Differences in Prescription Drug Use Among 5-year Survivors of Childhood, Adolescent, and Young Adult Cancer and the General Population in British Columbia, Canada

by

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Ethics Statement

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Abstract

In this project, we analyze the prescription drug use of childhood, adolescent, and young adult cancer survivors identified by the CAYACS program in BC. Understanding the patterns of prescription use and factors associated with the tendency to be on prescriptions is important to policy and health care planners. Since data on actual prescription usage are not available, we use prescription dispensing data as a proxy. We examine the differences in prescription use between survivors and matched controls selected from the general population, and assess the impact of age and other clinical and sociodemographic factors on prescription use. Specifically, we model subjects' on-/off-prescription status by a first-order Markov transition model, and handle the between-subject heterogeneity using a random effect. Our method captures the differences in prescription drug use between survivors and the general population, as well as differences within the survivor population. Our results show that survivors tend to exhibit a higher probability of going on prescriptions compared to the general population over the course of their lifetime. Further, females appear to have a higher probability of going on prescriptions than males over the course of their lifetime. A simulation study is conducted to assess the performance of the estimators of the model.

Keywords: Health Services Utilization; Longitudinal Analysis; Markov Model; Prescription Drugs

Dedication

To my family.

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Disclaimer statement: All inferences, opinions, and conclusions drawn in this report are those of the authors, and do not reflect the opinions or policies of the British Columbia Data Steward(s).

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Chapter 1

Introduction

The Childhood, Adolescent, and Young Adult Cancer Survivors (CAYACS) research program of British Columbia is a comprehensive population-based cohort study of 5 year survivors of a cancer or tumour diagnosed before 25 years of age in British Columbia, Canada (McBride et al. (2010)). The CAYACS program utilizes a large database linkage system that allows for the construction of datasets using multiple sources, such as population-based registries, administrative databases, prescription drug databases, and health records. This linkage methodology uses existing databases, providing savings in both time and costs compared to conventional data collection methods.

According to the Canadian Institute for Health Information, hospitals, physicians, and prescription drugs accounted for more than 60% of the health care spending in Canada in 2014. Drugs (prescribed and non-prescribed) accounted for the second largest category (16%, $29.4 billion) of health care spending in Canada in 2014. Prescription drug spending has continued to grow consistently over time; from 1985 to 2005 there was an average increase of 10.6% per year and between 2005 and 2010, there was an average increase of 7.6% per year. [1]

The 5 year survival rate of young cancer survivors is greater than 80% [2]; as a result a large survivor population exists. These individuals may be at an increased risk of late or even chronic health problems that require increased use of health care services. This project focuses on the prescription drug use aspect of the health service utilization outcomes of the CAYACS program. It is important to gain a detailed understanding of the impact of cancer survivors on health service utilization in order to have better health care planning. This project aims to describe the age-based trends and patterns in prescription drug use among young cancer survivors compared to those of the general population, and to evaluate the impact of sociodemographic, clinical, and health system variables.

[1] *https://secure.cihi.ca/free_products/Prescribed%20Drug%20Spending%20in%20Canada_2016_EN_web.pdf*
[2] Canadian Cancer Statistics 2016

Cross-sectional analyses of prescription drug utilization in childhood cancer studies exist in the literature (Deyell et al. (2013), Brinkman et al. (2013), Lund et al. (2015)), however we are unaware of work that uses a longitudinal approach. Wang (2015) analyzed physician visits data, one of the health service utilization outcomes of the CAYACS program, using a longitudinal approach. The advantages of performing a longitudinal analysis are that patterns over time may be assessed, and time dependent effects may be taken into account. For example, the effect of sex may change over time because of changing reproductive health needs of females. We aim to use a longitudinal analysis to capture the prescription patterns of childhood cancer survivors over time, and provide a better understanding of the factors that may affect the propensity of going on prescriptions.

Chapter 2

Prescription Drug Data

The CAYACS Research Program team, based at BC Cancer, assembled the data for this project from a number of linked databases, namely PharmaNet, the BC Cancer Registry, the Provincial Health Insurance Client Registry, and health records. The data were also cleaned and formatted by the team.

