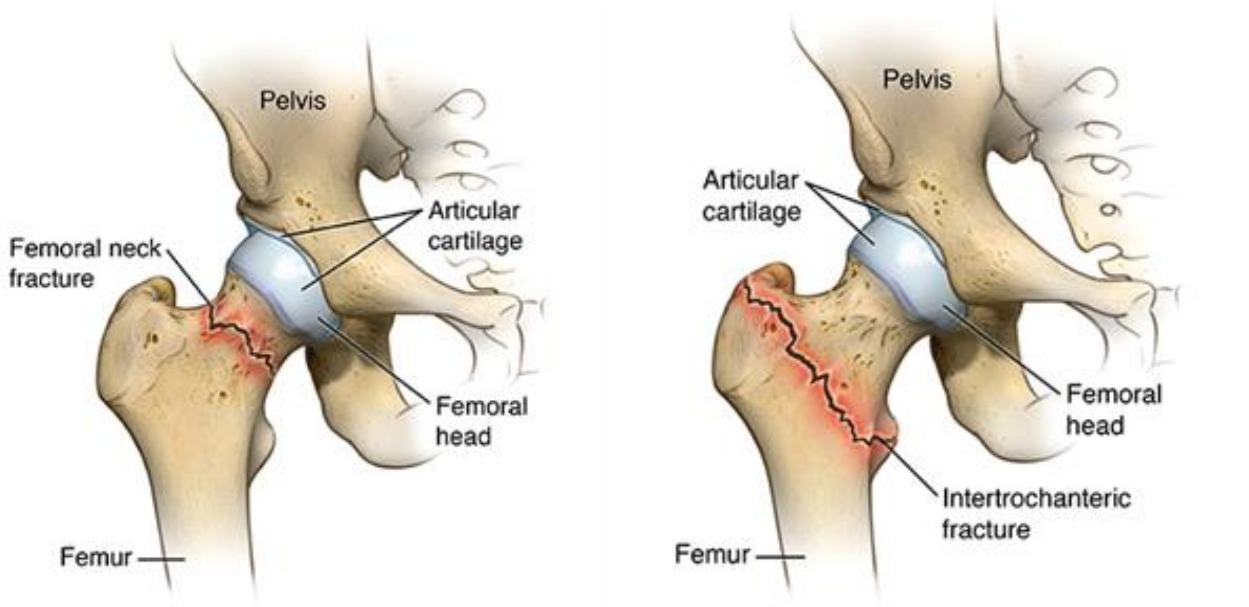


Figure 1.1: A hip fracture is a break in the thigh bone or femur of the hip joint. The left picture exhibits the Femoral neck fracture which is the most common type of hip fracture and the right picture shows Intertrochanteric hip fracture.

Among geriatric population, those who cannot live independently at home due to chronic illnesses, or decline in physical or cognitive functions are most likely brought to long term care facilities (LTCFs) or other residential-based care facilities. LTCFs offer 24 hour, 7 day a week nursing services to their residents, most of whom live permanently in the facility until death. This population, thus, is more vulnerable than community with the same age such that they tend to develop hip fracture 4 times more and fall 3 times more than elderly people in community [4]. The estimated prevalence of hip fracture in LTCFs is approximately 20%, and is even higher as residents approach 90 years of age or older [5]. Residents who suffer from a hip fracture are less likely to regain function than elderly people in community, and are twice as likely to die within 3 months as those without fracture [6]. Conclusively, hip

fracture contributes in substantial suffering for the patient living in these facilities, as well as a severe economic burden for society [7].

Despite much research has been conducted to identify the risk factors associated with hip fracture, few research has been conducted to fully utilize the information on time from entering into the LTCFs until the first time the elderly people got hip fracture [8, 9]. Such information on time to event is critical to evaluate the quality of the health care delivered at LTCFs. The shared frailty models can be utilized to incorporate the within cluster correlation in modeling the time to event data [10, 11]. Furthermore, recent studies [12, 13, 14] have suggested seniors from rural areas tend to have a higher risk of getting hip fracture compared with those from urban areas, suggesting that risk of hip fracture could potentially be geographically dependent. If macro-environmental factors are contributing to the risk of getting hip fracture among the elderly at the LTCFs, then differential risk of hip fracture should be expected within a large geographic area in which variation in these factors is present. Hence, for seniors residing in the LTCFs in close proximity to each other, we would expect some degree of residual spatial correlation in the risk of getting hip fracture after adjustment for patient-level characteristics known to be associated with hip fracture.

To date, no study has investigated spatial patterns of initial hip fracture in elderly residing in LTCFs. The shared spatial frailty model [15, 16] controls for unmeasured spatial confounders by including a flexible baseline that is spatially varying. This approach allows us to borrow information across spatial units to estimate the baseline hazard, which is often implemented using Bayesian Markov Chain Monte Carlo method; however, this method comes at the price of slow mixing rates and heavy computational cost, which may reader it impractical for data intensive application. Therefore, the objectives of this thesis include:

(1) modeling time to first hip fracture among elderly people from LTCFs in British Columbia to determine the risk factors associated with the hazard of having the first hip fracture based on the shared frailty survival model; (2) testing if there is any spatial correlation in the residual after accounting for individual level risk factors; and (3) through simulation studies, investigating if there is any bias and efficiency loss in the estimated regression coefficients under the models with misspecified correlation structures and if the bias and efficiency loss depend on the percentage of censoring, the number of clusters and relative strength of the residual spatial correlation.

1.2 Survival Analysis

Survival analysis is a branch of statistics that focuses on modeling time duration between a starting point until a specific endpoint, such as from birth until death in biological organisms, time to recovery after being diagnosed with certain disease or time to failure in mechanical systems [17].

In many situations, we do not observe the event for all individuals included in a study. A survival time is right censored when the individual did not develop the disease of interest by the end of study, or left the study due to immigration or death or other reasons than the event of interest. Left censoring is when the event of interest has already occurred before enrollment. Interval censored data arises when the failure time cannot be observed, but can only be determined to lie in an interval obtained from a sequence of examination times. The right censoring is the most common type of censoring in many applications [18].

The time interval between an individual entering in the study until experiencing the event

of interest or loss to follow up (due to some reason other than the disease of interest) are called survival time and censored time, respectively.

1.2.1 Survival and Hazard Functions

Let T denote the survival time following distribution $f(t)$. Survival function is defined as the probability of not experiencing the event between time t:

$$S(t) = P(T > t) = 1 - P(T \leq t) = 1 - F(t). \tag{1.1}$$

which is a non-increasing function of t with $S(0) = 1$, $0 < S(t) < 1$.

The hazard function is another commonly used distribution function for describing the survival time [19] which is defined as:

$$h(t) = \lim_{\Delta \to 0} \frac{P(t \leq T < t + \Delta | T \geq t)}{\Delta}, \tag{1.2}$$

which calculates the instantaneous failure rate at time t, given that the individual survives until time. This function is simplified by applying the conditional probability formula:

$$h(t) = \lim_{\Delta \to 0} \frac{P(t \leq T < t + \Delta)}{\Delta} \frac{1}{P(T \geq t)} = \frac{\frac{dF(t)}{dt}}{S(t)} = \frac{f(t)}{S(t)}. \tag{1.3}$$

The hazard function must be non-negative, $h(t) \geq 0$, and its integral over $[0, \infty)$ must be infinite, but is not otherwise constrained; it may be increasing or decreasing, non-monotonic,

or discontinuous. One can also write

$$h(t) = \frac{\frac{dF(t)}{dt}}{1 - F(t)} = -\frac{d\log(1 - F(t))}{dt}. \tag{1.4}$$

which implies

$$S(t) = e^{-\int_0^t h(s)ds}. \tag{1.5}$$

Cumulative hazard, $H(t)$ is another important function in survival analysis which is defined as

$$H(t) = \int_0^t h(s)ds, \tag{1.6}$$

which implies that

$$S(t) = e^{-H(t)}. \tag{1.7}$$

Therefore, by knowing either of $f(t)$, $F(t)$, $h(t)$, $S(t)$ or $H(t)$, other functions can be derived.

1.2.2 Accelerated Failure Time Model

To model the effect of covariates on the survival time, popular choices of regression models to incorporate the covariates are the proportional hazards model [20, 21], the additive hazards model [22], the proportional odds model [23] and the accelerated failure time model [24]. This thesis will focus on accelerated failure time models.

In accelerated failure time (AFT) models, we assume that the effect of the covariates will be a multiplication of the expected survival time. For AFT models, it is common to use the log-linear representation

$$Y_i = \log(T_i) = \mu + \boldsymbol{\alpha}' X_i + \sigma\epsilon_i, \tag{1.8}$$

where μ is the intercept, $\boldsymbol{\alpha}$ are unknown regression coefficients reflecting the effect that each explanatory variable has on the survival time and X_i is a vector of covariates, σ is the scale parameter and ϵ_i is the error term, $i = 1, \cdots, n$. The distribution of the error term, ϵ_i is assumed to be known, and determines the distribution of T and vice versa.

Weibull is one of the mostly used distributions in survival analysis. It is the only distribution that can be expressed as both an accelerated failure time model and a proportional hazard model. If T follows a Weibull distribution, ϵ has a Gumbel distribution [19] with the survival function $e^{-e^{\epsilon}}$.

The probability distribution function of T under a Weibull distribution is specified by

$$f(t_i) = \lambda_i \rho t_i^{\rho-1} e^{-\lambda_i t_i^{\rho}}. \tag{1.9}$$

Assuming the log-linear form (1.8) for the survival times, the survival function can be expressed as,

$$\begin{aligned} S(t_i) &= P\left(\mu + \boldsymbol{\alpha}' X_i + \sigma\epsilon_i \geq \log(t_i)\right) && (1.10)\\ &= P\left(\epsilon_i \geq \frac{\log(t_i) - \mu - \boldsymbol{\alpha}' X_i}{\sigma}\right) && (1.11)\\ &= S_{\epsilon_i}\left(\frac{\log(t_i) - \mu - \boldsymbol{\alpha}' X_i}{\sigma}\right) && (1.12)\\ &= e^{-e^{\frac{\log(t_i) - \mu - \boldsymbol{\alpha}' X_i}{\sigma}}} && (1.13)\\ &= e^{-\lambda_i t_i^{1/\sigma}} && (1.14) \end{aligned}$$

where $\lambda_i = e^{\left(\frac{-\mu - \boldsymbol{\alpha}' X_i}{\sigma}\right)}$, which is the scale parameter for the Weibull distribution, so the covariates can be included within λ_i and the parameter $\rho = 1/\sigma$ provides the shape of the

distribution.

Therefore, the hazard function for the Weibull regression is expressed as:

$$h(t_i) = f(t_i)/S(t_i) = \rho t_i^{\rho-1}\lambda_i = \rho t_i^{\rho-1} e^{\boldsymbol{\beta}' X_i}, \tag{1.15}$$

where $\boldsymbol{\beta} = (\beta_0, \beta_1, ..., \beta_p)'$ such that $\beta_0 = \frac{-\mu}{\sigma}$ and $\beta_i = \frac{-\alpha_i}{\sigma}$, for $i = 1, ..., p$ and p is the number of risk factors. Weibull regression also belongs to the proportional hazard family, since the covariates are multiplicatively related to the hazard [25].

Let δ_i denote the event indicator for the ith subject, $i = 1, \cdots, n$, where $\delta_i = 1$ if the ith individual experienced the event and $\delta_i = 0$ if censored. The likelihood function can be then written as

$$L(\boldsymbol{\theta}|\boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X}) = \prod_{i=1}^{n} f(t_i)^{\delta_i} \big(S(t_i)\big)^{1-\delta_i}. \tag{1.16}$$

where $\boldsymbol{\theta} = (\boldsymbol{\beta}, \rho)'$ denotes the vector of parameters in the model, $\boldsymbol{t} = \{t_i\}_{i=1}^n$ denotes the collection of times to event or censoring and $\boldsymbol{\delta} = \{\delta_i\}_{i=1}^n$ is the collection of event indicators for all subjects and $\boldsymbol{X}$ is the collection of all the covariates. The likelihood function can be also written as,

$$L(\boldsymbol{\theta}|\boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X}) = \prod_{i=1}^{n} h(t_i)^{\delta_i} S(t_i). \tag{1.17}$$

For the Weibull regression model, the likelihood function can be then expressed as,

$$L(\boldsymbol{\theta}|\boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X}) = \prod_{i=1}^{n} \left(\rho t_i^{\rho-1} e^{\boldsymbol{\beta}' X_i}\right)^{\delta_i} \exp\left(-t_i^{\rho} e^{\boldsymbol{\beta}' X_i}\right). \tag{1.18}$$

The maximum likelihood estimators (MLE) of the parameters can be obtained by taking the

derivatives of the log likelihood with respect to the parameters, which are consistent and asymptotically normal [26].

1.3 Overview

The remaining of the thesis is organized as follows: Chapter 2 introduces shared frailty model and its mathematical formulation, maximum likelihood estimation and inference, which is followed by an analysis of hip fracture data. Chapter 3 introduces the shared spatial frailty model to test if there is any residual spatial correlation. In Chapter 4, we conduct a simulation study to understand if there is any bias and efficiency loss in the estimated regression coefficients under the models with misspecified correlation structure. Further, how the bias and efficiency loss depend on the percentage of censoring, the number of clusters and the relative strength of the spatial correlation. Chapter 5 concludes the thesis with conclusions and future works.

Chapter 2

Shared Frailty Model

In the first section of this chapter, an introduction to the hip fracture data and the potential risk factors for hip fracture will be provided. In the next section, the shared frailty model formulation will be presented, followed by application of this model on the hip fracture data.

2.1 Hip Fracture Data

2.1.1 Study Population and Design

The cohort of the study includes 36629 seniors who are above 65 years of age and entered LTCFs from January 2010 to December 2014 in the the province of British Columbia (BC), Canada. The study population comes from 298 LTCFs. Canadian hospitals and acute care facilities record information about admitted individuals. The individuals were assessed every three months and the data were recorded. This information comprises demographic information, diagnosis of related diseases, date of entry and discharge of the patients and so forth. The information periodically is submitted to the Canadian Institute for Health Information (CIHI) by acute care facilities and/or regional health authorities (RHAs) in all territories and provinces except Quebec. CIHI, accordingly, records these data in databases such as

Discharge Abstract Database (DAD), Continuing Care Reporting System (CCRS), Hospital Morbidity Database (HMD) and National Ambulatory Care Reporting System (NACRS). DAD and CCRS are the main sources used in this research to retrieve information for the individuals.

2.1.2 Potential Risk Factors

For many years, osteoporosis was the only well-known cause of fractures in geriatric population. Osteoporosis is a medical condition in which the bones become brittle and fragile from loss of tissue. One way of diagnosing osteoporosis is to determine the bone mineral density (BMD). If BMD is 2.5 or more below the BMD of a 30 years old healthy adult, the individual has osteoporosis. Despite the osteoporotic people are extremely prone to fracture, majority of fractures occur in people without osteoporosis [27]. The immediate conclusion, thus, is that BMD score does not provide the only source for prediction of hip fracture and efforts must be made to recognize all the risk factors which are independent from osteoporosis. On the other hand, 90% of those who get hip fracture is due to falling [28]. That is, even if the person has osteoporosis, hip fracture would not happen if the patient does not fall. If falls can be prevented in LTCFs, the long-term survival and quality of life of seniors in LTCFs can be extended [29]. Henceforth, risk factors which result in falls must be detected as well as their contribution to hip fracture risk.

The potential demographic risk factors for hip fracture are age over 65, female gender [30], geography region [31], and the possible non-demographic factors including low body mass index (BMI) [32], falls [33], co-morbidities [34], and poly-pharmacy [35], calcium and vitamin D deficiency [36, 37] and etc.

A short review of these risk factors is presented as follows:

Osteoporosis

Annually, more than 8.9 million fractures occur worldwide due to osteoporosis [38]. Osteoporosis is a condition that causes bones to become thin and porous, decreasing bone strength and leading to an increase in risk of breaking a bone [39]. In Canada, osteoporosis causes 70-90% of 30,000 hip fractures annually. One of the reasons is that the osteoporosis is undiagnosed. As an evidence for this, 80% of patients with a history of fractures are not given osteoporosis diagnosis or therapies [1]. Therefore, the focus has increasingly been on the identification of patients at high risk of fracture rather than the identification of people with osteoporosis by BMD.

Age

Age is one the most important risk factors of osteoporosis, especially in women. In recent decades, the incidence of hip fracture has gone up substantially partly due to the extended life expectancy. Between 1990 and 2000, there was nearly a 25% grow in hip fractures worldwide [40]. In Canada, 80% of hip fractures happen in people over 50 years of age [1] and 52% of hip fractures occur in the age group 80 and over [41].

Sex

It is shown that women have higher chance of getting hip fracture than men due to higher life expectancy and experiencing menopausal which both increase risk of osteoporosis [42]. Worldwide, 1 in 3 women over age 50 will experience osteoporotic fractures, as will 1 in 5 men aged over 50 [43]. Overall, 70% and 61% of hip and osteoporotic fractures occur in

women.

BMI

Low body mass index (binomial) is a well-documented risk factor for future fracture, whereas a high BMI is widely believed that obesity is protective against fracture [44]. BMI is also one of determinants of bone mineral density (BMD) [45] so that the higher BMI, the lower is the risk of osteoporosis. In obese people, a protective layer of fat padding around the hip may protect the bone from fracture [46].

Falls

Although bone and muscle weaknesses, low bone mineral density (BMD) and osteoporosis are most prominent predictors of hip fracture in literature, more than 90% of hip fractures in elderly population take place as a consequence of falls [28]. The evidence highlight the substantial negative impact of falls on the quality of life of Canadians and Canada's health care system [47]. Even a minor fall or injury can lead to a fracture for someone, especially with osteoporosis highlighting the importance of fall predictors and fall prevention. Evidence indicates that falls may interact with geographical regions, socio-economic status, so forth [46, 48, 49, 50, 51]. Therefore, it is vital to identify risk factors of falls resulting in hip fracture. Major risk factors of falls in the elderly include functional decline, musculoskeletal problems, neurological diseases, psychosocial characteristics and medications [52].

Poly-pharmacy

Polypharmacy, usually defined as the concurrent use of multiple medications [53]. Elderly

population are more prone to multiple medical conditions, such as hypertension, arthritis, heart disease, cancer, and diabetes mellitus, which require multiple medications for proper treatment [54]. Residents of LTCFs, also, are not exceptional and, as a matter of fact, consume a relatively higher volume of medications while residing in LTCFs [55]. Studies have demonstrated that the use of multiple medications enlarges the hazard of adverse drug effects, drug-drug interactions, electrolyte imbalance, decreased drug clearance rates, and impaired balance [56, 57]. The probability of potential drug interactions is markedly related to the number of medications used. When 2 drugs are taken per day, the potential for drug interactions is approximately 6%; however, the risk rises to 50% with 5 drugs per day and is as high as 100% with 8 drugs per day [58]. The main group of drugs resulting in these drug complications are benzodiazepines, antidepressants, antipsychotics and antiepileptics [59]. As a result, polypharmacy increases the risk of falls higher than twofold [60, 61] and consequently increases the risk of hip fracture [35]

Geographical Region

The incidence of hip fracture also varies throughout the world. Statistics show that Scandinavian countries have the highest fracture rate comparing with other regions of the globe [62, 63, 64, 65]. Within North America, the United States is categorized as 'very high' fracture risk, similar to the Scandinavian countries and Iceland and Canada is categorized as 'high' fracture risk, similar to Great Britain [63].

The risk of hip fracture may also vary within a smaller geographic area. There is a general trend of the risk of hip fracture being higher in urban areas [66], which might be attributed to the longer life expectancy, more mobility and even poorer nutrition intake for the residents

in the urban areas [67, 68]. However, evidence in literature is mixed with some reports that reveal higher risk in urban areas. Some studies have reported higher risk in urban areas [69], and other study report no significant difference [70].