In this project, we examine a group of 3982 5-year survivors of a cancer or tumour diagnosed before the age of 25, in British Columbia, Canada, with diagnoses occurring from 1970 onwards and with follow-up data collected to the end of 2010. Childhood cancer survivors are those diagnosed between ages 0 to 14; and adolescent and young adult (AYA) cancer survivors are those diagnosed between ages 15 to 24. The number of childhood and AYA cancer survivors is 1830 and 2152, respectively. A comparison group 10 times the size of the survivors group and matched by birth date and gender was randomly selected from the BC provincial health insurance plan data.

2.1 Responses of interest

Prescription related data are available from PharmaNet, a central database linking all B.C. pharmacies and their corresponding dispensing information[1]. Prescription data are available from 1996-01-01 to 2010-12-31, and include the date of filling the prescription, dispensed quantity, days of supply, and drug details (dosage form, strength, drug class, etc).

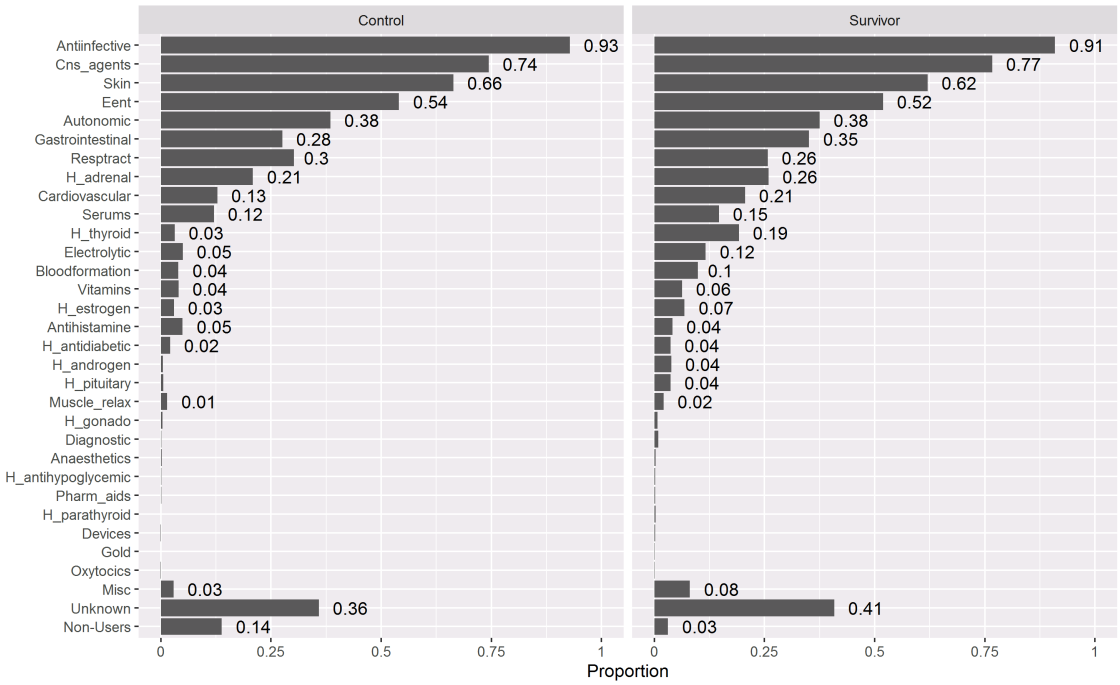
In the dataset, all prescriptions had been classified according to 31 drug classes. Figure 2.1 shows the proportion of subjects ever using each drug class. Overall, 93% of survivors have filled a prescription during their observation period compared to 86% of controls. Antiinfectives, central nervous system (CNS) agents, skin, and ear, eye, nose, throat (EENT) are among the most commonly used prescription drug classes. More than 90% of all survivors and controls have used antiinfectives, and 60 - 70% have used central nervous system

[1] http://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents/pharmanet

(CNS) agents and skin related prescriptions. The most notable observed difference between controls and survivors is their use of thyroid hormones, 19% of survivors compared to 3% of controls. A number of drug classes were used by less than 1% of users, hence they were removed from the analysis.

In this project, our responses of interest are the dates of filling the prescriptions and days of supply.

Figure 2.1: Proportion of controls and survivors who have ever been prescribed a drug in each drug class. Proportions without labels indicate a proportion less than 0.01.