Co-morbidities

Patients with hip fracture frequently have multiple illnesses [71]. Such people may take multiple medications for the sicknesses they carry, they become depressed, get anxiety and other possibilities may happen which inflate risk of falls. Various studies have shown impact of certain diseases in inflation of hip fracture risk: rheumatoid arthritis [72], diabetes [73], sedentary life style [74], cognitive impairment [75] and dementia [76], Alzheimer's [77], hypotension and stroke [78], and Parkinson's disease [79].

Size of LTCF

Size of an LTCF indicates the number of seniors living in the LTCFs and defined based on the number of beds having three categories: small: ≤ 30 beds; medium: $30 >$ and ≤ 100; large: > 100.

Small sized and medium facilities are more likely to suffer from the lack of expert nurses, professional doctors and having access to high-level care their residents may need. As a result, incidence of different clinical outcomes may be higher in such facilities than large ones [80].

Other Factors

Other factors, at individual, facility or even regional level, may be influential in developing

hip fracture which may not be retrievable. Examples of such factors include socio-economic status, Vitamin D and Calcium intake, glococorticoid, parental history of fracture, alcohol consumption and smoking. WHO report (2008) [38] gives a comprehensive overview of these risk factors along with other factors.

2.2 Shared Frailty Model

In practice, survival data are often collected from certain groups or clusters within which individuals tend to share common characteristics, i.e. gene traits, environmental effects, socio-economic status and so forth. For instance, in our motivating example, within each LTCF, the elderly are likely from nearby areas with similar quality of life, having access to the similar doctors, nurses and drug plans and even similar activities. As such, individuals sharing the same hidden features may correlate with each other. The shared frailty models [10, 11] are utilized in the hip fracture analysis to take into account the within cluster correlation.

2.2.1 Model Formulation

Let t_{ij} be the time to event or censoring for subject j in stratum i, $j = 1, \cdots, n_i$, $i = 1, \cdots, n$. Let X_{ij} be a vector of individual-specific covariates. The shared frailty model has the generic form as follows:

$$h(t_{ij}) = h_0(t_{ij}) e^{\boldsymbol{\beta}' X_{ij} + V_i}, \tag{2.1}$$

where $h_0(t_{ij})$ is the baseline hazard, which is affected only multiplicatively by the exponential term involving the covariates and V_i is the stratum-specific random effect term capturing the

correlation among the individuals within each cluster. Typically, V_i follows an independent and identically distributed (iid) normal distribution, with mean zero and variance σ_V^2. In this thesis, the focus is on Weibull frailty model, which is one of the mostly used frailty model in survival analysis. In Weibull frailty model, we assume the baseline survival time follows a Weibull distribution:

$$h_0(t_{ij}) = \lambda \rho t_{ij}^{\rho-1}, \tag{2.2}$$

where λ and ρ are the scale and shape parameters.

Hazard ratio (HR) is the ratio of hazards of the event of interest for two categories of a risk factor, which is often used in survival analysis to describe to what extent the covariate can shorten the time to event.

2.2.2 Statistical Inference

In this section, a quick review of the estimation and inference procedures for a full parametric shared frailty model with Weibull baseline hazard will be given.

When positing the baseline time to follow the Weibull distribution with shape ρ, and scale λ parameters, the likelihood function is given by

$$L(\boldsymbol{\beta}, \rho, \sigma_V^2 | \boldsymbol{t}, \delta, \boldsymbol{X}, \boldsymbol{V}) = \prod_{i=1}^{n} \prod_{j=1}^{n_i} \left(\rho t_{ij}^{\rho-1} e^{\boldsymbol{\beta}' X_{ij} + V_i}\right)^{\delta_{ij}} \exp\left(-t_{ij}^{\rho} e^{\boldsymbol{\beta}' X_{ij} + V_i}\right), \tag{2.3}$$

where λ being absorbed as the intercept in the fixed part of the regression, $\beta_0 = \log(\lambda)$. The random effects V_i are unobserved which cannot be estimated directly by the observed data. Taking average of the likelihood function over the random effects will result in the

unconditional or marginal likelihood (probably not in a closed form) which only depends on the regression parameters, i.e. the Weibull shape and regression parameters and the variance component. Therefore, the maximum likelihood estimates can be evaluated based on the unconditional likelihood function.

The first step to approximate the parameters is to integrate out the unobserved terms. Hence, the resulting unconditional likelihood will form

$$L(\boldsymbol{\beta}, \rho, \sigma_V^2 | \boldsymbol{t}, \delta, \boldsymbol{X}) = \int_{\mathbb{R}^n} L(\boldsymbol{\beta}, \rho, \sigma_V^2 | \boldsymbol{t}, \delta, \boldsymbol{X}, V_1, ..., V_n)\ dV_1 ... dV_n = \prod_{i=1}^{n} \prod_{j=1}^{n_i} \int_{-\infty}^{\infty} \left(\rho t_{ij}^{\rho-1} e^{\boldsymbol{\beta}' X_{ij} + V_i}\right)^{\delta_{ij}} \exp\left(-t_{ij}^{\rho} e^{\boldsymbol{\beta}' X_{ij} + V_i}\right) \phi(V_i | \sigma_V^2)\ dV_i, \quad (2.4)$$

where V_i follow normal distribution with mean zero and variance σ_V^2.

The solution to this integral is not in a closed form. Hence, methods such as Taylor series expansion, importance sampling and adaptive quadrature Gaussian rules method have been proposed to approximate the likelihood function [81, 82, 83]. In adaptive Gaussian quadrature method, the summand is calculated at Q predetermined quadrature points $z_q^\star$ $(q = 1, ..., Q)$ over the random sample V_i. The Gauss-Hermite weights w_q and quadrature points $z_q^\star$ can be obtained from tables (e.g. Abramowitz and Stegun 1964, table 25.10) [84]. In this thesis, as also recommended by [82], the adaptive Gaussian quadrature integral approximation will be used. A short description of this method is presented in A.1. The NLMIXED procedure was utilized in SAS to maximize an approximation to the likelihood integrated over the random effects (2.4).

Once the approximation is performed, the maximum likelihood estimates of parameters can be found by utilizing conventional optimization techniques such as quasi-Newton opti-

mizations. This method is also computationally efficient for medium to large-scale problems such as ours. This technique needs more steps to converge, but since there is no need to calculate the second order derivatives, each step is evaluated much faster compared to the Newton-Raphson method [85]. This method is also not sensitive to the initial values while the Newton-Raphson and gradient descent may fail for non-convex problems with an inappropriate starting point [86].

2.3 Hip Fracture Data Analysis

2.3.1 Results

Descriptive statistics of potential risk factors for the first hip fracture since entering the LTCFs in BC are given in Table 2.1. This table shows the distribution of seniors in LTCFs across different categories of the risk factors considered in our analysis.

In our study, age was stratified into three categories: 65-79 as the youngest group, 80-89 as middle age, and ≥ 90 as the oldest group. The individual level income is not provided, so neighborhoods after-tax income level categorized as below average (less than $\$26,500$), average ($\$26,500$-$\$47,700$) and above average income (greater than $\$80,200$)[87], was used as a proxy of the individual level income. To evaluate an overall effect of commodities on hip fracture, a variable was constructed as to whether a senior suffers from at least two of the diseases: diabetes, hypotension, arthritis, alzheimer's, dementia, parkinson's disease, and seizure, which are shown to be significantly associated with hip fracture [71]. Polypharmacy is another potential risk factor for hip fracture, but none of our databases contain reliable

information regarding the prescription drugs. Nevertheless, CCRS records the number of days in the last week on antipsychotic, antianxiety and antidepressant drugs, which were used to create an indicator variable which compares more than 2 days on such drugs versus less than 2 days. Having experienced hip fracture before entering an LTCF might also be an indicator of a hip fracture after entering to the LTCF. In our study, we considered two measurements of falls with one being defined as within one month prior to the first assessment in a LTCF and the other being defined as fall in last five months before a month prior to the first assessment in a LTCF. BMI was calculated based on self-reported information on weights and heights measured during the assessments by the nurses in LTCFs, which was categorized as under-weight (less than 18.5 kg/m^2), normal (between 18.5 kg/m^2 and 25 kg/m^2), over-weight (between 25 kg/m^2 and 30 kg/m^2), and obese (over 30 kg/m^2).

Overall, 3219 out of 36629 patients in our cohort (8.79%) experienced hip fracture during the course of our retrospective study. The median years of residing in LTCFs for our cohort is 2.03 (95% CI 2.00-2.05). Demographic and non-demographic characteristics of the study population by hip fracture status are presented in Table 2.2. We have adopted Weibull shared frailty model for this analysis and the Weibull assumption is examined by checking the $\log(-\log(S(t)))$ vs. $\log(t)$ plot. If the model is correct, the dots should fall into a straight line. In Figure B.1, a slight curvature in the line can be observed, but is not strong enough to seriously violate the Weibull assumption and such curvature may be explained by covariates. Therefore, we also generated similar plots by stratifying the data according to the different combinations of risk factors. For example, as depicted in Figure B.2, by stratifying the data by age and sex, and further in Figure B.3, by stratifying the data by age, sex and fall history, the curvatures are quite minor, which indicate satisfaction of Weibull assumption. As such,

we proceed with the bivariate and multivariate analyses based on the Weibull frailty model.

Table 2.1: Distribution of the characteristics of the elderly over age 65 from the LTCFs, BC, Canada, 2010 − 2014.

Characteristics	**Levels**	**N**	**Percentage**	**95% CI**
Age	65-79	7582	20.7	(20.28, 21.11)
	80-89	17560	47.94	(47.43, 48.45)
	≥90	11487	31.36	(30.89, 31.84)
Sex	Male	12227	33.38	(32.9 , 33.86)
	Female	24402	66.62	(66.14, 67.10)
Fall in last month	No	30860	84.25	(83.88, 84.62)
	Yes	5769	15.75	(15.38, 16.12)
Fall 6 months before	No	29473	80.46	(80.06, 80.87)
until last month	Yes	7156	19.54	(19.13, 19.94)
Prior hip fracture	No	35108	95.85	(95.64, 96.05)
	Yes	1521	4.15	(3.95 , 4.36)
Co-morbidities	≤1	23331	63.7	(63.2 , 64.19)
	≥2	13298	36.3	(35.81, 36.80)
Number of days on	≤2	15254	41.64	(41.14, 42.15)
psychiatric medication	≥3	21375	58.36	(57.85, 58.86)
BMI	Obese	4479	12.23	(11.89, 12.56)
	Over weight	9533	26.03	(25.58, 26.48)
	Normal weight	18244	49.81	(49.3 , 50.32)
	Under weight	4373	11.94	(11.61, 12.27)
Income	Above average	11106	30.32	(29.85, 30.79)
	Average	8657	23.63	(23.20 , 24.07)
	Below average	16866	46.05	(45.54, 46.56)
Rural-Urban	Rural	2844	7.76	(7.49 , 8.04)
	Urban	33785	92.24	(91.96, 92.51)
Facility size	Large	21128	57.68	(57.18, 58.19)
	Medium	14863	40.58	(40.07, 41.08)
	Small	638	1.74	(1.61 , 1.88)

Table 2.2: Distribution of the characteristics of the elderly over age 65 from the LTCFs who developed hip fracture vs. those who did not, BC, Canada, 2010 – 2014.

Characteristics	**Levels**	**hip fracture**					
		Yes			**No**		
		N	%	**95% CI**	**N**	%	**95% CI**
Age	65-79	525	1.43	(1.31, 1.56)	7057	19.27	(18.86, 19.67)
	80-89	1681	4.59	(4.37, 4.80)	15879	43.35	(42.84, 43.86)
	≥90	1013	2.77	(2.60, 2.93)	10474	28.59	(28.13, 29.06)
Sex	Females	2388	6.52	(6.27, 6.77)	22014	60.1	(59.60, 60.60)
	Males	831	2.27	(2.12, 2.42)	11396	31.11	(30.64, 31.59)
Fall in last month	Yes	690	1.88	(1.74, 2.02)	5079	13.87	(13.51, 14.22)
	No	2529	6.9	(6.64, 7.16)	28331	77.35	(76.92, 77.77)
Fall 6 months before	Yes	715	1.95	(1.81, 2.09)	6441	17.58	(17.19, 17.97)
until last month	No	2504	6.84	(6.58, 7.09)	26969	73.63	(73.18, 74.08)
Prior hip fracture	Yes	188	0.51	(0.44, 0.59)	1333	3.64	(3.45, 3.83)
	No	3031	8.27	(7.99, 8.56)	32077	87.57	(87.23, 87.91)
Co-morbidities	≤1	1999	5.46	(5.22, 5.69)	21332	58.24	(57.73, 58.74)
	≥2	1220	3.33	(3.15, 3.51)	12078	32.97	(32.49, 33.46)
Number of days on	≤2	1210	3.3	(3.12, 3.49)	14044	38.34	(37.84, 38.84)
psychiatric medication	≥3	2009	5.48	(5.25, 5.72)	19366	52.87	(52.36, 53.38)
BMI	Under weight	203	0.55	(0.48, 0.63)	4276	11.67	(11.34, 12.00)
	Normal weight	664	1.81	(1.68, 1.95)	8869	24.21	(23.77, 24.65)
	Over weight	1900	5.19	(4.96, 5.41)	16344	44.62	(44.11, 45.13)
	Obese	452	1.23	(1.12, 1.35)	3921	10.7	(10.39, 11.02)
Income	Below average	1442	3.94	(3.74, 4.14)	15424	42.11	(41.60, 42.61)
	Average	749	2.04	(1.90, 2.19)	7908	21.59	(21.17, 22.01)
	Above average	1028	2.81	(2.64, 2.98)	10078	27.51	(27.06, 27.97)
Rural-Urban	Rural	286	0.78	(0.69, 0.87)	2558	6.98	(6.72, 7.24)
	Urban	2933	8.01	(7.73, 8.29)	30852	84.23	(83.86, 84.60)
Facility size	Small	58	0.16	(0.12, 0.20)	580	1.58	(1.46, 1.71)
	Medium	1377	3.76	(3.56, 3.95)	13486	36.82	(36.32, 37.31)
	Large	1784	4.87	(4.65, 5.09)	19344	52.81	(52.30, 53.32)

The bivariate relationships of the potential risk factors with the hazard of hip fracture are shown in Table 2.3. All variables with p-values for the unconditional association was < 0.20 were considered in building the final model. The results of the multivariate analysis (Table 2.4) indicate that the risk of HF for the seniors who entered LTCFs between 80-90 years of age is 1.32 (95% CI: 1.19-1.45) times higher as compared with those who are 65-79.

Similarly, the hazard of getting HF for those over 90 years of age is 1.22 (95% CI: 1.09-1.36) times higher as compared with those who are aged 65-79. In addition, risk of developing HF among females is 1.24 (95% CI: 1.14-1.34) times higher than males. Risk of HF among those who had experienced falls in last month before entering an LTCF vs. those who had not experienced falls is 1.58 (95% CI: 1.45-1.73). Moreover, hazard of HF among those who had experienced falls within last six-one months before entering an LTCF vs. those who had not is 1.09 (95% CI: 1.000 -1.18). A prior HF almost doubles the risk of HF, 1.98 (95% CI: 1.71-2.30). The elderly with more than one Co-morbidities vs. at most one co-morbidity carry more risk of HF with the hazard of HF elevated by 16% (95% CI: 1%-16%). Having taken a psychiatric medication more than three days before entering a LTCFs vs. less than three days inflates hazard by 8% (95% CI: 8%-25%). The hazard ratios for people who are under-weight, normal and over-weight vs. obese people are 1.57 (95% CI: 1.34-1.83), 2.44 (95% CI: 2.11-2.83) and 2.86 (95% CI: 2.41-3.38), respectively, so being obese tends to have a protective effect against hip fracture. Hazard of HF for seniors who registered to LTCFs in rural areas vs. those who enter urban areas is 20% (95% CI: 10%-30%) more. Comparing seniors living in average and high income neighborhoods reveals no significant difference (p-value = 0.3720), while the hazard of HF in seniors living in low income neighborhoods is almost 9% less than those who live in high income neighborhoods (95% CI: 1%-11%, p-value = 0.0311).

To determine if the frailty term improves the model fit, we compared the Weibull frailty model with the Weibull model without frailty term in terms of AIC. The Weibull frailty model gives much lower AIC = 26633 than the Weibull model without the random effect term, AIC = 26649. This implies that there is some unmeasured confounders at the LTCF level. The

comparison is further confirmed by the likelihood ratio test (p-value = < 0.0001). Also, to verify the Weibull assumption for the baseline survival time, $\log(-\log(S(t)))$ versus $\log(t)$ were plotted, stratified by several covariates including age and sex (B.1-B.3). Lines do not fall perfectly on straight lines, but they are straight enough to confirm that this assumption is not violated [19].

Table 2.3: The bivariate analysis reporting the estimated hazard ratios (HR), the corresponding 95% confidence interval (CI) and p-values for all the potential risk factors in the hip fracture analysis.

Characteristic	**Levels**	**HR**	**95% CI**	**P-value**
Age	80-89 vs 65-79	1.43	(1.30, 1.58)	$< .0001$
	$\geq$90 vs. 65-79	1.42	(1.28, 1.58)	$< .0001$
Sex	Females vs. Males	1.29	(1.19, 1.39)	$< .0001$
Fall in last month	Yes vs. No	1.68	(1.55, 1.83)	$< .0001$
Fall 6 months before until last month	Yes vs. No	1.21	(1.11, 1.31)	$< .0001$
Prior hip fracture	Yes vs No	2.13	(1.83, 2.46)	$< .0001$
Co-morbidities	$\geq$2 vs. $\leq$1	1.09	(1.02, 1.17)	0.0133
Number of days on psychiatric medication	$\geq$3 vs. $\leq$2	1.15	(1.07, 1.23)	$< .0001$
BMI	Under weight vs. Obese	1.59	(1.35, 1.86)	$< .0001$
	Normal weight vs. Obese	2.55	(2.20, 2.94)	$< .0001$
	Over weight vs. Obese	3.05	(2.59, 3.60)	$< .0001$
Income	Average vs. High	0.95	(0.86, 1.04)	0.2420
	Low vs. High	0.90	(0.83, 0.98)	0.0134
Rural-Urban	Rural vs. Urban	1.21	(1.06, 1.35)	0.00032
Facility size	Small or Medium vs. Large	1.10	(1.02, 1.17)	0.0102

2.3.2 Discussion

Results of the previous section shows that older ages, female sex, history of falls and hip fracture, Co-morbidities, psychiatric drugs, higher income or socio-economic status, lower BMI and being a resident of rural areas are significant predictors of hip fracture in seniors

Table 2.4: The multivariate analysis of the the hip fracture data using the Weibull model with independent frailty term. The table reports the estimated hazard ratio (HR) and the corresponding 95% confidence intervals (CI) and p-values for all the significant risk factors.

Characteristic	**Levels**	**HR**	**95% CI**	**P-value**
Age	80-89 vs. 65-79	1.32	(1.19, 1.45)	$< .0001$
	$\geq$90 vs. 65-79	1.22	(1.09, 1.36)	$< .0001$
Sex	Females vs. Males	1.24	(1.14, 1.34)	$< .0001$
Fall in last month	Yes vs. No	1.58	(1.45, 1.73)	$< .0001$
Fall 6 months before until last month	Yes vs. No	1.09	(1.00, 1.18)	0.0485
Prior hip fracture	Yes vs. No	1.98	(1.71, 2.30)	$< .0001$
Co-morbidities	$\geq$2 vs. $\leq$1	1.08	(1.01, 1.16)	0.0283
Number of days on psychiatric medication	$\geq$3 vs. $\leq$2	1.16	(1.08, 1.25)	$< .0001$
BMI	Under weight vs. Obese	1.57	(1.34, 1.83)	$< .0001$
	Normal weight vs. Obese	2.44	(2.11, 2.83)	$< .0001$
	Over weight vs. Obese	2.86	(2.41, 3.38)	$< .0001$
Income	Average vs. High	0.96	(0.86, 1.06)	0.3720
	Low vs. High	0.91	(0.84, 0.99)	0.0311
Rural-Urban	Rural vs. Urban	1.25	(1.11, 1.43)	$< .0001$
σ_V^2		1.09	(1.02, 1.16)	0.0145
λ		1.02	(1.01, 1.02)	$< .0001$
ρ		2.14	(2.09, 2.19)	$< .0001$

after entering LTCFs. These results more or less confirm the findings of other researchers for predicting hip fracture incidence, but the results vary in magnitude which reinforces the importance of such an independent research on LTCFs' dwellers rather than community residents.

Our analysis showed that age group 80-89 is most prone to HF compared to 65-79 and over 90 groups. The literature showed the risk of HF increases by aging as a general trend. For instance, in Canada, a report in 2005 showed that incidence of HF arises substantially with age for both men and women [88]. However, for institutionalized residents, different results have been reported. A systematic review [89] indicated small to no association between age and hip fracture risk, whereas a study in Ontario revealed that risk of fracture is higher among $\geq$85 age group. In another recent study from Ontario, a similar pattern as our study revealed that HF incidence declines in the extremely older group. The less number of HF in the extremely older group may be attributed to the prevalence of frailty and immobility in this age group which bound seniors on bed, resulting in a decrease in risk of falls and sudden movements.

With regards to the effect of gender on HF, our study revealed higher risk of hip fracture among women. Similar findings were reported in other studies evaluating the HF risk for the residents in the LTCFs from Ontario [8, 9]. As well, they identified higher rates among males, but only in higher age group, which might be partly due to comparatively higher prevalence of frailty among male 85 years and older. However, we did not observe a significant interaction between age groups and sex in our study. The overall higher prevalence of HF among females as compared to males is probably attributable to a significantly higher proportion of women carrying conditions considered as risk factors for HF such as osteoporosis, dementia,

fracture of extremities, and rheumatologic diseases as compared to men [90], while significantly higher proportions of men have diabetes, respiratory, heart, and renal diseases that have comparatively low risk for HF [91].

Fall is one of the most important factors associated with HF among the elderly population. Evidence has shown that fall happens more frequent among institutionalized residents than senior community dwellers [92, 93]. Our results revealed that the hazard of getting first HF is 58% higher if fall occurred within one month prior to the first assessment in a LTCF, and only 9% with the senior experienced fall in preceding six months excluding immediate last 30 days before the first assessment. These results are consistent with other studies, which revealed that the frequency of falls is higher among institutionalized residents, e.g. half of elderly individuals fall more than once in LTCFs [92, 93].

Our study also found that history of HF prior to entering LTCFs nearly doubles the hazard of HF. Prior history of fracture has been reported among LTCFs residents as a moderate risk factor, though [94, 95]. In a recent meta analysis on the general population [8], reported prior HF is a moderate risk factor. Nevertheless, these results admit a lower risk than our results probably due to conducting studies on general population and also due to variation in methodology used in these studies.

Low BMI is a well-documented risk factor for HF, whereas a high BMI appears to be protective [32, 38, 96]. Our findings indicate that risk of hip fracture decreases with the increased BMI. A recent meta analysis based on 25 prospective cohorts also showed higher BMI has a protective effect on HF[97]. From a clinical point of view, a protective layer of fat padding around the hip may protect the bone from fracture [46]. We also speculate that obese seniors are at lower risk of falls, since they tend to be less mobile than seniors with

normal weights. [98].

In addition, to study the effect of drugs on hazard of hip fracture, we considered the number of days on three psychiatric drugs, i.e. antipsychotic, antianxiety and antidepressant. Although a wide spectrum of drugs being used may predict time-to-hip fracture, we only considered use of psychotropic drugs alone due to limited information on all medications taken. Moreover, psychiatric conditions such as dementia, Alzheimers, depression are very common reason for LTCFs admission [55]. In our analysis, we found that the use of either of the three psychiatric drugs for 3 or more days inflates the risk of hip fracture for about 18 percent compared to 2 or less days on these drug. Similar to our findings, several studies have demonstrated that the use of multiple medications increases the risk of adverse drug effects, drug-drug interactions, electrolyte imbalance, decreased drug clearance rates, and impaired balance [56, 57]. The probability of potential drug interactions is markedly related to the number of medications used. When 2 drugs are taken per day, the potential for drug interactions is approximately 6%; however, the risk rises to 50% with 5 drugs per day and is as high as 100% with 8 drugs per day [58]. The main group of drugs resulting in these drug complications are benzodiazepines, antidepressants, antipsychotics and anti-epileptics [59]. As a result, polypharmacy increases the risk of falls higher than twofold [60, 61] and consequently increases the risk of hip fracture. However, our results do show only small decrease (18%) of hazards among this vulnerable population. Considering differences in methodology and geography, further studies are warranted to further explore the impact of medications on HF in LTCFs.

In the context of geographical variation in HF epidemiology, various published reports describe different role of urban or rural on incidence of HF. In literature, urban settings

predominantly showed higher incidence rates of HF than rural settings [12, 13, 14]. These findings are more sensible in large cities [66]. However, these reports are for general population and not specific to elderly or LTCFs residents. Reports exploring link between HF and urban and rural differences from Canadian jurisdictions are scarce for the community dwellers and even not yet reported for the LTCFs. Urban-rural status may also result in different health care outcomes which are indirectly correlated with incidence of HF [99, 100, 101, 102].

Despite general pattern of higher HF occurrence in urban areas, some studies revealed mixed patterns. For example, Oslo, Norway, an urban city that shows high incidence rate of HF compared to other rural Norwegian areas [103], whereas from the same country, another study showed no significant difference in HF between urban and rural areas [12]. A study from Poland with two third rural proportion revealed significantly contrasting result that the risk of HF is higher in the rural areas than the urban areas [104]. In Asia, a study in Shiraz, an Iranian city, showed that the HF rate was higher in the urban areas than the rural areas[105], but a study from Shanghai city in China, which is a typical megapolis center revealed relatively lower rates in the urban areas as compared to the rural areas. The differences in methodology, recruitment criteria and the targeted study populations may lead to the mixed findings [106]. In our study, residents from the LTCFs located in the rural areas had higher risk of HF than those from the urban areas, which might implies the lack of adequate health care provided in the LTCFs in the rural areas.

Chapter 3

Shared Spatial Frailty Model

In practice, survival data are often collected over clinical sites or geographical regions. In this case, random effects corresponding to geographical regions in closer proximity to each other might also be similar in magnitude, due to environmental characteristics, necessitating further epidemiology study [15, 16]. As shown in Chapter 2, the seniors from the rural areas are at a higher risk of getting hip fracture as compared with the seniors from the urban areas. This may imply a potential spatial effect among the LTCFs. The aim of the data analysis in this chapter is to provide an illustrative example by applying shared spatial frailty model on the hip fracture data. In order to model the spatial correlation among the LTCFs, only a few covariates can be included in the model due to the limitation of computation rescouses involved in Bayesian Markov Chain Monte Carlo inference approach, as introduced in Section 3.2. Here, we are particularly interested in studying the association of falls and the risk of hip fracture; therefore, we chose falls as the primary risk factor of interests and age, prior hip fracture and residential region (rural versus urban) as the confounding variables. We conducted the analysis for males and females separately due to the computational burden in modeling the large scale survival data.

3.1 Model formulation

Let t_{ij} be the time to event or censoring for subject j in stratum i, $j = 1, \cdots, n_i$, $i = 1, \cdots, n$. Let $\boldsymbol{X}_{ij}$ be a vector of individual-specific covariates. The general form of shared spatial and non-spatial frailty model is then defined as,

$$h(t_{ij}) = h_0(t_{ij}) e^{\boldsymbol{\beta}' \boldsymbol{X}_{ij} + W_i + V_i}, \tag{3.1}$$

where $h_0(t_{ij})$ is the baseline hazard which can be assumed to be $\rho t_{ij}^{\rho-1} e^{\beta_0}$ and is affected only multiplicatively by the exponential term involving the covariates and W_i is the stratum-specific random effect term capturing the spatial correlation among the strata, which can be modeled as a conditional autoregressive (CAR) structure (Besag et al, 1991) [107],

$$W_i | W_{\partial_i} \sim N(\overline{W}_{\partial_i}, \sigma_W^2 / m_i), \tag{3.2}$$

where ∂_i represents the neighbours of the i^{th} region, $\overline{W}_{\partial_i}$ is the average of $W_{i' \neq i}$ that are adjacent to W_i and m_i is the number of adjacent neighbors for region i and σ_W^2 is the variance parameter. The joint probability distribution for $\boldsymbol{W} = (W_1, \cdots, W_n)'$ is expressed as,

$$\boldsymbol{W} | \sigma_W^2 \sim MVN(\boldsymbol{0}, \sigma_W^2 \big(\boldsymbol{D} - \boldsymbol{A}\big)^{-1}), \tag{3.3}$$

where $\boldsymbol{D}$ is a diagonal matrix with D_{ii} being the number of neighbours for the i^{th} region and $\boldsymbol{A}$ is a matrix, such that $A_{ij} = 1$, if i^{th} and j^{th} regions are neighbors and $A_{ij} = 0$, otherwise.

In model (2.1), V_i denotes the region-specific random effect capturing any residual varia-

tion that are not spatially correlated,

$$V_i \sim N(0, \sigma_V^2), \tag{3.4}$$

where σ_V^2 represents the variance parameter for V_i, $i = 1, \cdots, n$.

The shared spatial frailty model is a special case of the full model with reduced random effect structure only including W as the random effect term.

3.2 Bayesian Inference

To take the spatial and/or nonspatial Weibull regression can be implemented in a Bayesian framework using Markov chain Monte Carlo (MCMC) procedures. The likelihood function $L(\boldsymbol{\theta}|\boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X})$ corresponding to the full frailty model (3.1) is expressed as,

$$L(\boldsymbol{\theta}|\boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X}) = \prod_{i=1}^{n} \prod_{j=1}^{n_i} \left(\rho t_{ij}^{\rho-1} e^{\boldsymbol{\beta}' \boldsymbol{X}_{ij} + W_i + V_i} \right)^{\delta_{ij}} \exp\left(-t_{ij}^{\rho} e^{\boldsymbol{\beta}' \boldsymbol{X}_{ij} + W_i + V_i} \right), \tag{3.5}$$

where δ_{ij} is the event indicator for the jth individual from the ith region, $i = 1, \cdots, n$ and $j = 1, \cdots, n_i$; $\delta_{ij} = 1$ if the individual experienced the event and $\delta_{ij} = 0$ if censored.

Let $\boldsymbol{\theta} = (\rho, \boldsymbol{\beta}, \boldsymbol{W}, \boldsymbol{V}, \sigma_W^2, \sigma_V^2)'$ denote the vector of all the parameters in the spatial Weibull regression model and $\boldsymbol{t} = \{t_{ij}\}$ denote the collection of times to event or censoring, $\boldsymbol{X} = \{X_{ij}\}$ is the collection of covariate vectors and $\boldsymbol{\delta} = \{\delta_{ij}\}$ is the collection of event indicators for all subjects in all the geographical regions. The joint posterior distribution is

then expressed as

$$p(\boldsymbol{\theta}|\boldsymbol{t},\boldsymbol{\delta},\boldsymbol{X}) \propto L(\boldsymbol{\theta}|\boldsymbol{t},\boldsymbol{\delta},\boldsymbol{X})p(\boldsymbol{W}|\sigma_W^2)p(\boldsymbol{V}|\sigma_V^2)p(\rho)p(\boldsymbol{\beta})p(\sigma_W^2)p(\sigma_V^2), \tag{3.6}$$

where the first term in the right hand-side is the Weibull likelihood, the second and third terms are the distributions for the spatially correlated and uncorrelated random effect terms, as defined in (3.3) and (3.4), respectively.

The model specification in the Bayesian setup is completed by assigning prior distributions for $\boldsymbol{\beta}$, ρ, σ_W^2 and σ_V^2. The normal prior is chosen for $\boldsymbol{\beta} \sim N(0, \sigma_0^2)$, while vague but proper priors are chosen for $\rho \sim G(a, b)$; $\sigma_W^2 \sim IG(c, d)$ and $\sigma_V^2 \sim IG(c', d')$, where G and IG denote the Gamma and inverse (reciprocal) Gamma distributions, respectively.

3.2.1 Gibbs Sampling Formulation

The Gibbs sampler [108] is used to update the parameters in the model, which requires drawing samples sequentially from the full conditional distributions. The conditional distributions

required by Gibbs sampling are given as follows:

$$
\begin{aligned}
&\boldsymbol{\beta}^{(l)} \sim \boldsymbol{\beta}|\rho^{(l-1)}, {\sigma_V^2}^{(l-1)}, \boldsymbol{V}^{l-1}, {\sigma_W^2}^{(l-1)}, \boldsymbol{W}^{(l-1)}, \boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X} \\
&\rho^{(l)} \sim \rho|\boldsymbol{\beta}^{(l)}, {\sigma_V^2}^{(l-1)}, \boldsymbol{V}^{l-1}, {\sigma_W^2}^{(l-1)}, \boldsymbol{W}^{(l-1)}, \boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X} \\
&{\sigma_V^2}^{(l)} \sim \sigma_V^2|\boldsymbol{\beta}^{(l)}, \rho^{(l)}, \boldsymbol{V}^{l-1}, {\sigma_W^2}^{(l-1)}, \boldsymbol{W}^{(l-1)}, \boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X} \\
&\boldsymbol{V}^{(l)} \sim \boldsymbol{V}|\boldsymbol{\beta}^{(l)}, \rho^{(l)}, {\sigma_V^2}^{(l)}, {\sigma_W^2}^{(l-1)}, \boldsymbol{W}^{(l-1)}, \boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X} \\
&{\sigma_W^2}^{(l)} \sim \sigma_W^2|\boldsymbol{\beta}^{(l)}, \rho^{(l)}, {\sigma_V^2}^{(l)}, \boldsymbol{V}^{l}, \boldsymbol{W}^{(l-1)}, \boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X} \\
&\boldsymbol{W}^{(l)} \sim \boldsymbol{W}|\boldsymbol{\beta}^{(l)}, \rho^{(l)}, {\sigma_V^2}^{(l)}, \boldsymbol{V}^{l}, {\sigma_W^2}^{(l)}, \boldsymbol{t}, \boldsymbol{\delta}, \boldsymbol{X}.
\end{aligned} \tag{3.7}
$$

More specifically:

$$
\begin{aligned}
&\boldsymbol{\beta} \sim \Big[\prod_{i=1}^{n}\prod_{j=1}^{n_i}(e^{\delta_{ij}\boldsymbol{\beta}'X_{ij}})e^{-t_{ij}^{\rho}e^{\boldsymbol{\beta}'X_{ij}+W_i+V_i}}\Big]e^{-\frac{\boldsymbol{\beta}^2}{2\sigma_0^2}} \\
&\rho \sim \Big[\prod_{i=1}^{n}\prod_{j=1}^{n_i}(\rho t_{ij}^{\rho-1})^{\delta_{ij}}e^{-t_{ij}^{\rho}e^{\boldsymbol{\beta}'X_{ij}+W_i+V_i}}\Big]\rho^{a-1}e^{-b\rho} \\
&\sigma_V^2 \sim \Big[\prod_{i=1}^{n}\prod_{j=1}^{n_i}e^{\delta_{ij}V_i}e^{-t_{ij}^{\rho}e^{\boldsymbol{\beta}'X_{ij}+W_i+V_i}}\Big]\Big[\prod_{i=1}^{n}e^{-\frac{(V_i)^2}{2\sigma_{\boldsymbol{V}}^2}}\Big]\sigma_{\boldsymbol{V}}^{-c-1}e^{\frac{-d}{\sigma_{\boldsymbol{V}}^2}} \\
&V_k \sim \big(e^{\delta_{kj}V_k}e^{-t_{kj}^{\rho}e^{\boldsymbol{\beta}'X_{kj}+W_k+V_k}}\big)e^{-\frac{V_k^2}{2(\sigma_{\boldsymbol{V}}{}^2)^2}}; \quad k=1,2,\ldots,n \\
&\sigma_W^2 \sim \Big[\prod_{i=1}^{n}\prod_{j=1}^{n_i}e^{\delta_{ij}W_i}e^{-t_{ij}^{\rho}e^{\boldsymbol{\beta}'X_{ij}+W_i+V_i}}\Big]\sigma_{\boldsymbol{W}}^{-c'-1}e^{\frac{-d'}{\sigma_{\boldsymbol{W}}^2}}e^{-\frac{1}{2\sigma_{\boldsymbol{W}}^2}\boldsymbol{W}'(\boldsymbol{D}-\boldsymbol{A})\boldsymbol{W}} \\
&\boldsymbol{W} \sim \Big[\prod_{i=1}^{n}\prod_{j=1}^{n_i}e^{\delta_{ij}W_i}e^{-t_{ij}^{\rho}e^{\boldsymbol{\beta}'X_{ij}+W_i+V_i}}\Big]e^{-\frac{1}{2(\sigma_{\boldsymbol{W}})^2}\boldsymbol{W}'(\boldsymbol{D}-\boldsymbol{A})\boldsymbol{W}}.
\end{aligned} \tag{3.8}
$$

To implement Gibbs sampling, OpenBUGS software was utilized and the built-in function car.normal was used to sample from the multivariate normal distribution for the spatial random effect.

3.2.2 Model Comparison Criteria

Deviance information criterion (DIC) is a Bayesian tool for model comparison. This criterion was established by Spiegelhalter et al. (2002), and is an extension of frequentists' criteria which takes the number of parameters in the model into account [109]. This criterion is based on the posterior distribution of the deviance statistic,

$$D(\boldsymbol{\theta}) = -2\log f(\boldsymbol{y}|\boldsymbol{\theta}) + 2\log h(\boldsymbol{y}), \tag{3.9}$$

where $f(\boldsymbol{y}|\boldsymbol{\theta})$ is the likelihood function for the observed data $\boldsymbol{y}$, given the parameter vector $\boldsymbol{\theta}$, and $h(\boldsymbol{y})$ is the standardizing function of the data alone. The posterior mean of the deviance, $\bar{D} = E_{\boldsymbol{\theta}|\boldsymbol{y}}(D)$ measures the model adequacy and p_D is effective number of parameters measuring the model complexity, which is defined as

$$p_D = E_{\boldsymbol{\theta}|\boldsymbol{y}}(D) - D(E_{\boldsymbol{\theta}|\boldsymbol{y}}(\boldsymbol{\theta})) = \bar{D} - D(\bar{\hat{\boldsymbol{\theta}}}), \tag{3.10}$$

The DIC is then defined as,

$$\text{DIC} = \bar{D} + p_D. \tag{3.11}$$

Models with lower DIC scores are preferred as they achieve a more optimal combination of fit and parsimony [109].

3.3 Bayesian Model Checking Strategies

Checking the model fit is one of the steps required to confirm if the model used is appropriate and is not under-fitting the data. One way to check the model fit is to define a scalar 'test quantity' which is able to measure the discrepancies of the model fitted and the observed data. Unlike the frequentist approach in which the test statistics are independent of the parameter of interest, test quantities depend on both the observed data and (posterior distribution of) parameters in Bayesian statistics and are denoted by $T(\boldsymbol{y}, \boldsymbol{\theta})$ here, where $\boldsymbol{y}$ is the observed data, and $\boldsymbol{\theta}$ is the set of parameters gained after the model fit. Noted that in the survival analysis context $\boldsymbol{y}$ represents time:

$$T(\boldsymbol{y}, \boldsymbol{\theta}) = \sum_{i=1}^{N} \frac{(y_i - E(y_i|\boldsymbol{\theta}))^2}{\text{var}(y_i|\boldsymbol{\theta})}, \tag{3.12}$$

which is referred to as the Chi-square discrepancy measurement. Two other discrepancy measurements can be defined as the minimum and maximum value of the observed survival times,

$$\begin{aligned} T(\boldsymbol{y}, \boldsymbol{\theta}) &= y_{\min}, \\ T(\boldsymbol{y}, \boldsymbol{\theta}) &= y_{\max}. \end{aligned} \tag{3.13}$$

Let $\boldsymbol{y}$ denote the observed data and $\boldsymbol{y_{rep}}$ denote the replicated data. A posterior predictive p-value is a summary measure which evaluates extremeness of $T(\boldsymbol{y}|\boldsymbol{\theta})$ with respect to

$T(\boldsymbol{y_{rep}}|\boldsymbol{\theta})$,

$$P(T(\boldsymbol{y_{rep}},\boldsymbol{\theta}) \geq T(\boldsymbol{y},\boldsymbol{\theta})|\boldsymbol{y}) = \int P(T(\boldsymbol{y_{rep}},\boldsymbol{\theta}) \geq T(\boldsymbol{y},\boldsymbol{\theta})|\boldsymbol{\theta})P(\boldsymbol{\theta}|\boldsymbol{y})d\boldsymbol{\theta}. \tag{3.14}$$

The purpose of a p-value or diagnostic of fit is to reveal systematic differences between the model prediction and the data. A p-value that is close to 0.50 represents adequate model fit, whereas p-values near 0 or 1 indicate lack of fit [110].