2.2 Predictors

2.2.1 Socio-demographic factors

The modifying factors of interest are sex (M/F), socio-economic status (SES) quintile (1 = lowest - 5 = highest), residential status (urban/rural), and affiliated health authority (Vancouver Coastal, Interior, Fraser, Vancouver island, Northern, unknown). These data were determined using Statistics Canada census data and derived for both the survivor and comparison groups at the start of follow-up.

2.2.2 Clinical predictors

Diagnosis Type

Clinical information for all cancer patients is available since the start of diagnosis. Clinical information includes the diagnosis, age at diagnosis, treatment era, treatment modality, relapse 5 years post diagnosis (if any), and second primary cancer (a new cancer arising at a different site than first primary cancer, if any).

Diagnosis classifications were based on the International Classification of Childhood Cancer (ICCC) (Steliarova-Foucher, Stiller, Lacour, & Kaatsch, 2005) for those diagnosed under age of 20, or the AYA Cancer Classification (Birch et al., 2002) for those diagnosed between the ages of 15 and 24 years. The most common childhood cancers include acute lymphoblastic leukemia (ALL), other leukemia, Hodgkins and non-Hodgkins lymphoma, central nervous system (CNS) lymphoma, renal, and bone sarcoma. The most common AYA cancers include: lymphoma, carcinoma, germ cell, melanoma, CNS, bone, soft tissue sarcoma, and leukemia. Diagnosis type was categorized into five major groups, leukemia, lymphoma, CNS, bone and soft tissue, and germ cell. All other types were classified as "other". Table 2.1 summarizes the total number of survivors diagnosed in each cancer category.

Table 2.1: Number of survivors of each major cancer type

Diagnosis Type	Female	Male	Total	Proportion
Lymphoma	407	381	788	0.198
Leukemia	364	308	672	0.169
CNS	267	268	535	0.134
Bone and Soft Tissue Sarcoma	198	176	374	0.094
Germ Cell	288	47	335	0.084
Other	462	816	1278	0.321

Treatment Modality

Treatment modality includes combinations of surgery, chemotherapy and radiation. To simplify, a treatment modality categorization was defined: surgery only, surgery and chemotherapy, any radiation, and unknown.

Table 2.2: Number of survivors receiving each treatment modality

Treatment Modality	Number of Survivors
Surgery Only	946
Surgery and Chemotherapy	1292
Any Radiation	1212
Unknown	532

2.3 Data anomalies and missing data

2.3.1 Zero days of supply

Each prescription event consists of the dispensing date and quantity (from which the days of supply is calculated and entered into PharmaNet by pharmacists). However, some prescription events (<0.001%) were recorded as having 0 days of supply but dispensing quantity greater than 1. It is difficult to impute the estimated days of supply based on the observed data because other prescription events of the same drug and dispensing quantity do not consistently have the same days of supply. For this reason, and because of their low frequency, these prescription events were removed from the analysis.

2.3.2 Prescription date earlier than birthdate

Fewer than 30 prescription events were recorded as having a prescription date earlier than the subject's birthdate. Under the assumption that drug usage begins once a prescription has been filled, drug use cannot begin before birth. Hence, we used the subject's birthdate as the prescription date.

2.3.3 Treatment modality

Fifty survivors have treatment modality coded as "treatment only after relapse". However, of these subjects, most did not have a relapse recorded. The remainder have missing treatment modalities. Given these inconsistencies and missing information, we coded this category as "unknown".

2.3.4 Missing sociodemographic variables

Many subjects are either missing sociodemographic variables completely or missing data over a few years. For the cases where we have some information, we impute the missing values by carrying the last observed value forward (under the assumption that the chance of subjects' moving to a different category during a short time period is low).

Chapter 3

Methods

3.1 Model specification

PharmaNet provides information on dispensed prescriptions, but it is unknown whether or not a subject follows the consumption instructions completely. Therefore, we use the prescription dispensing information as an indicator for drug usage. We assume that if a subject fills a prescription, he/she will use the drug for the total number of days for which the prescription was supplied, so that during this time he/she is considered "on" prescriptions, and "off" prescriptions otherwise.

Steele (2011) used a first-order Markov model to study the transitions between employment and unemployment. Similarly, we characterize the on-off prescription patterns for each subject as a two state process using a first-order Markov model.