3.4 Hip Fracture Data Analysis

In order to determine if there is any spatial correlation in the hazard of getting hip fracture among the LTCFs at the FSA level after adjusting for various individual level risk factors, we applied spatial frailty model to the hip fracture data. In our analysis, the geographic unit is forward sortation area (FSA), since the exact spatial locations for the LTCFs are not given due to the confidentiality issue. Post Canada defines an FSA as a geographical region in which all postal codes start with the same three characters. The first letter of an FSA code denotes a particular "postal district", which, outside of Quebec and Ontario, corresponds to an entire province or territory [111]. Our analysis includes 124 FSAs from BC, while generalizations made at one level of spatial aggregation may not necessarily hold at another level. Future work is needed to investigate the spatial effect at other levels of spatial aggregation.

To determine if there is any spatial and/or non-spatial residual left unexplained by the risk factors, we consider three competing models including the models: (1) with only the

spatially correlated frailty term; (2) with only the spatial uncorrelated frailty term; and (3) with both the spatially correlated and spatial uncorrelated frailty terms. The DIC goodness-of-fit method is used to determine which model fits better and Bayesian model checking strategies is used to examine the model fit. The computations were performed on a Windows 7 operator, with 8 Gigabyte ram and Core(Tm) i5-3337U CPU @ 1.80Hz system.

3.4.1 Models

The cohort comprises patients who meet the criteria outlined in Chapter 2. The covariates include age, sex, urban-rural status, history of falls and hip fracture as well as start and end points for patients inclusion, whether or not the elderly have developed hip fractures. The models under comparison include the full model with $V_i + W_i$ as the frailty, the spatial model with W_i as the frailty and the non-spatial frailty model with V_i as the frailty. To be more specific, the models are listed as follows:

(1) shared frailty model with independent frailty term:

$$h(t_{ij}) = \rho t_{ij}^{\rho-1} e^{\eta_{ij}+V_i}, \tag{3.15}$$

(2) shared frailty model with spatially correlated frailty term:

$$h(t_{ij}) = \rho t_{ij}^{\rho-1} e^{\eta_{ij}+W_i}, \tag{3.16}$$

(3) shared frailty model with independent and spatially correlated frailty terms:

$$h(t_{ij}) = \rho t_{ij}^{\rho-1} e^{\eta_{ij}+V_i+W_i}, \tag{3.17}$$

where $\eta_{ij} = \beta_0 + \beta_1 \text{Age}_{ij} + \beta_2 \text{Falls}_{ij} + \beta_3 \text{PriorHF}_{ij} + \beta_4 \text{UrbanRural}_{ij}$, $i = 1, 2, ..., n$ and $j = 1, 2, ..., n_i$ such that n is the number of FSAs ($n = 124$) and n_i is the number of patients in the i^{th} FSA. The priors for the parameters are specified as: $\beta_i \sim N(0, 1)$, $\rho, \tau_V, \tau_W \sim G(1, 1)$ such that $\sigma_V^2 = 1/\tau_V$ and $\sigma_W^2 = 1/\tau_W$.

3.4.2 Results

Due to the computational burden analyzing the entire dataset (N = 36629), the dataset was divided to two smaller datasets, one for males and another for females. Table 3.1 - 3.3 include posterior means and posterior standard deviation (SD) along with the 95% credible intervals of model parameter estimates, under the three competing models listed in the subsection 3.4.1, respectively.

Table 3.4 reports the Bayesian posterior predictive p-values when the discrepancy measurements are Chi-square, min and max, as specified in (3.12) and (3.13). The results indicate that all the models fit the data reasonably well with the Bayesian posterior predictive p-values around 0.5. Table 3.5 reports the DICs for the three models. The comparison of the DICs shows that the minimum value is cast by applying the non-spatial frailty model, which indicates that the non-spatial frailty model performs the best as compared to the other two competing models. As such, no spatial correlation in the hazard of hip fracture among the FSAs were identified after accounting for known individual level risk factors. Further, the

running time of non-spatial frailty was about the same as the running time of spatial frailty and substantially smaller than the running time of the full model.

Table 3.1: Posterior means (Mean), standard deviations (SD), 95% credible intervals (CI) and the hazard ratios (HR) of the estimated parameters for the non-spatial frailty model.

	Females				Males			
Parameter	Mean	SD	95% CI	HR	Mean	SD	95% CI	HR
Age	0.04	0.04	(-0.04, 0.13)	1.04	0.13	0.07	(-0.01, 0.28)	1.14
Falls	0.39	0.05	(0.28, 0.49)	1.48	0.49	0.08	(0.32, 0.65)	1.63
Prior HF	0.51	0.09	(0.32, 0.68)	1.67	0.33	0.16	(0.000, 0.65)	1.39
Urban Rural	-0.08	0.11	(-0.31, 0.12)	0.92	-0.02	0.18	(-0.37, 0.36)	0.98
σ_V^2	0.07	0.01	(0.05, 0.10)	-	0.11	0.03	(0.07, 0.17)	-
λ	0.75	0.08	(0.61, 0.94)	-	0.78	0.14	(0.53, 1.08)	-
ρ	1.12	0.02	(1.09, 1.16)	-	1.16	0.03	(1.10, 1.22)	-

Table 3.2: Posterior means (Mean), standard deviations (SD), 95% credible intervals (CI) and the hazard ratios (HR) of the estimated parameters for the spatial frailty model.

	Females				Males			
Parameter	Mean	SD	95% CI	HR	Mean	SD	95% CI	HR
Age	0.05	0.04	(-0.03, 0.13)	1.05	0.13	0.07	(-0.02, 0.27)	1.14
Falls	0.39	0.05	(0.28, 0.49)	1.48	0.48	0.08	(0.32, 0.63)	1.62
Prior HF	0.50	0.09	(0.33, 0.68)	1.65	0.30	0.16	(-0.01, 0.59)	1.35
Urban Rural	-0.06	0.09	(-0.24, 0.11)	0.94	-0.07	0.15	(-0.36, 0.22)	0.93
σ_W^2	0.09	0.02	(0.06, 0.14)	-	0.15	0.04	(0.08, 0.24)	-
λ	0.74	0.06	(0.62, 0.87)	-	0.81	0.12	(0.60, 1.06)	-
ρ	1.12	0.02	(1.08, 1.15)	-	1.15	0.03	(1.09, 1.21)	-

Table 3.3: Posterior means (Mean), standard deviations (SD), 95% credible intervals (CI) and the hazard ratios (HR) of the estimated parameters for the full model.

	Females				Males			
Parameter	Mean	SD	95% CI	HR	Mean	SD	95% CI	HR
Age	0.05	0.05	(-0.04, 0.13)	1.05	0.14	0.08	(-0.01, 0.28)	1.15
Falls	0.39	0.06	(0.28, 0.49)	1.48	0.50	0.09	(0.34, 0.67)	1.65
Prior HF	0.50	0.09	(0.33, 0.68)	1.65	0.35	0.16	(0.03, 0.65)	1.42
UrbanRural	-0.05	0.12	(-0.29, 0.20)	0.95	-0.07	0.19	(-0.44, 0.30)	0.93
σ_V^2	0.08	0.02	(0.05, 0.11)	-	0.11	0.03	(0.07, 0.18)	-
σ_W^2	0.10	0.02	(0.06, 0.15)	-	0.14	0.04	(0.08, 0.23)	-
λ	0.73	0.09	(0.57, 0.91)	-	0.79	0.15	(0.54, 1.11)	-
ρ	1.13	0.02	(1.09, 1.16)	-	1.17	0.03	(1.11, 1.24)	-

Table 3.4: Bayesian posterior predictive p-values for three discrepancy measurements defined in (3.12) and (3.13).

Model	**Discrepancy Measures**	**Bayesian p-value**	
	$T(\boldsymbol{y}_{\text{rep}}\|\theta)$	Females	Males
Non-spatial	Ch-Square	0.52	0.43
	min	0.51	0.54
	max	0.53	0.51
Spatial	p-value	0.51	0.44
	min	0.52	0.54
	max	0.52	0.51
Full	p-value	0.48	0.44
	min	0.53	0.52
	max	0.51	0.51

Table 3.5: Deviance information criterion (DIC) for competing models of in the hip fracture data analysis.

Model	**DIC**	
	Females	Males
Non-spatial	5627.16	1681.36
Spatial	5628.46	1681.06
Full	5643.65	1693.64

Chapter 4

Simulation Studies

In modeling a large scale survival data, it might be ideal to incorporate the spatial correlation among the clusters in the model, when clusters exhibit spatial autocorrelation. However, inference for these models is challenging. The Bayesian MCMC method, as the mostly commonly used inference procedure in spatial statistics, often poses computational challenges modeling large scale spatially correlated data.

For example, in our data analysis presented in Chapter 2, more than 20 covariates can be modeled through fitting an independent frailty model; however in order to model the spatial correlation among the LTCFs, as presented in Chapter 3, only a few covariates can be included in the model due to the limitation of computation rescouses. Additional, it only takes a few minutes to fit an independent frailty model through generalized linear mixed effect model in SAS (by selecting an efficient optimization algorithm), whereas it took at least 10 hours to fit a spatial frailty model with only limited number of covariates.

In spite of the non-significance of the spatial autocorrelation in our motivating example, we strive to understand how much benefit we can gain through modeling the spatial effect in a large scale survival data. Further, we aim to investigate if there is any bias and efficiency loss in the estimated regression coefficients under the misspecified correlation structure and if the bias and efficiency loss depends on the percentage of censoring, the number of clusters

and the relative strength of the residual spatial correlation.

4.1 Simulation Design

To examine the bias and efficiency loss in the estimated regression coefficients under mis-specified residual correlation structure, we conducted a series of simulation studies.

First, we consider simulating the failure/censoring time from the full model as:

$$h(t_{ij}) = \rho t_{ij}^{\rho-1} e^{\beta_0+\beta_1 X_{1ij}+\beta_2 X_{2ij}+W_i+V_i}, \tag{4.1}$$

where $\beta_0 = \log(\lambda)$, where λ is the scale parameter of Weibull distribution, and

$$\boldsymbol{W}|\sigma_W^2 \sim MVN(\mathbf{0}, \sigma_W^2(\boldsymbol{D}-\boldsymbol{A})^{-1}), \tag{4.2}$$

where $\boldsymbol{D}-\boldsymbol{A}$ is the neighborhood structure and

$$V_i \sim N(0, \sigma_V^2). \tag{4.3}$$

A simulated dataset was derived by dividing the area into $5 \times 5 = 25$ equally sized squares. We also considered increase the number of areas as $10 \times 10 = 100$ and $16 \times 16 = 196$. The covariates are simulated as $X_{1ij} \sim N(0,1)$ and $X_{2ij} \sim Bernoulli(0.5)$ in order to make the simulation studies general applicable. To evaluate the percentage of censoring on the bias of the estimated regression coefficients, we considered varying the percentage of censoring as 20%, 70%, 85%, 90% and 95% under the right censoring mechanism. These censoring

variables are generated from binomial distribution. The fixed values for parameters other than σ_V^2 have been chosen purposefully. The fixed values are: $\lambda = e^{\beta_0} = .55$, $\rho = 1.5$, $\beta_1 = 2$, $\beta_2 = 1.5$, $\sigma_W^2 = 5$. To evaluate the impact of the residual spatial correlation on the estimated regression coefficients, we specify $\sigma_V^2 = 0, 1, 4, 15$. That is, for $\sigma_V^2 = 0$, the model is reduced to be model with only the spatially correlated random effect, and as σ_V^2 increases over 1, 4, and 15, the spatial effect becomes less dominant compared with the overall residual variation.

We created 100 of the defined simulated datasets for each simulation scenario and on each dataset, three models were fitted including: (1) the full model with the independent and spatially correlated random effect terms, (2) the spatial model with only the spatially correlated random effect term and (3) the non-spatial model with only the spatially uncorrelated random effect term.

We assigned a vague Normal prior with mean 0 and variance 1000, $N(0, 1000)$, to β_i's, a Gamma distribution prior with mean 0 and variance 1000, $G(0.0001, 0.0001)$, for ρ, τ_V, τ_W, where $\tau_V = 1/\sigma_V^2$ and $\tau_W = 1/\sigma_W^2$. Two independent sequences of Markov chain simulation with overdispersed starting points were generated. Each chain ran for 15,000 MCMC iterations using a burn-in of 5000, and thin number 10, which were sufficient to ensure convergence based on trace plots and $\hat{R}$ statistic. The simulation were carried out in R version 3.0.3, using parallel computing capabilities of a high performance computing system.

4.2 Simulation Results

Tables 4.1- 4.6 show the percent relative bias (RB) [112] of posterior means, mean square error (MSE) for the posterior means and the coverage probability (CP) of the 95% credible interval for the parameter estimate for $\lambda, \rho, \beta_1, \beta_2, \sigma_V^2, \sigma_W^2$, respectively, with varying number of clusters (25, 100 and 196) and percent of censorship (20, 70, 85, 90 and 95), when the values for σ_V^2 and σ_W^2 are set as 4.

The results for λ as presented in Table 4.1 indicate that all the three models yield substantial bias in estimating λ when the number of clusters is small, i.e 25 clusters; however as the number of clusters increases, the RB and MSE decrease at the same level of percentage of censorship. By increasing the percentage of censorship given the same number of cluster size, RB and MSE increases. Under all scenarios, the RB and MSE tends to be larger for the spatial model and not much difference between non-spatial and the full models. Further, the CP under the spatial model is substantially lower than the non-spatial and the full models, especially when the percentage of censoring and the number of clusters is low.

The RB, MSE and CP for the posterior estimate of the parameter ρ are presented in Table 4.2. The results indicate that as the percentage of censoring increases, the RB and MSE increase and CP decreases for all three models. Nevertheless, when the percentage of censoring is less than 90%, bias remains small and coverage probability were approximatively 0.95, especially when the number of clusters is large. The RB and MSE for the spatial model appear to be larger than the full and non-spatial model; whereas the CP tends to be lower for the spatial model as compared with the full and non-spatial model.

As for the posterior estimates of the regression coefficients β_1 and β_2, presented in Tables

4.3 and 4.4. The patterns or RB, MSE and CP are consistent with the posterior estimate for ρ (Table 4.2). When the percentage of censoring is not extremely high ($> 90\%$), and when the number of clusters is high, all the models perform reasonably well with the $RB < 5\%$ and the CP is close to 95%; however, when the number of clusters is small, especially when the percentage of censoring is high, the spatial model yield much larger RB, MSE and lower CP. For example, when the number of clusters is 25 and the percentage of censoring is 95%, the RB under the spatial model is 36.629 and the CP dropped to as low as 0.65. Although the RB for the full and non-spatial models are also high in this scenario, the CPs are all over 80%.

Table 4.4 shows similar pattern for estimates for all the three models, but shows that estimates are more sensitive to size of clusters and censorship. For instance, when number of clusters is 25, the estimate of β_2 are biased for censorship equal or greater than 70%; and for larger clusters, censorship equal or over 85% and 90% result in relative bias over 5%. In all scenarios, non-spatial and full model are not significantly different, but always perform better than spatial model.

In general, under all scenarios, the RB, MSE and CP depend on the percentage of censoring the the number of clusters in the data. The spatial model yields the most inaccurate and unstable posterior estimates as compared to the full and the non-spatial models. The performance of the non-spatial model and the full model are fairly comparable, which indicates the gains of modeling the spatial correlation in addition to the non-spatial correlation is only marginal.

Tables 4.5 and 4.6 present the RB, MSE and CP for the variance components σ^2_W and σ^2_V for the spatially correlated random effect and spatially uncorrelated random effect, respec-

tively. The results indicate that the full model performs reasonably well in estimating the σ_W^2 and σ_V^2 when the percentage of censoring is lower than 90% and the number of clusters is above 100. By contrast, the spatial model completely missed modeling the spatial random effect with zero coverage probability and substantial RB and MSE. The 95% credible interval for the variance component of the spatially uncorrelated effect also completely missed the true parameter, but the RB (Table 4.6) is much smaller as compared with the RB for variance component of the spatially correlated random effect term (Table 4.5). To better display the results, we also generated the boxplots of the posterior mean estimates of λ, ρ, β_1, β_2, σ_W^2 and σ_V^2, as displayed in Figures 4.1-4.6.

Tables 4.7-4.12 contain the average of posterior means and their 95% credible intervals along with the average of estimates for $\hat{R}$ over the repeatedly simulated data. The results show that by increasing the percentage of censorship and decreasing the number of clusters, the posterior mean of λ tend to overestimate its true value and the posterior means of ρ, β_1 and β_2 tend to overestimate their true values, and the credible intervals for all parameters become wider. By comparing the three competing models, when the percentage of censoring is not overly high, i.e. $< 95\%$ and the number of clusters is not very low, i.e. > 25, the parameter estimates based on the non-spatial model are fairly close to the parameter estimates based on the full model (true model), as compared to the spatial model. The $\hat{R}$ estimates are all close to 1 and do not vary across different simulation scenarios, which indicates the convergence of the MCMC chains.

Table 4.1: Percent relative bias (%RB), mean square error (MSE) and coverage probability (CP) of the estimated λ based on the non-spatial model, spatial model and the full model, when the data is simulated from the full model. The true value for $\lambda = 0.55$.

Cluster		25			100			196		
%Censor	Model	%RB	MSE	CP	%RB	MSE	CP	%RB	MSE	CP
20	non-spatial	35.440	0.122	0.960	6.840	0.016	0.990	3.169	0.001	1.000
	Spatial	20.455	0.110	0.275	1.994	0.015	0.220	0.090	0.001	0.370
	Full	30.514	0.114	0.940	6.498	0.017	0.940	2.391	0.001	0.960
70	non-spatial	40.000	0.133	0.960	1.722	0.000	0.990	3.293	0.001	0.980
	Spatial	21.524	0.111	0.516	2.527	0.016	0.424	0.182	0.001	0.600
	Full	36.092	0.131	0.940	7.016	0.018	0.960	2.529	0.001	0.970
85	non-spatial	45.590	0.163	0.950	12.255	0.026	0.960	5.568	0.001	0.990
	Spatial	27.082	0.120	0.656	5.478	0.021	0.646	1.766	0.001	0.747
	Full	42.373	0.159	0.930	10.943	0.026	0.920	4.612	0.001	0.959
90	non-spatial	54.506	0.217	0.950	12.452	0.022	0.990	7.718	0.013	0.970
	Spatial	34.838	0.164	0.790	4.903	0.016	0.880	2.781	0.010	0.870
	Full	51.981	0.218	0.930	10.562	0.020	0.960	6.548	0.012	0.930
95	non-spatial	73.380	0.337	0.920	27.983	0.066	0.960	11.051	0.016	1.000
	Spatial	44.388	0.189	0.880	16.842	0.045	0.880	5.703	0.012	0.960
	Full	77.557	0.389	0.900	25.209	0.061	0.930	10.260	0.015	0.990

Table 4.2: Percent relative bias (%RB), mean square error (MSE) and coverage probability (CP) of estimator of ρ based on the non-spatial model, spatial model and the full model, when the data is simulated from the full model. The true value for $\rho = 1.5$.

Cluster		25			100			196		
%Censor	Model	%RB	MSE	CP	%RB	MSE	CP	%RB	MSE	CP
20	non-spatial	1.383	0.000	0.960	0.288	0.000	0.960	0.174	0.000	0.960
	Spatial	1.700	0.000	0.956	0.378	0.000	0.950	0.188	0.000	0.960
	Full	1.370	0.000	0.960	0.377	0.000	0.950	0.194	0.000	0.960
70	non-spatial	3.107	0.011	0.930	0.568	0.000	0.960	0.543	0.000	0.970
	Spatial	3.506	0.012	0.926	0.699	0.000	0.939	0.685	0.000	0.980
	Full	3.070	0.011	0.940	0.573	0.000	0.940	0.601	0.000	0.990
85	non-spatial	5.642	0.028	0.910	2.014	0.001	0.930	0.824	0.000	0.940
	Spatial	7.490	0.034	0.885	2.614	0.001	0.919	1.497	0.000	0.929
	Full	5.271	0.026	0.910	2.145	0.001	0.930	0.892	0.000	0.948
90	non-spatial	11.853	0.055	0.890	2.731	0.014	0.920	1.591	0.001	0.950
	Spatial	15.533	0.081	0.810	4.074	0.017	0.870	2.846	0.001	0.930
	Full	11.106	0.049	0.920	2.881	0.014	0.910	1.794	0.001	0.950
95	non-spatial	19.250	0.113	0.850	8.140	0.034	0.930	5.500	0.022	0.930
	Spatial	29.186	0.221	0.630	12.809	0.060	0.840	9.833	0.039	0.820
	Full	16.295	0.089	0.890	8.408	0.034	0.910	5.908	0.022	0.900

Table 4.3: Percent relative bias (%RB), mean square error (MSE) and coverage probability (CP) of estimator of β_1 based on the non-spatial model, spatial model and the full model, when the data is simulated from the full model. The true value for $\beta_1 = 2$.

Cluster		25			100			196		
%Censor	Model	%RB	MSE	CP	%RB	MSE	CP	%RB	MSE	CP
20	non-spatial	1.862	0.011	0.920	0.237	0.000	0.930	0.038	0.000	0.910
	Spatial	2.325	0.010	0.945	0.364	0.000	0.950	0.052	0.000	0.910
	Full	1.840	0.011	0.930	0.359	0.000	0.950	0.057	0.000	0.910
70	non-spatial	3.202	0.029	0.930	0.325	0.000	0.930	0.549	0.000	0.990
	Spatial	3.534	0.030	0.926	1.015	0.001	0.949	0.683	0.000	1.000
	Full	3.157	0.028	0.930	0.874	0.001	0.950	0.609	0.000	0.990
85	non-spatial	8.292	0.093	0.880	1.955	0.016	0.940	0.742	0.010	0.960
	Spatial	10.075	0.101	0.865	2.590	0.018	0.939	1.349	0.011	0.949
	Full	7.937	0.089	0.900	2.082	0.016	0.940	0.748	0.010	0.959
90	non-spatial	15.569	0.170	0.860	4.322	0.039	0.910	2.485	0.018	0.960
	Spatial	19.437	0.225	0.830	5.611	0.044	0.850	3.719	0.022	0.950
	Full	14.903	0.159	0.870	4.406	0.039	0.920	2.710	0.018	0.950
95	non-spatial	29.830	0.436	0.830	12.624	0.121	0.860	7.039	0.065	0.860
	Spatial	36.629	0.618	0.650	16.787	0.177	0.780	11.113	0.098	0.830
	Full	27.408	0.380	0.870	12.882	0.122	0.840	7.381	0.067	0.870

Table 4.4: Percent relative bias (%RB), mean square error (MSE) and coverage probability (CP) of the estimated β_2 based on the non-spatial model, spatial model and the full model, when the data is simulated from the full model. The true value for $\beta_2 = 1.5$.

Cluster		25			100			196		
%Censor	Model	%RB	MSE	CP	%RB	MSE	CP	%RB	MSE	CP
20	non-spatial	2.633	0.018	0.960	0.584	0.000	0.990	0.227	0.000	0.930
	Spatial	2.989	0.018	0.934	0.723	0.000	0.990	0.250	0.000	0.930
	Full	2.634	0.018	0.950	0.710	0.000	0.970	0.250	0.000	0.940
70	non-spatial	7.996	0.055	0.910	1.164	0.001	0.990	0.599	0.010	0.920
	Spatial	8.826	0.055	0.916	1.844	0.014	0.919	0.720	0.010	0.930
	Full	8.027	0.055	0.920	1.641	0.014	0.920	0.660	0.010	0.930
85	non-spatial	16.503	0.132	0.970	4.045	0.036	0.910	2.324	0.017	0.960
	Spatial	18.620	0.150	0.938	4.960	0.038	0.889	2.774	0.017	0.970
	Full	16.317	0.130	0.970	4.366	0.036	0.910	2.447	0.017	0.959
90	non-spatial	24.809	0.246	0.940	5.972	0.061	0.910	4.725	0.025	0.950
	Spatial	27.354	0.274	0.920	7.470	0.064	0.900	5.673	0.027	0.950
	Full	24.132	0.239	0.950	6.134	0.061	0.920	4.771	0.025	0.940
95	non-spatial	48.099	0.697	0.840	18.534	0.150	0.920	13.033	0.088	0.940
	Spatial	51.381	0.768	0.780	22.133	0.187	0.900	16.786	0.115	0.870
	Full	47.128	0.677	0.840	18.778	0.154	0.930	13.397	0.090	0.920

Table 4.5: Percent relative bias (%RB), mean square error (MSE) and coverage probability (CP) of the estimated σ_V^2 based on the non-spatial model, spatial model and the full model, when the data is simulated from the full model. The true value for $\sigma_W^2 = 5$.

Cluster		25			100			196		
%Censor	Model	%RB	MSE	CP	%RB	MSE	CP	%RB	MSE	CP
20	Spatial	465.040	646.380	0.000	554.910	798.890	0.000	581.540	860.590	0.000
	Full	18.340	18.450	0.970	3.450	15.770	0.950	1.840	10.960	0.930
70	Spatial	435.760	590.370	0.000	536.280	751.360	0.000	565.690	818.340	0.000
	Full	10.450	13.260	0.930	4.080	17.590	0.930	2.260	10.800	0.950
85	Spatial	371.990	484.590	0.000	491.850	650.010	0.000	536.970	742.450	0.000
	Full	6.540	12.280	0.930	3.660	16.310	0.930	1.500	12.010	0.980
90	Spatial	262.020	282.870	0.000	462.200	605.070	0.000	509.140	693.270	0.000
	Full	5.740	10.240	0.940	6.520	24.100	0.950	1.310	13.680	0.920
95	Spatial	99.880	108.620	0.000	320.010	333.670	0.000	368.350	404.690	0.000
	Full	24.810	5.480	0.950	1.280	12.640	0.930	2.190	13.300	0.960

Table 4.6: Percent relative bias (%RB), mean square error (MSE) and coverage probability (CP) of the estimated σ_W^2 based on the non-spatial model, spatial model and the full model, when the data is simulated from the full model. The true value for $\sigma_V^2 = 4$.

Cluster		25			100			196		
%Censor	Model	%RB	MSE	CP	%RB	MSE	CP	%RB	MSE	CP
20	Non-spatial	31.910	4.640	0.000	36.160	3.000	0.000	39.600	3.140	0.000
	Full	5.650	2.320	1.000	1.570	1.010	0.920	1.850	0.510	0.900
70	Non-spatial	28.430	4.500	0.000	39.270	2.200	0.000	38.700	3.080	0.000
	Full	6.530	2.430	1.000	0.280	1.120	0.960	2.060	0.570	0.910
85	Non-spatial	20.300	4.820	0.000	31.890	2.900	0.000	37.950	3.160	0.000
	Full	11.910	2.950	0.990	4.140	1.370	0.960	1.870	0.600	0.920
90	Non-spatial	3.740	3.880	0.000	30.990	3.650	0.000	37.870	3.530	0.000
	Full	23.690	3.090	0.990	5.160	1.890	0.950	1.540	1.410	0.920
95	Non-spatial	18.260	3.710	0.000	17.180	2.920	0.000	25.910	3.390	0.000
	Full	31.550	3.810	0.990	17.620	2.350	0.990	10.690	1.970	0.940

Table 4.7: Posterior mean, %95 credible interval (CI) and $\hat{R}$ for the estimated λ based on the non-spatial model, spatial model and the full model, when the data is simulated from the full model. The true value for $\lambda = 0.55$.

Cluster		25			100			196		
%Censor	Model	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$
	Non-spatial	0.74	0.30 - 1.56	1.003	0.59	0.36 - 0.90	1.003	0.57	0.40 - 0.78	1.003
20	Spatial	0.66	0.56 - 0.77	1.001	0.56	0.52 - 0.61	1.001	0.55	0.52 - 0.58	1.001
	Full	0.72	0.33 - 1.41	1.003	0.59	0.39 - 0.86	1.002	0.56	0.42 - 0.74	1.002
	Non-spatial	0.77	0.31 - 1.63	1.002	0.56	0.44 - 0.71	1.002	0.57	0.40 - 0.79	1.003
70	Spatial	0.67	0.49 - 0.87	1.001	0.56	0.48 - 0.65	1.001	0.55	0.49 - 0.61	1.001
	Full	0.75	0.33 - 1.50	1.003	0.59	0.38 - 0.87	1.002	0.56	0.41 - 0.75	1.002
	Non-spatial	0.80	0.31 - 1.75	1.002	0.62	0.36 - 0.98	1.002	0.58	0.39 - 0.83	1.003
85	Spatial	0.70	0.42 - 1.08	1.002	0.58	0.45 - 0.73	1.002	0.56	0.46 - 0.67	1.001
	Full	0.78	0.33 - 1.62	1.003	0.61	0.38 - 0.92	1.003	0.58	0.41 - 0.79	1.002
	Non-spatial	0.85	0.32 - 1.89	1.003	0.62	0.35 - 1.01	1.003	0.59	0.39 - 0.87	1.003
90	Spatial	0.74	0.39 - 1.27	1.002	0.58	0.41 - 0.78	1.002	0.57	0.44 - 0.71	1.002
	Full	0.84	0.34 - 1.78	1.002	0.61	0.36 - 0.95	1.003	0.59	0.40 - 0.83	1.003
	Non-spatial	0.95	0.33 - 2.31	1.003	0.70	0.36 - 1.26	1.004	0.61	0.36 - 0.96	1.004
95	Spatial	0.79	0.35 - 1.58	1.003	0.64	0.39 - 0.99	1.003	0.58	0.40 - 0.82	1.003
	Full	0.98	0.34 - 2.35	1.003	0.69	0.37 - 1.19	1.003	0.61	0.38 - 0.93	1.004

Table 4.8: Posterior mean, %95 credible interval (CI) and $\hat{R}$ for the the estiamted ρ based on the non-spatial model, spatial model and the full model, when the data is simulated from the full model. The true value of $\rho = 1.5$.

Cluster		25			100			196		
%Censor	Model	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$
	Non-spatial	1.48	1.36 - 1.60	1.001	1.50	1.44 - 1.56	1.001	1.50	1.45 - 1.54	1.001
20	Spatial	1.47	1.35 - 1.60	1.001	1.49	1.43 - 1.56	1.001	1.50	1.45 - 1.54	1.001
	Full	1.48	1.36 - 1.60	1.001	1.49	1.43 - 1.56	1.001	1.50	1.45 - 1.54	1.001
	Non-spatial	1.45	1.25 - 1.67	1.001	1.49	1.41 - 1.57	1.001	1.49	1.41 - 1.57	1.001
70	Spatial	1.45	1.24 - 1.66	1.001	1.49	1.38 - 1.60	1.002	1.49	1.41 - 1.57	1.001
	Full	1.45	1.25 - 1.67	1.001	1.49	1.39 - 1.60	1.001	1.49	1.41 - 1.57	1.001
	Non-spatial	1.42	1.11 - 1.75	1.002	1.47	1.31 - 1.64	1.002	1.49	1.36 - 1.62	1.002
85	Spatial	1.39	1.08 - 1.72	1.003	1.46	1.30 - 1.63	1.002	1.48	1.35 - 1.61	1.002
	Full	1.42	1.12 - 1.75	1.002	1.47	1.31 - 1.64	1.002	1.49	1.36 - 1.62	1.002
	Non-spatial	1.32	0.96 - 1.73	1.003	1.46	1.25 - 1.69	1.004	1.48	1.31 - 1.65	1.004
90	Spatial	1.27	0.91 - 1.68	1.004	1.44	1.23 - 1.67	1.004	1.46	1.29 - 1.63	1.004
	Full	1.33	0.98 - 1.74	1.003	1.46	1.24 - 1.68	1.003	1.47	1.31 - 1.64	1.004
	Non-spatial	1.21	0.75 - 1.83	1.005	1.38	1.05 - 1.75	1.009	1.42	1.15 - 1.71	1.009
95	Spatial	1.06	0.65 - 1.65	1.006	1.31	0.98 - 1.68	1.009	1.35	1.09 - 1.65	1.009
	Full	1.26	0.80 - 1.87	1.005	1.37	1.06 - 1.74	1.008	1.41	1.15 - 1.70	1.009

Table 4.9: Posterior mean, %95 credible interval (CI) and $\hat{R}$ for the estimated β_1 based on the non-spatial model, spatial model and the full model, when the data is simulated from the full model. The true value of $\beta_1 = 2$.

Cluster		25			100			196		
%Censor	Model	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$
	Non-spatial	1.96	1.77 - 2.16	1.001	2	1.90 - 2.09	1.001	2.00	1.93 - 2.07	1.001
20	Spatial	1.95	1.76 - 2.15	1.001	1.99	1.90 - 2.09	1.001	2.00	1.93 - 2.07	1.001
	Full	1.96	1.77 - 2.16	1.001	1.99	1.90 - 2.09	1.001	2.00	1.93 - 2.07	1.001
	Non-spatial	1.94	1.60 - 2.28	1.001	1.99	1.87 - 2.12	1.001	1.99	1.86 - 2.12	1.001
70	Spatial	1.93	1.60 - 2.27	1.001	1.98	1.81 - 2.15	1.001	1.99	1.86 - 2.12	1.001
	Full	1.94	1.61 - 2.28	1.001	1.98	1.81 - 2.16	1.001	1.99	1.86 - 2.12	1.001
	Non-spatial	1.83	1.33 - 2.37	1.002	1.96	1.70 - 2.24	1.002	1.99	1.78 - 2.19	1.002
85	Spatial	1.80	1.30 - 2.33	1.002	1.95	1.68 - 2.22	1.002	1.97	1.77 - 2.18	1.002
	Full	1.84	1.34 - 2.37	1.002	1.96	1.69 - 2.23	1.002	1.99	1.78 - 2.19	1.002
	Non-spatial	1.69	1.08 - 2.35	1.002	1.91	1.57 - 2.28	1.003	1.95	1.69 - 2.23	1.003
90	Spatial	1.61	1.01 - 2.28	1.003	1.89	1.54 - 2.25	1.003	1.93	1.66 - 2.20	1.003
	Full	1.70	1.10 - 2.36	1.003	1.91	1.57 - 2.27	1.002	1.95	1.68 - 2.22	1.004
	Non-spatial	1.40	0.59 - 2.32	1.004	1.75	1.23 - 2.32	1.007	1.86	1.44 - 2.32	1.007
95	Spatial	1.27	0.52 - 2.15	1.004	1.66	1.15 - 2.23	1.007	1.78	1.36 - 2.23	1.008
	Full	1.45	0.63 - 2.38	1.004	1.74	1.23 - 2.31	1.007	1.85	1.44 - 2.30	1.008

Table 4.10: Posterior mean, %95 credible interval (CI) and $\hat{R}$ for the estimated $\beta_2 = 1.5$ based on the non-spatial model, spatial model and the full model, when the data is simulated from the full model. The true value of $\beta_2 = 1.5$.

Cluster		25			100			196		
%Censor	Model	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$
	Non-spatial	1.46	1.21 - 1.71	1.001	1.49	1.37 - 1.62	1.001	1.50	1.40 - 1.59	1.001
20	Spatial	1.46	1.20 - 1.71	1.001	1.49	1.36 - 1.61	1.001	1.50	1.40 - 1.59	1.001
	Full	1.46	1.21 - 1.71	1.001	1.49	1.36 - 1.61	1.001	1.50	1.40 - 1.59	1.001
	Non-spatial	1.38	0.94 - 1.82	1.001	1.48	1.32 - 1.64	1.001	1.49	1.32 - 1.66	1.001
70	Spatial	1.37	0.93 - 1.81	1.001	1.47	1.25 - 1.69	1.001	1.49	1.32 - 1.66	1.001
	Full	1.38	0.94 - 1.82	1.001	1.48	1.25 - 1.70	1.001	1.49	1.32 - 1.66	1.001
	Non-spatial	1.25	0.59 - 1.93	1.001	1.44	1.09 - 1.79	1.002	1.47	1.20 - 1.73	1.002
85	Spatial	1.22	0.56 - 1.89	1.002	1.43	1.08 - 1.78	1.002	1.46	1.20 - 1.72	1.002
	Full	1.26	0.59 - 1.93	1.001	1.43	1.09 - 1.78	1.001	1.46	1.20 - 1.73	1.002
	Non-spatial	1.13	0.30 - 1.97	1.002	1.41	0.95 - 1.88	1.002	1.43	1.08 - 1.78	1.002
90	Spatial	1.09	0.27 - 1.93	1.002	1.39	0.93 - 1.85	1.002	1.41	1.07 - 1.76	1.002
	Full	1.14	0.31 - 1.98	1.002	1.41	0.95 - 1.87	1.002	1.43	1.08 - 1.78	1.002
	Non-spatial	0.78	-0.37 - 1.94	1.002	1.22	0.54 - 1.94	1.003	1.30	0.76 - 1.87	1.003
95	Spatial	0.73	-0.36 - 1.83	1.002	1.17	0.51 - 1.86	1.004	1.25	0.72 - 1.80	1.003
	Full	0.79	-0.37 - 1.96	1.002	1.22	0.54 - 1.92	1.003	1.30	0.76 - 1.86	1.004

Table 4.11: Posterior mean, %95 credible interval (CI) and $\hat{R}$ for the estimated σ_W^2 based on the spatial model and the full model, when the data is simulated from the full model. The true value for $\sigma_W^2 = 5$.

Cluster		25			100			196		
%Censor	Model	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$
20	Spatial	28.25	15.41 - 50.30	1.001	32.75	24.31 - 43.82	1.001	34.08	27.52 - 42.05	1.001
	Full	5.92	0.37 - 23.06	1.007	5.17	0.82 - 15.71	1.007	5.09	1.31 - 12.59	1.008
70	Spatial	26.79	13.05 - 50.63	1.001	31.81	22.54 - 44.08	1.001	33.28	25.93 - 42.27	1.001
	Full	5.52	0.37 - 22.85	1.005	5.20	0.81 - 15.87	1.007	4.89	1.22 - 12.42	1.008
85	Spatial	23.60	8.66 - 51.13	1.002	29.59	18.92 - 44.12	1.002	31.85	22.96 - 42.95	1.002
	Full	5.33	0.33 - 23.42	1.003	5.18	0.76 - 16.13	1.007	4.93	1.05 - 13.27	1.008
90	Spatial	18.10	4.65 - 45.56	1.003	28.11	15.89 - 45.33	1.003	30.46	20.11 - 43.81	1.003
	Full	4.71	0.31 - 21.26	1.004	5.33	0.75 - 17.15	1.009	4.93	1.01 - 13.82	1.009
95	Spatial	9.99	0.85 - 38.02	1.006	21.00	7.48 - 43.12	1.008	23.42	10.94 - 41.69	1.008
	Full	3.76	0.28 - 20.06	1.005	4.94	0.48 - 18.16	1.011	4.89	0.76 - 15.12	1.013

Table 4.12: Posterior mean, %95 credible interval (CI) and $\hat{R}$ for the estimated σ_V^2 based on the non-spatial model and the full model, when the data is simulated from the full model. The true value of $\sigma_V^2 = 4$

Cluster		25			100			196		
%Censor	Model	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$	Mean	%95 CI	$\hat{R}$
20	Non-spatial	5.28	2.90 - 9.35	1.001	5.45	4.05 - 7.28	1.001	5.58	4.52 - 6.88	1.001
	Full	3.77	0.98 - 7.97	1.009	4.06	2.11 - 6.09	1.012	4.07	2.65 - 5.49	1.01
70	Non-spatial	5.14	2.56 - 9.60	1.001	2.43	1.88 - 3.10	1.001	5.55	4.35 - 7.02	1.001
	Full	3.74	0.89 - 8.23	1.006	4.01	2.00 - 6.21	1.011	4.08	2.59 - 5.63	1.01
85	Non-spatial	4.81	1.91 - 10.11	1.002	5.28	3.45 - 7.74	1.002	5.52	4.04 - 7.36	1.002
	Full	3.52	0.69 - 8.68	1.004	3.83	1.72 - 6.35	1.01	4.07	2.34 - 5.95	1.013
90	Non-spatial	4.15	1.30 - 9.74	1.002	5.24	3.09 - 8.26	1.003	5.51	3.75 - 7.78	1.003
	Full	3.05	0.53 - 8.34	1.004	3.79	1.51 - 6.79	1.012	4.06	2.13 - 6.30	1.011
95	Non-spatial	3.27	0.54 - 10.70	1.005	4.69	1.97 - 9.00	1.007	5.04	2.66 - 8.41	1.008
	Full	2.74	0.37 - 9.64	1.005	3.30	0.86 - 7.36	1.013	3.57	1.33 - 6.73	1.017

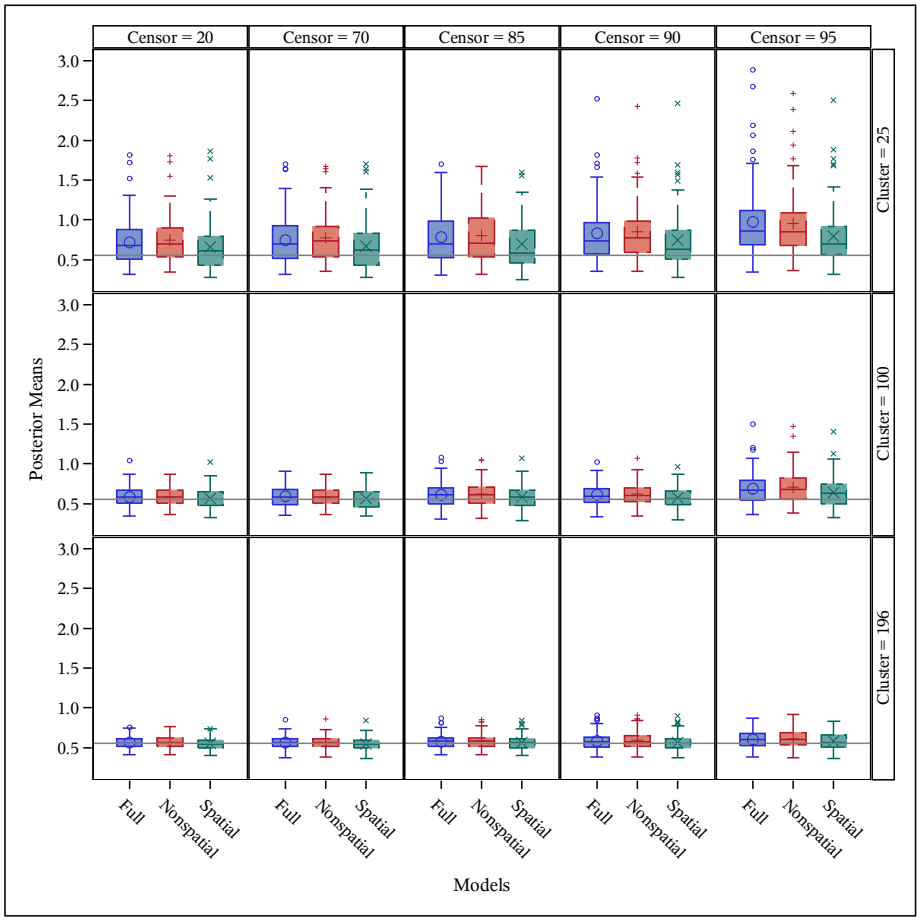


Figure 4.1: Boxplots of the posterior mean estimates of λ from the 100 samples generated from the full model. The reference line shows the true value of λ.

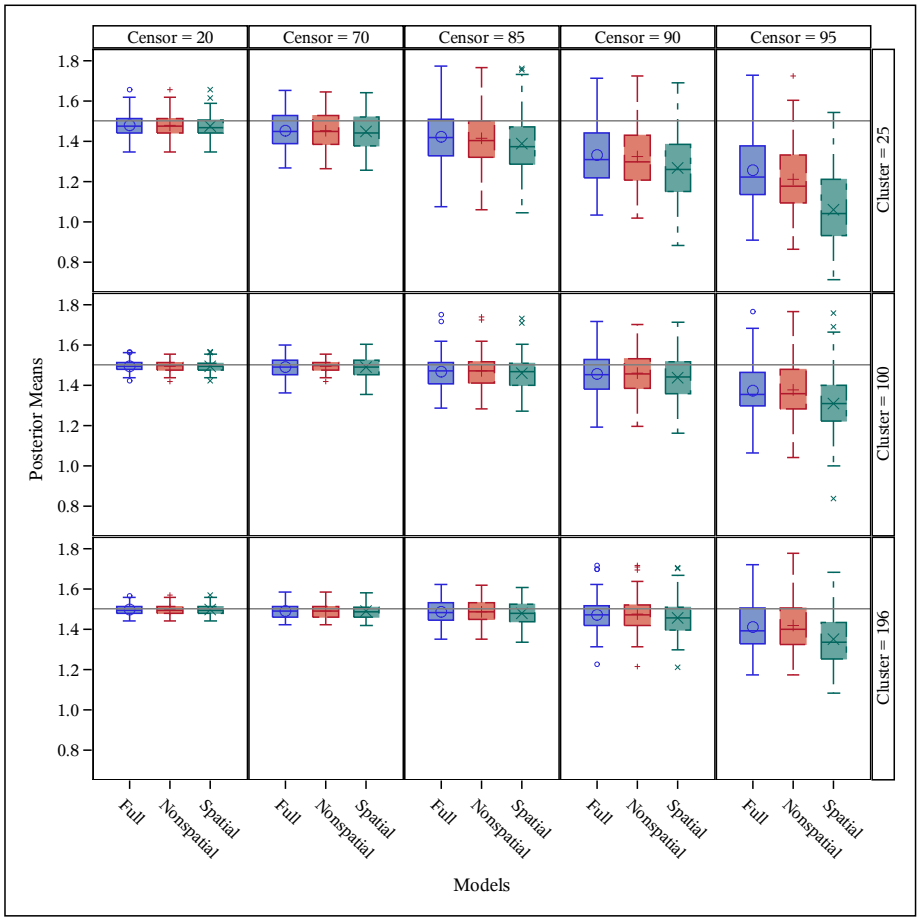


Figure 4.2: Boxplots of the posterior mean estimates of ρ from the 100 samples generated from the full model. The reference line shows the true value of ρ.

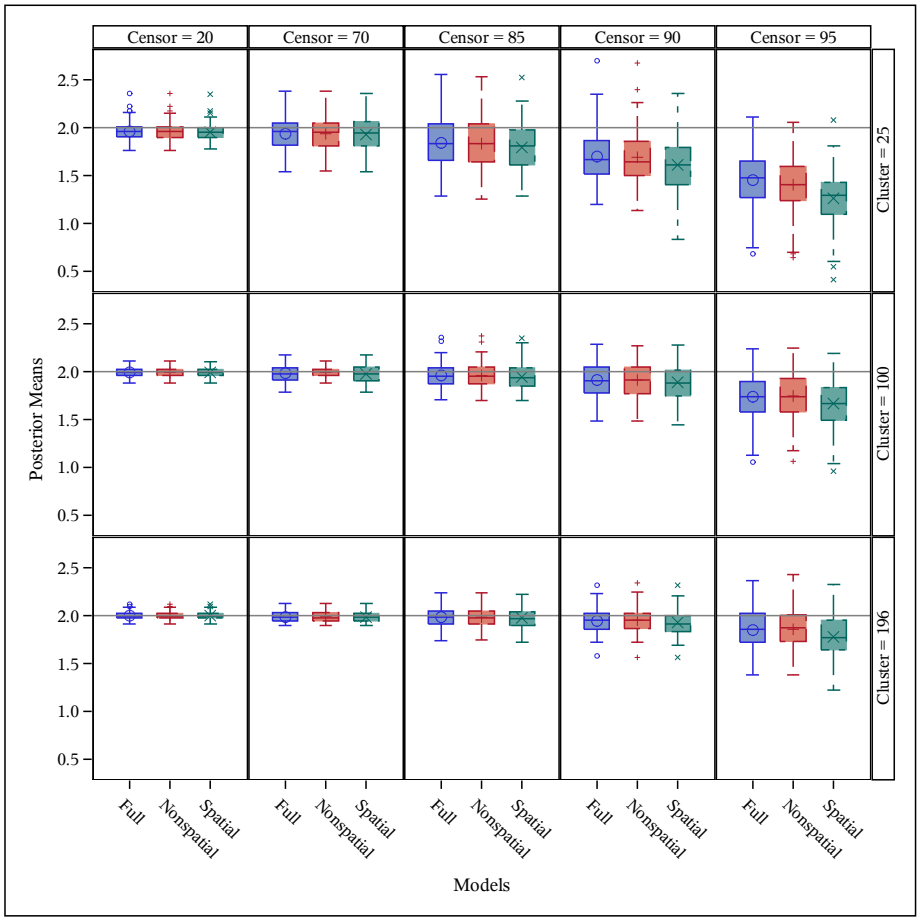


Figure 4.3: Boxplots of the posterior mean estimates of β_1 from the 100 samples generated from the full model. The reference line shows the true value of β_1.

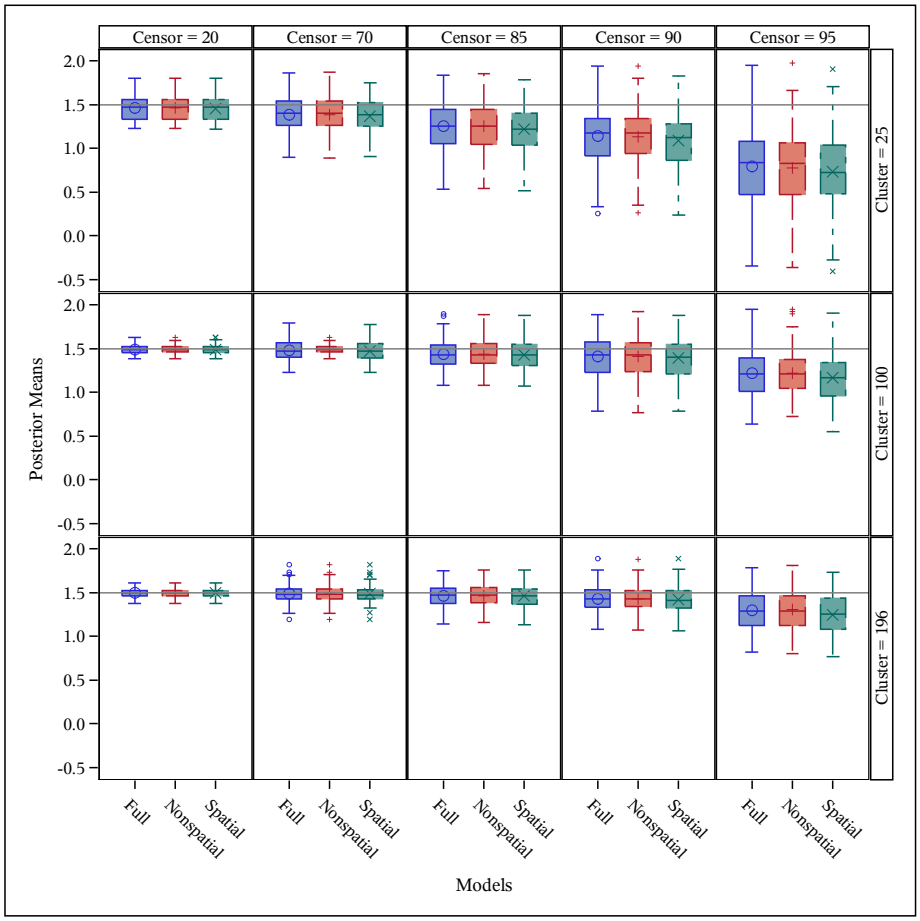


Figure 4.4: Boxplots of the posterior mean estimates of β_2 from the 100 samples generated from the full model. The reference line shows the true value of β_2.

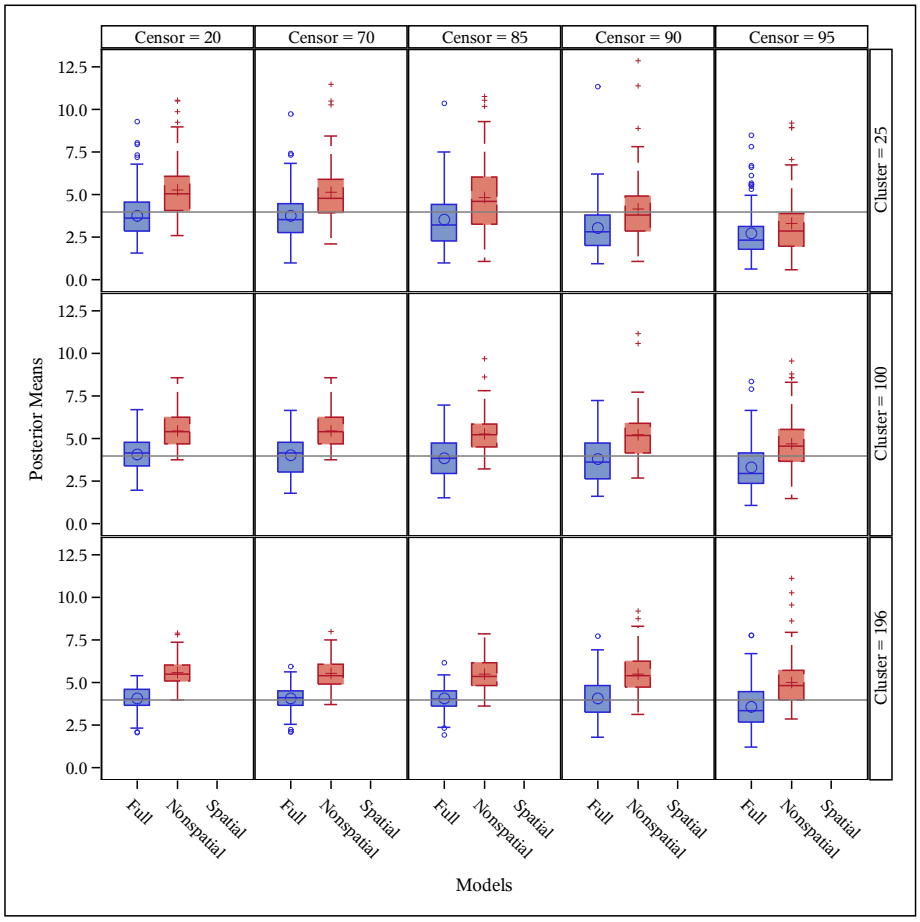


Figure 4.5: Boxplots of the posterior mean estimates of σ_V^2 from the 100 samples generated from the full model. The reference line shows the true value of σ_V^2.

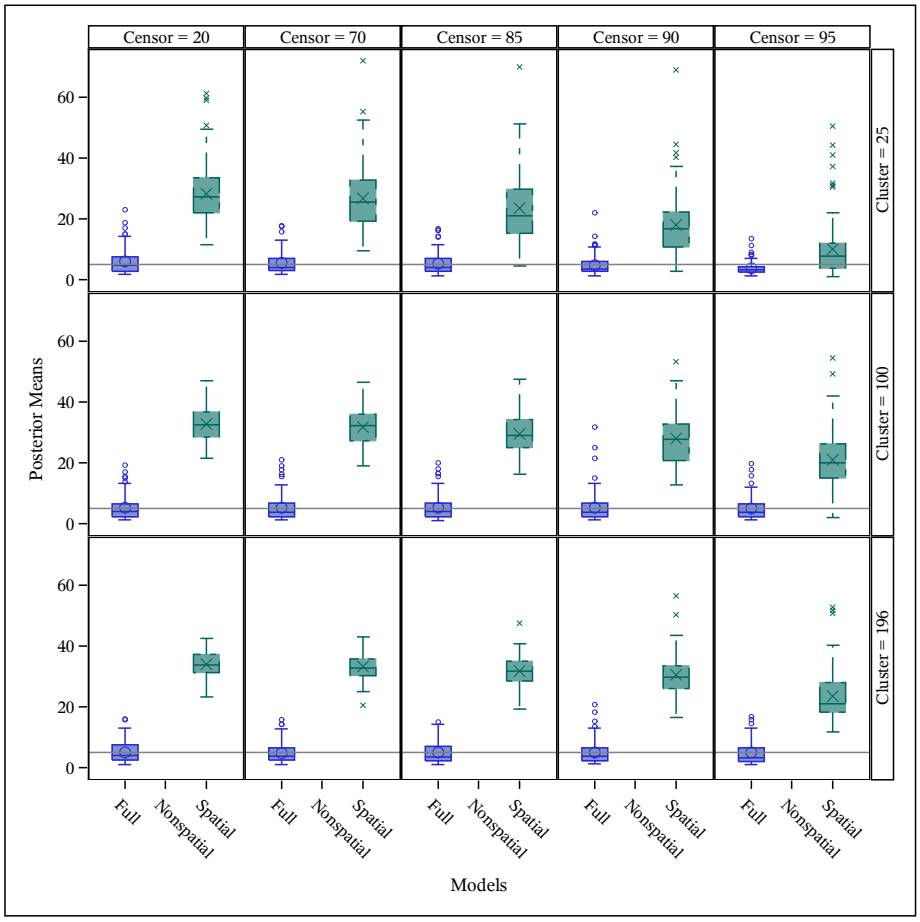


Figure 4.6: Boxplots of the posterior mean estimates of σ_W^2 from the 100 samples generated from the full model. The reference line shows the true value of σ_W^2.

Chapter 5

Conclusion and Future Work

In this thesis, motivated by the computational challenges encountered in modeling spatial correlation in a real application with large scale survival data, we used simulations to assess the efficiency loss in the parameter estimates if residual spatial correlation is present but using the spatially uncorrelated random effect term in the model.

This is particularly relevant in many public health or medical studies in modeling large scale survival data, when researchers strive to build complicated spatial frailty model to model spatial correlation in the residuals. To model such complex statistical problems, Bayesian MCMC methods are often used. The method comes at the price of slow mixing rates and heavy computation cost, which may render it impractical for data intensive applications. Further, the information on detailed neighboring structure is often not released to public due to confidentiality or when it is not clear what sort of spatial or neighborhood structure may be appropriate.

By simulating the data from the full model including the spatially correlated and iid random effect terms and then fit the models with reduced random effect structures, our simulation study shows that under all the simulation scenarios, by increasing the percentage of censorship, relative bias (RB) and mean square error (MSE) increase and the coverage probability (CP) become much lower than the nominal level. As well, as the number of clusters

increases, the performances in all the models improve. In particular, when the percentage of censoring is low and the number of clusters is high, all the competing models perform equivalently well in estimating the regression and Weibull parameters. The performance of the three models differs when the percentage of censoring is high with small number of clusters or when estimating the variance components. To be more specific, the RB and MSE tend to be larger for the model which only includes the spatial term and do not tend to differ that much between the non-spatial and the full models. Further, the CP under the spatial model is substantially lower than the nominal level as compared to the non-spatial and the full models, especially when the percentage of censoring and the number of clusters are low. This implies that the shared frailty model with only the spatially correlated random effect may not be sufficient enough to govern the total residual variation, whereas the simpler model with only the spatially uncorrelated random effect term performs surprisingly well in estimating the regression and Weibull parameters compared with the true model. Noted that these results are based on one specific adjacency matrix. It would be interesting to investigate the impact of different adjacency structures on the parameter estimates in the spatial frailty model through further simulation studies.

In short, the shared frailty model with the independent frailty term provides a straightforward method for estimating the covariate effects for large scale survival data, which is computationally infeasible for the spatial frailty model, particularly when exploring the effects of a large number of covariates is of interests.

This is not to say that the shared frailty model with independent frailty term should be preferred over the spatial frailty model in all cases. Indeed, when the primary goal of inference is predicting the hazard for specific covariates group, additional care need to be given due

to the bias in the scale parameter associated with the Weibull distribution. Future research can be carried out to examine the frailty model with different random effect structures when the primary goal is estimating the hazard functions.

One alternative to the shared frailty model is to simply use the random effect logistic regression model for analyzing the dichotomized event outcome variable. In this case, computations become remarkably cheap, but the interpretation of regression parameters differs. However, when the disease of interest is rare, such as in our motivating example related to hip fracture in LTCFs, the log odds and log relative risk (hazard ratio) become even more similar [113]. Knowing that the percent of hip fracture in our data analysis was only around 8%, one potential future research is to apply a random effect logistic regression on the hip fracture data to estimate hazard ratios.

Appendix A

Appendix

A.1 Optimization Methods

A.1.1 Adaptive Gaussian Quadrature Optimization

Let β denote the vector of fixed-effects parameters and θ the vector of covariance parameters. θ includes the G-side parameters and a possible scale parameter ϕ, provided that the conditional distribution of the data contains such a scale parameter. $\theta_{-\phi}$ is the vector of the G-side parameters. The marginal distribution of the data for subject i in a mixed model can be expressed as

$$p(y_i) = \int ... \int p(y_i|b_i, \beta, \phi)p(b_i|\theta_{-\phi})\ db_i. \tag{A.1}$$

Noted that this multi-dimensional integral will be reduced to a one-dimensional integral in case of an intercept random model, or a shared frailty model.

Let N_q denote the number of quadrature points in each dimension (for each random effect) and r denotes the number of random effects. The adaptive Gaussian quadrature approximate to the multi-dimensional integral (A.1) is

$$\int ... \int p(y_i|b_i, \beta, \phi)p(b_i|\theta_{-\phi})\ db_i \approx 2^{\frac{n}{2}} |f''(y_i, \beta, \theta; \hat{b_i})|^{-\frac{1}{2}} \Sigma_{j_1=1}^{N_q} ... \Sigma_{j_r=1}^{N_q} \Big[p(y_i|a_i, \beta, \phi)p(a_j|\theta_\phi) \prod_{q=1}^{r} e^{z_{j_q}^2} w_{j_q} \Big], \tag{A.2}$$

where $\hat{b_i}$ are called empirical Bayes estimates which minimize

$$-\log(p(y_i|a_i, \beta, \phi)p(a_j|\theta_{-\phi})) = f(y_i, \beta, \theta; b_i). \tag{A.3}$$

Also

$$a_j = \hat{b_i} + \sqrt{\frac{1}{2}} |f''(y_i, \beta, \theta; \hat{b_i})|^{-\frac{1}{2}} z_j^\star \tag{A.4}$$

such that $z_j^\star = [z_{j_1}, ..., z_{j_r}]$ is a point on the r-dimensional quadrature grid, $z = [z_1, ..., z_q]$ are standard quadrature points, $w = [w_1, ..., w_{N_q}]$ are Gauss-Hermite weights, and

$$f''(y_i, \beta, \theta; \hat{b_i}) = \frac{\partial^2 f(y_i, \beta, \theta; b_i)}{\partial b_i \partial b_i'}|_{\hat{b_i}} \tag{A.5}$$

Having this approximation for the integral, we can estimate the likelihood function. Let $f(\boldsymbol{\beta}, \rho, \boldsymbol{X}, t_{ij}, \delta_{ij}, \sigma_V^2|V_i) = \left(\rho t_{ij}^{\rho-1} e^{\boldsymbol{\beta}' X_{ij} + V_i}\right)^{\delta_{ij}} \exp\left(-t_{ij}^\rho e^{\boldsymbol{\beta}' X_{ij} + V_i}\right)$. Hence,

$$l(\boldsymbol{\beta}, \rho, \boldsymbol{X}, \boldsymbol{\delta}, \sigma_V^2) = \log\left(L(\boldsymbol{\beta}, \rho, \boldsymbol{X}, \boldsymbol{\delta}, \sigma_V^2)\right) \approx$$
$$\frac{\log n}{2} \sum_{i=1}^{n} \sum_{j=1}^{n_i} \log \left[f''(\boldsymbol{\beta}, \rho, \boldsymbol{X}, t_{ij}, \delta_{ij}, \sigma_V^2 | \hat{V}_i)^{\frac{-1}{2}} \sum_{q=1}^{Q} \left(\rho t_{ij}^{\rho-1} e^{\boldsymbol{\beta}' X_{ij} + a_{i,q}}\right)^{\delta_{ij}} e^{-t_{ij}^{\rho} e^{\boldsymbol{\beta}' X_{ij} + a_{i,q}}} e^{\frac{z_q^{\star 2}}{2}} w_q \right], \tag{A.6}$$

where $a_{i,q} = \hat{V}_i + \sigma_V^2 f''(\boldsymbol{\beta}, \rho, \boldsymbol{X}, t_{ij}, \delta_{ij}, \sigma_V^2 | \hat{\boldsymbol{V}})^{-\frac{1}{2}} z_q^{\star}$ such that $\hat{V}_i$ are empirical bayes estimates which maximize

$$f''(\boldsymbol{\beta}, \rho, \boldsymbol{X}, t_{ij}, \delta_{ij}, \sigma_V^2 | \hat{\boldsymbol{V}}) = \frac{\partial^2 f(\boldsymbol{\beta}, \rho, \boldsymbol{X}, t_{ij}, \delta_{ij}, \sigma_V^2 | \hat{\boldsymbol{V}})}{\partial V_i^2} |_{\hat{\boldsymbol{V}}}. \tag{A.7}$$

A.1.2 Quasi-Newton Optimization

Suppose $f(x)$ is a function in $\mathbb{R}^p$ and one needs to maximize it. Let

$$\begin{aligned} p_k &= x_{k+1} - x_k, \\ q_k &= \nabla f(x_k) - \nabla f(x_{k+1}) \end{aligned} \tag{A.8}$$

Then the Davidon-Fletcher-Powell (DFP) inverse-Hessian approximation is [86]:

$$B_{k+1} = B_k + \frac{p_k p_k^T}{p_k^T q_k} - \frac{B_k q_k q_k^T B_k}{q_k^T B_k q_k}, \tag{A.9}$$

where B_0 is usually I_p. If one defines $\delta_k = \text{argmin} f(x_k + \delta_k R_k)$ and $r_k = -B_k \nabla f(x_k)$, the update step is

$$x_{k+1} = x_k + \delta_k r_k. \tag{A.10}$$

Appendix B

Appendix

B.1 Verification of Weibull Assumption

The Weibull assumption for the Weibull frailty model is examined by checking the $\log(-\log(S(t)))$ vs. $\log(t)$ plot, which should give approximately a straightly line if the Weibull distributed assumption of baseline survival time is satisfied.

Figure B.1: Plot of $\log(-\log(S(t)))$ vs. $\log(t)$.

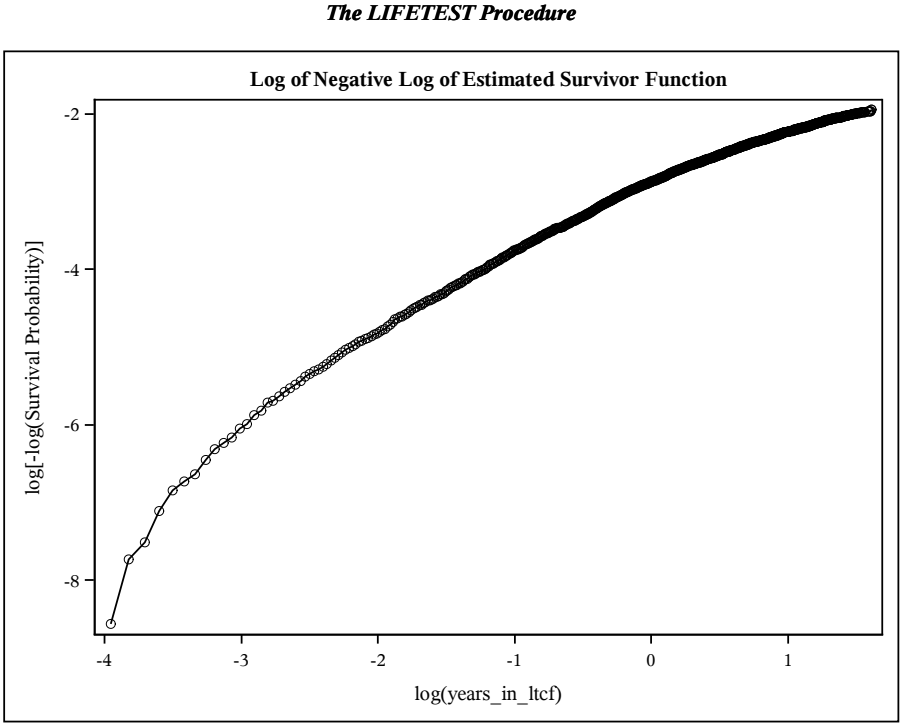


Figure B.2: Plot of $\log(-\log(S(t)))$ vs. $\log(t)$ stratified by age and sex variables.

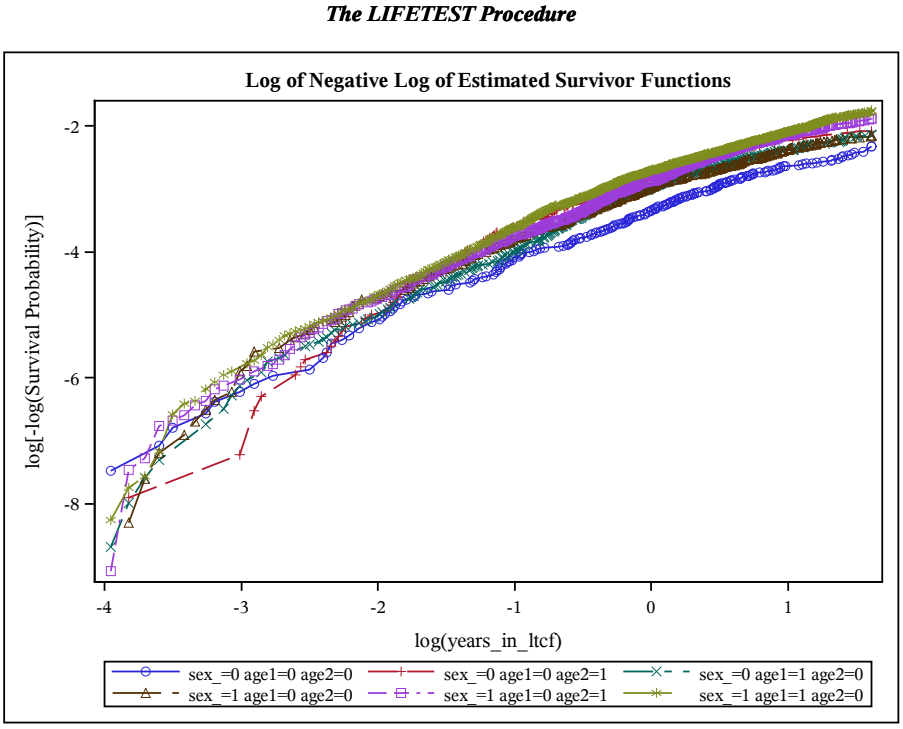
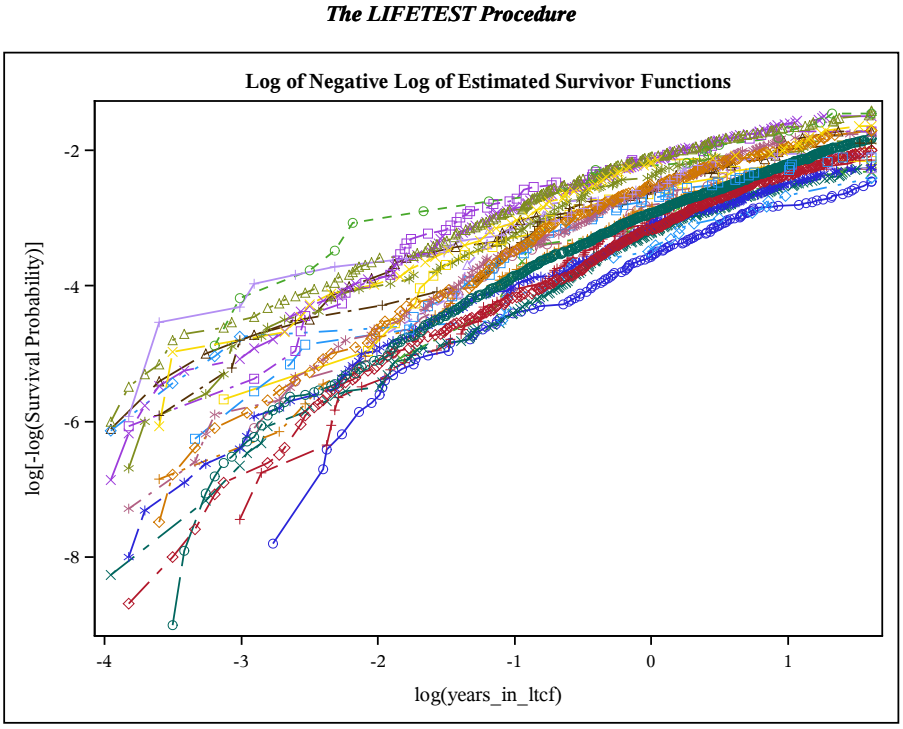


Figure B.3: Plot of $\log(-\log(S(t)))$ vs. $\log(t)$ stratified by age, sex and falls history variables.



Bibliography

[1] National report card on osteoporosis care, 2008. URL http://www.osteoporosis.ca/multimedia/images/english/home/2008nationalReportCard_Eng.pdf.

[2] JA Cauley, NS Wampler, JM Barnhart, L Wu, M Allison, Z Chen, S Hendrix, J Robbins, and RD Jackson. Incidence of fractures compared to cardiovascular disease and breast cancer: the womens health initiative observational study. *Osteoporosis international*, 19(12):1717–1723, 2008.

[3] ME Wiktorowicz, R Goeree, A Papaioannou, Jonathan D Adachi, and E Papadimitropoulos. Economic implications of hip fracture: health service use, institutional care and cost in Canada. *Osteoporosis International*, 12(4):271–278, 2001.

[4] Richard G Crilly, David A Tanner, Marita Kloseck, and Bert M Chesworth. Hip fractures in long-term care: is the excess explained by the age and gender distribution of the residents? *Journal of aging research*, 2010, 2010.

[5] Olof Johnell and JA Kanis. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporosis International*, 15(11):897–902, 2004.

[6] Ania Basiukiewicz Julie M. Foley, Famida Jiwa. osteoporosis update a practical guide for Canadian physicians focus on long-term care. 13(1), 2009.

[7] WHO global report on falls prevention in older age, 2007. URL http://www.who.int/ageing/publications/Falls_prevention7March.pdf.

[8] A Papaioannou, CC Kennedy, G Ioannidis, C Cameron, R Croxford, JD Adachi, S Mursleen, and S Jaglal. Comparative trends in incident fracture rates for all long-term care and community-dwelling seniors in Ontario, Canada, 2002–2012. *Osteoporosis International*, pages 1–11, 2016.

[9] Richard G Crilly, David A Tanner, Marita Kloseck, and Bert M Chesworth. Hip fractures in long-term care: is the excess explained by the age and gender distribution of the residents? *Journal of aging research*, 2010, 2010.

[10] Anatoli I Yashin, James W Vaupel, and Ivan A Iachine. Correlated individual frailty: an advantageous approach to survival analysis of bivariate data. *Mathematical Population Studies*, 5(2):145–159, 1995.

[11] Kelvin KW Yau. Multilevel models for survival analysis with random effects. *Biometrics*, 57(1):96–102, 2001.

[12] Andreas P Diamantopoulos, Gudrun Rohde, Irene Johnsrud, Inger Marie Skoie, Villy Johnsen, Marc Hochberg, and Glenn Haugeberg. Incidence rates of fragility hip fracture in middle-aged and elderly men and women in southern Norway. *Age and ageing*, 41 (1):86–92, 2012.

[13] SY Cheng, AR Levy, KA Lefaivre, P Guy, L Kuramoto, and B Sobolev. Geographic trends in incidence of hip fractures: a comprehensive literature review. *Osteoporosis International*, 22(10):2575–2586, 2011.

[14] Kerrie Margaret Sanders, Geoffrey Charles Nicholson, AM Ugoni, E Seeman, Julie Anne Pasco, and MA Kotowicz. Fracture rates lower in rural than urban communities: the Geelong osteoporosis study. *Journal of epidemiology and community health*, 56(6): 466–470, 2002.

[15] Sudipto Banerjee, Melanie M Wall, and Bradley P Carlin. Frailty modeling for spatially correlated survival data, with application to infant mortality in Minnesota. *Biostatistics*, 4(1):123–142, 2003.

[16] Yi Li and Louise Ryan. Modeling spatial survival data using semiparametric frailty models. *Biometrics*, 58(2):287–297, 2002.

[17] Leonid A Gavrilov and Natalia S Gavrilova. The reliability theory of aging and longevity. *Journal of theoretical Biology*, 213(4):527–545, 2001.

[18] David J Hand. Encyclopedia of quantitative risk analysis and assessment edited by Edward l. Melnick, Brian s. Everitt. *International Statistical Review*, 77(2):313–314, 2009.

[19] David Collett. *Modelling survival data in medical research*. CRC press, 2015.

[20] DR Cox. Regression models and life-tables. Breakthroughs in statistics, 1992.

[21] DR Cox. Partial likelihood. biometrika, 62, 269-276. *Mathematical Reviews (MathSciNet): MR400509 Zentralblatt MATH*, 312, 1975.

[22] Odd O Aalen. A linear regression model for the analysis of life times. *Statistics in medicine*, 8(8):907–925, 1989.

[23] Steve Bennett. Analysis of survival data by the proportional odds model. *Statistics in medicine*, 2(2):273–277, 1983.

[24] Patricia M Odell, Keaven M Anderson, and Ralph B D'Agostino. Maximum likelihood estimation for interval-censored data using a Weibull-based accelerated failure time model. *Biometrics*, pages 951–959, 1992.

[25] Göran Broström. *Event history analysis with R*. CRC Press, 2012.

[26] Whitney K Newey and Daniel McFadden. Large sample estimation and hypothesis testing. *Handbook of econometrics*, 4:2111–2245, 1994.

[27] Stacey A Wainwright, Lynn M Marshall, Kristine E Ensrud, Jane A Cauley, Dennis M Black, Teresa A Hillier, Marc C Hochberg, Molly T Vogt, and Eric S Orwoll. Hip fracture in women without osteoporosis. *The Journal of Clinical Endocrinology & Metabolism*, 90(5):2787–2793, 2005.

[28] J Parkkari, P Kannus, M Palvanen, A Natri, J Vainio, H Aho, I Vuori, and M Jarvinen. Majority of hip fractures occur as a result of a fall and impact on the greater trochanter of the femur: a prospective controlled hip fracture study with 206 consecutive patients. *Calcified Tissue International*, 65(3):183–187, 1999.

[29] Ilona S Nurmi, Peter MJ Luthje, and J Matti Kataja. Long-term survival after falls among the elderly in institutional care. *Archives of gerontology and geriatrics*, 38(1): 1–10, 2004.

[30] Jes Bruun Lauritzen, PA McNair, and B Lund. Risk factors for hip fractures. a review. *Danish medical bulletin*, 40(4):479–485, 1993.

[31] DK Dhanwal, C Cooper, and EM Dennison. Geographic variation in osteoporotic hip fracture incidence: the growing importance of asian influences in coming decades. *Journal of osteoporosis*, 2010, 2010.

[32] John Anthony Kanis, World Health Organization, et al. *Assessment of osteoporosis at the primary health care level*. WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, 2008.

[33] Piet Geusens, Tineke van Geel, and Joop van den Bergh. Can hip fracture prediction in women be estimated beyond bone mineral density measurement alone? *Therapeutic advances in musculoskeletal disease*, 2(2):63–77, 2010.

[34] Ula Hwang, Lynne D Richardson, Tolulope O Sonuyi, and R Sean Morrison. The effect of emergency department crowding on the management of pain in older adults with hip fracture. *Journal of the American Geriatrics Society*, 54(2):270–275, 2006.

[35] Shih-Wei Lai, Kuan-Fu Liao, Chien-Chang Liao, Chih-Hsin Muo, Chiu-Shong Liu, and Fung-Chang Sung. Polypharmacy correlates with increased risk for hip fracture in the elderly: a population-based study. *Medicine*, 89(5):295–299, 2010.

[36] Heike A Bischoff-Ferrari, B Dawson-Hughes, Hannes B Staehelin, John E Orav, AE Stuck, R Theiler, John B Wong, A Egli, Douglas P Kiel, and J Henschkowski. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *Bmj*, 339:b3692, 2009.

[37] Natural health products ingredients database, 2007. URL http://webprod.hc-sc.gc.ca/nhpid-bdipsn/monoReq.do?id=183&lang=eng.

[38] FRAX WHO fracture risk assessment, 2008. URL http://www.shef.ac.uk.

[39] Susan L Greenspan, Elizabeth R Myers, Lauri A Maitland, Tamiko H Kido, Meryl B Krasnow, and Wilson C Hayes. Trochanteric bone mineral density is associated with type of hip fracture in the elderly. *Journal of bone and mineral research*, 9(12):1889–1894, 1994.

[40] B Gullberg, O Johnell, and JA Kanis. World-wide projections for hip fracture. *Osteoporosis international*, 7(5):407–413, 1997.

[41] Dinesh K Dhanwal, Elaine M Dennison, Nick C Harvey, Cyrus Cooper, et al. Epidemiology of hip fracture: Worldwide geographic variation. *Indian journal of orthopaedics*, 45(1):15, 2011.

[42] Ethel S Siris, Ya-Ting Chen, Thomas A Abbott, Elizabeth Barrett-Connor, Paul D Miller, Lois E Wehen, and Marc L Berger. Bone mineral density thresholds for pharmacologic intervention to prevent fractures. *Obstetrical & gynecological survey*, 59(11): 769–771, 2004.

[43] JA Kanis, Olof Johnell, A Oden, Ingemar Sernbo, Inga Redlund-Johnell, A Dawson, C De Laet, and B Jonsson. Long-term risk of osteoporotic fracture in malmø. *Osteoporosis international*, 11(8):669–674, 2000.

[44] RJ Honkanen, K Honkanen, H Krøger, E Alhava, M Tuppurainen, and S Saarikoski. Risk factors for perimenopausal distal forearm fracture. *Osteoporosis international*, 11 (3):265–270, 2000.

[45] DJM Van der Voort, PP Geusens, and GJ Dinant. Risk factors for osteoporosis related to their outcome: fractures. *Osteoporosis International*, 12(8):630–638, 2001.

[46] Jeane Ann Grisso, Jennifer L Kelsey, Brian L Strom, Grace Y Ghiu, Greg Maislin, Linda A O'Brien, Susie Hoffman, and Frederick Kaplan. Risk factors for falls as a cause of hip fracture in women. *New England Journal of Medicine*, 324(19):1326–1331, 1991.

[47] Quality of care and outcomes, 2014. URL http://www.cihi.ca/CIHI-ext-ortalternet/en/Document/health+system+performance/quality+of+care+and+outcomes/patient+safety/RELEASE_28OCT14.

[48] WC Graafmans, ME Ooms, HMA Hofstee, PD Bezemer, LM Bouter, and PTAM Lips. Falls in the elderly: a prospective study of risk factors and risk profiles. *American journal of epidemiology*, 143(11):1129–1136, 1996.

[49] Tahir Masud and Robert O Morris. Epidemiology, of falls. *Age and ageing*, 30:3–7, 2001.

[50] P Kannus, J Parkkari, H Sievänen, Ari Heinonen, I Vuori, and M Järvinen. Epidemiology of hip fractures. *Bone*, 18(1):S57–S63, 1996.

[51] J West, Julia Hippisley-Cox, Carol AC Coupland, GM Price, LM Groom, Denise Kendrick, and Elizabeth Webber. Do rates of hospital admission for falls and hip fracture in elderly people vary by socio-economic status? *Public health*, 118(8):576–581, 2004.

[52] Pekka Kannus, Harri Sievanen, Mika Palvanen, Teppo Jarvinen, and Jari Parkkari. Prevention of falls and consequent injuries in elderly people. *The Lancet*, 366(9500): 1885–1893, 2005.

[53] Reamer L Bushardt, Emily B Massey, Temple W Simpson, Jane C Ariail, and Kit N Simpson. Polypharmacy: misleading, but manageable. *Clinical interventions in aging*, 3(2):383, 2008.

[54] Emily R Hajjar, Angela C Cafiero, and Joseph T Hanlon. Polypharmacy in elderly patients. *The American journal of geriatric pharmacotherapy*, 5(4):345–351, 2007.

[55] Kasandra Harriman, Lisa Howard, and Rita McCracken. Deprescribing medication for frail elderly patients in nursing homes: A survey of Vancouver family physicians. *British Columbia Medical Journal*, 56(9), 2014.

[56] Joseph V Agostini, Ling Han, and Mary E Tinetti. The relationship between number of medications and weight loss or impaired balance in older adults. *Journal of the American Geriatrics Society*, 52(10):1719–1723, 2004.

[57] Lisa A Cranwell-Bruce. The connection between patient falls and medication. *Medsurg Nursing*, 17(3):189, 2008.

[58] Jeffrey C Delafuente. Understanding and preventing drug interactions in elderly patients. *Critical reviews in oncology/hematology*, 48(2):133–143, 2003.

[59] Sirpa Hartikainen, Eija Lønnroos, and Kirsti Louhivuori. Medication as a risk factor for falls: critical systematic review. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 62(10):1172–1181, 2007.

[60] Shobha S Rao. Prevention of falls in older patients. *Am Fam Physician*, 72(1):81–8, 2005.

[61] Laura Corsinovi, Mario Bo, Nicoletta Ricauda Aimonino, Renata Marinello, Federico Gariglio, Cristina Marchetto, Laura Gastaldi, Laura Fissore, Mauro Zanocchi, and Mario Molaschi. Predictors of falls and hospitalization outcomes in elderly patients admitted to an acute geriatric unit. *Archives of gerontology and geriatrics*, 49(1):142–145, 2009.

[62] W Edward Bacon, Gordon S Smith, and Susan P Baker. Geographic variation in the occurrence of hip fractures among the elderly white US population. *American journal of public health*, 79(11):1556–1558, 1989.

[63] John A Kanis. Diagnosis of osteoporosis and assessment of fracture risk. *The Lancet*, 359(9321):1929–1936, 2002.

[64] Gun-Britt Jarnlo, Berit Jakobsson, Leif Ceder, and Karl-Goran Thorngren. Hip fracture incidence in Lund, Sweden, 1966–1986. *Acta Orthopaedica Scandinavica*, 60(3):278–282, 1989.

[65] P Lips, C Cooper, D Agnusdei, F Caulin, P Egger, O Johnell, JA Kanis, U Liberman, H Minne, J Reeve, et al. Quality of life as outcome in the treatment of osteoporosis: the development of a questionnaire for quality of life by the european foundation for osteoporosis. *Osteoporosis international*, 7(1):36–38, 1997.

[66] Kuan Yu Huang, Je Ken Chang, Sen Yen Ling, Naoto Endo, and Hideaki E Takahashi. Epidemiology of cervical and trochanteric fractures of the proximal femur in 1996 in Kaohsiung City, Taiwan. *Journal of bone and mineral metabolism*, 18(2):89–95, 2000.

[67] Juanita R Bacsu, Bonnie Jeffery, Shanthi Johnson, Diane Martz, Nuelle Novik, and Sylvia Abonyi. Healthy aging in place: Supporting rural seniors health needs. *Online Journal of Rural Nursing and Health Care*, 12(2):77–87, 2012.

[68] Johan P Mackenbach, Irina Stirbu, Albert-Jan R Roskam, Maartje M Schaap, Gwenn Menvielle, Mall Leinsalu, and Anton E Kunst. Socioeconomic inequalities in health in 22 european countries. *New England Journal of Medicine*, 358(23):2468–2481, 2008.

[69] M Wildner and DE Clark. Hip fracture incidence in east and west Germany: reassessement ten years after unification. *Osteoporosis international*, 12(2):136–139, 2001.

[70] Andreas P Diamantopoulos, Gudrun Rohde, Irene Johnsrud, Inger Marie Skoie, Villy Johnsen, Marc Hochberg, and Glenn Haugeberg. Incidence rates of fragility hip fracture in middle-aged and elderly men and women in southern Norway. *Age and ageing*, 41 (1):86–92, 2012.

[71] Lucas E Nikkel, Edward J Fox, Kevin P Black, Charles Davis, Lucille Andersen, and Christopher S Hollenbeak. Impact of comorbidities on hospitalization costs following hip fracture. *J Bone Joint Surg Am*, 94(1):9–17, 2012.

[72] C Cooper, C Coupland, and M Mitchell. Rheumatoid arthritis, corticosteroid therapy and hip fracture. *Annals of the rheumatic diseases*, 54(1):49–52, 1995.

[73] Lora M Giangregorio, William D Leslie, Lisa M Lix, Helena Johansson, Anders Oden, Eugene McCloskey, and John A Kanis. FRAX underestimates fracture risk in patients with diabetes. *Journal of bone and mineral research*, 27(2):301–308, 2012.

[74] Michael Pfeifer, Mehrsheed Sinaki, Piet Geusens, Steven Boonen, Elisabeth Preisinger, and Helmut W Minne. Musculoskeletal rehabilitation in osteoporosis: a review. *Journal of Bone and Mineral Research*, 19(8):1208–1214, 2004.

[75] Orit Segev-Jacubovski, Talia Herman, Galit Yogev-Seligmann, Anat Mirelman, Nir Giladi, and Jeffrey M Hausdorff. The interplay between gait, falls and cognition: can cognitive therapy reduce fall risk? *Expert review of neurotherapeutics*, 11(7):1057–1075, 2011.

[76] Carol Van Doorn, Ann L Gruber-Baldini, Sheryl Zimmerman, J Richard Hebel, Cynthia L Port, Mona Baumgarten, Charlene C Quinn, George Taler, Conrad May, and Jay Magaziner. Dementia as a risk factor for falls and fall injuries among nursing home residents. *Journal of the American Geriatrics Society*, 51(9):1213–1218, 2003.

[77] Nicole L Baker, Michael N Cook, H Michael Arrighi, and Roger Bullock. Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988–2007. *Age and ageing*, page afq146, 2010.

[78] Lone Jørgensen, Torgeir Engstad, and Bjarne K Jacobsen. Higher incidence of falls in long-term stroke survivors than in population controls depressive symptoms predict falls after stroke. *Stroke*, 33(2):542–547, 2002.

[79] Natalie E Allen, Allison K Schwarzel, and Colleen G Canning. Recurrent falls in Parkinsons disease: a systematic review. *Parkinsons Disease*, 2013, 2013.

[80] Patricia Quigley, Tatjana Bulat, Ellen Kurtzman, Ronald Olney, Gail Powell-Cope, and Laurence Rubenstein. Fall prevention and injury protection for nursing home residents. *Journal of the American Medical Directors Association*, 11(4):284–293, 2010.

[81] Edward F Vonesh and Randy L Carter. Mixed-effects nonlinear regression for unbalanced repeated measures. *Biometrics*, pages 1–17, 1992.

[82] José C Pinheiro and Douglas M Bates. Approximations to the log-likelihood function in the nonlinear mixed-effects model. *Journal of computational and Graphical Statistics*, 4(1):12–35, 1995.

[83] Marie Davidian and A Ronald Gallant. Smooth nonparametric maximum likelihood estimation for population pharmacokinetics, with application to quinidine. *Journal of Pharmacokinetics and Biopharmaceutics*, 20(5):529–556, 1992.

[84] Milton Abramowitz and Irene A Stegun. *Handbook of mathematical functions: with formulas, graphs, and mathematical tables*, volume 55. Courier Corporation, 1964.

[85] SAS Institute Inc. Sas/stat 14.1 users guide. 2015.

[86] R Fletcher. Fortran subroutines for minimization by quasi-Newton methods. Technical report, Atomic Energy Research Establishment Harwell, England, 1972.

[87] Canadian Institute for Health Information. Health indicators 2013. March 25, 2014. URL https://secure.cihi.ca/free_products/HI2013_Jan30_EN.pdf.

[88] Carl Zetterberg, Stefan Elmerson, and Gunnar BJ Andersson. Epidemiology of hip fractures in Goteborg, Sweden, 1940-1983. *Clinical orthopaedics and related research*, 191:43–52, 1984.

[89] Rasha Khatib, Nancy Santesso, Laura Pickard, Osman Osman, Lora Giangregorio, Carly Skidmore, and Alexandra Papaioannou. Fracture risk in long term care: a systematic review and meta-analysis of prospective observational studies. *BMC geriatrics*, 14(1):1, 2014.

[90] Roy O Mathew, Wan-Hsiang Hsu, and Yuchi Young. Effect of comorbidity on functional recovery after hip fracture in the elderly. *American Journal of Physical Medicine & Rehabilitation*, 92(8):686–696, 2013.

[91] Mohammad Auais, Suzanne Morin, Lyne Nadeau, Lois Finch, and Nancy Mayo. Changes in frailty-related characteristics of the hip fracture population and their implications for healthcare services: evidence from Quebec, Canada. *Osteoporosis International*, 24(10):2713–2724, 2013.

[92] Jeffrey M Hausdorff, Dean A Rios, and Helen K Edelberg. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Archives of physical medicine and rehabilitation*, 82(8):1050–1056, 2001.

[93] Silvia Deandrea, Francesca Bravi, Federica Turati, Ersilia Lucenteforte, Carlo La Vecchia, and Eva Negri. Risk factors for falls in older people in nursing homes and hospitals. a systematic review and meta-analysis. *Archives of gerontology and geriatrics*, 56(3): 407–415, 2013.

[94] Jian Sheng Chen, Philip N Sambrook, Judy M Simpson, Ian D Cameron, Robert G Cumming, Markus J Seibel, Stephen R Lord, and Lyn M March. Risk factors for hip fracture among institutionalised older people. *Age and ageing*, 38(4):429–434, 2009.

[95] Harald Dobnig, Jutta Claudia Piswanger-Solkner, Barbara Obermayer-Pietsch, Andreas Tiran, Andrea Strele, Elisabeth Maier, Peter Maritschnegg, Gunter Riedmuller, Carolin Brueck, and Astrid Fahrleitner-Pammer. Hip and nonvertebral fracture prediction in nursing home patients: role of bone ultrasound and bone marker measurements. *The journal of Clinical endocrinology & Metabolism*, 92(5):1678–1686, 2007.

[96] Pernille Ravn, G Cizza, NH Bjarnason, D Thompson, M Daley, RD Wasnich, M McClung, D Hosking, AJ Yates, and C Christiansen. Low body mass index is an important risk factor for low bone mass and increased bone loss in early postmenopausal women. *Journal of bone and mineral research*, 14(9):1622–1627, 1999.

[97] Helena Johansson, John A Kanis, Anders Odén, Eugene McCloskey, Roland D Chapurlat, Claus Christiansen, Steve R Cummings, Adolfo Diez-Perez, John A Eisman, Saeko Fujiwara, et al. A meta-analysis of the association of fracture risk and body mass index in women. *Journal of Bone and Mineral Research*, 29(1):223–233, 2014.

[98] Sari Stenholm, Päivi Sainio, Taina Rantanen, Erkki Alanen, and Seppo Koskinen. Effect of co-morbidity on the association of high body mass index with walking limitation among men and women aged 55 years and older. *Aging clinical and experimental research*, 19(4):277–283, 2007.

[99] Roderic Beaujot and Jianlin Niu. Aggregate level community characteristics and health. *Ottawa: Population Studies Centre Discussion Paper*, pages 05–14, 2005.

[100] D Omariba. Neighbourhood characteristics, individual and household attributes and health perception among elderly Canadians. *PSC Discussion Papers Series*, 20(1):1, 2006.

[101] Deanna Wanless, Barbara A Mitchell, and Andrew V Wister. Social determinants of health for older women in Canada: Does rural–urban residency matter? *Canadian Journal on Aging/La Revue canadienne du vieillissement*, 29(02):233–247, 2010.

[102] Juanita R Bacsu, Bonnie Jeffery, Shanthi Johnson, Diane Martz, Nuelle Novik, and Sylvia Abonyi. Healthy aging in place: Supporting rural seniors health needs. *Online Journal of Rural Nursing and Health Care*, 12(2):77–87, 2012.

[103] M Wildner and DE Clark. Hip fracture incidence in east and west Germany: reassessement ten years after unification. *Osteoporosis international*, 12(2):136–139, 2001.

[104] Robert Wilk, Michał Skrzypek, Małgorzata Kowalska, Damian Kusz, Artur Wielgórecki, Maciej Horyniecki, Justyna Śliwiak, Szczepan Piejczyk, and Wojciech Pluskiewicz. Standardized incidence and trend of osteoporotic hip fracture in Polish women and men: a nine year observation. *Maturitas*, 77(1):59–63, 2014.

[105] Mahmood Soveid, Ali Reza Serati, and Masoomeh Masoompoor. Incidence of hip fracture in Shiraz, Iran. *Osteoporosis international*, 16(11):1412–1416, 2005.

[106] Mika Matsuzaki, Rashmi Pant, Bharati Kulkarni, and Sanjay Kinra. Comparison of bone mineral density between urban and rural areas: Systematic review and meta-analysis. *PloS one*, 10(7):e0132239, 2015.

[107] Julian Besag, Jeremy York, and Annie Mollié. Bayesian image restoration, with two applications in spatial statistics. *Annals of the institute of statistical mathematics*, 43 (1):1–20, 1991.

[108] JS Liu. *Monte Carlo strategies in statistical computing*. Springer, New York, 2001.

[109] David J Spiegelhalter, Nicola G Best, Bradley P Carlin, and Angelika Van Der Linde. Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 64(4):583–639, 2002.

[110] Andrew Gelman, Xiao-Li Meng, and Hal Stern. Posterior predictive assessment of model fitness via realized discrepancies. *Statistica sinica*, pages 733–760, 1996.

[111] Statistics Canada. Section 4 technical specifications, 2011. URL http://www.statcan.gc.ca/pub/92-153-g/2011002/tech-eng.htm.

[112] Helene Wagner and Otto Wildi. Realistic simulation of the effects of abundance distribution and spatial heterogeneity on non-parametric estimators of species richness. *Ecoscience*, 9(2):241–250, 2002.

[113] Deborah D Ingram and Joel C Kleinman. Empirical comparisons of proportional hazards and logistic regression models. *Statistics in medicine*, 8(5):525–538, 1989.