Let $Z_{i,t}$ denote the prescription status of the i^{th} subject in month t where $Z_{i,t} = 1$ if subject i is on a prescription in month t and $Z_{i,t} = 0$ otherwise. Under the first-order Markov assumption,

$$\mathrm{P}(Z_{i,t} = z_{i,t} | Z_{i,t-1} = z_{i,t-1}, U_i = u_i) = \mathrm{P}(Z_{i,t} = z_{i,t} | Z_{i,t-1} = z_{i,t-1}, Z_{i,t-2} = z_{i,t-2}, \dots Z_{i,1} = z_{i,1}, U_i = u_i)$$

$$\text{and} \quad U_i \sim N(0, \sigma_u^2) \quad \text{is a subject-specific random effect.}$$

That is, for subject i, his/her probability of being in state z_t in month t is a function of the state occupied at month $t-1$, but not of states occupied prior to month $t-1$.

We define the transition probability given the covariates $\boldsymbol{X}_{it}$ and the random effect U_i for subject i at time t as

$$\mathrm{P}(Z_{it} = 1 | Z_{i,t-1} = z_{i,t-1}, \boldsymbol{X}_{it} = \boldsymbol{x}_{it}, U_i = u_i) = \mathrm{logit}^{-1}(\mu + \alpha z_{i,t-1} + \boldsymbol{\beta}^T \boldsymbol{x}_{it} + u_i). \quad (3.1)$$

The subject-specific random effect accounts for the natural heterogeneity across subjects and assumes that each subject has a different propensity to be on prescriptions.

Denote $\boldsymbol{\theta} = \{\mu, \alpha, \boldsymbol{\beta}, \sigma_u^2\}$ as the collection of all unknown parameters, $\boldsymbol{z}$ as the observed responses from all subjects, and $\boldsymbol{z_i}$ as the vector of observed responses for subject i. The conditional likelihood, given the random effect, for the i^{th} subject with n_i months of observation can be expressed as,

$$\mathcal{L}_i^C(\boldsymbol{\theta}; \boldsymbol{z_i}|u_i) = f_0(z_{i0}|u_i) \prod_{t=1}^{n_i} f(z_{it}|z_{it-1}, u_i), \tag{3.2}$$

where f_0 is the probability mass function (pmf) of the initial state and f is the transition probability function, both of which are conditional on the random effect.

Since we are interested only in estimating the parameters associated with the transition probabilities, for simplicity, we ignore the initial probabilities $f_0(z_{i0}|u_i)$ and assume that all subjects start without being on any prescriptions. The contribution of the initial probability to the likelihood is likely negligible as subjects have considerably long observation periods.

The marginal likelihood for subject i is therefore

$$\mathcal{L}_i(\boldsymbol{\theta}; \boldsymbol{z_i}) = \int_{-\infty}^{\infty} \prod_{t=1}^{n_i} f(z_{it}|z_{it-1}, u) g(u) \mathrm{d}u, \tag{3.3}$$

where g is the density function of the random effect.

The likelihood of the observed data is then

$$\begin{aligned}
\mathcal{L}(\boldsymbol{\theta}; \boldsymbol{z}) &= \prod_i \mathcal{L}_i(\boldsymbol{\theta}; \boldsymbol{z_i}) \\
&= \prod_i \int_{-\infty}^{\infty} \prod_{t=1}^{n_i} f(z_{it}|z_{it-1}, u) g(u) \mathrm{d}u \\
&= \prod_i \int_{-\infty}^{\infty} \prod_{t=1}^{n_i} f(z_{it}|z_{it-1}, u) \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{u^2}{2\sigma^2}} \mathrm{d}u.
\end{aligned}$$

Maximized likelihood estimation of $\boldsymbol{\theta}$ requires evaluation of the integral in the likelihood. However, the integral does not have a closed form solution or maximum likelihood estimates (MLEs). We can apply the method of Gaussian-Hermite quadrature, which approximates the integral as a weighted sum, to find the MLEs numerically.

Letting $w = \frac{u}{\sigma\sqrt{2}}$ and $\mathrm{d}u = \sigma\sqrt{2}\mathrm{d}w$,

$$\begin{aligned}
\mathcal{L}(\theta; \boldsymbol{z}) &= \prod_i \int_{-\infty}^{\infty} \prod_{t=1}^{n_i} f(z_{it}|z_{it-1}, \sigma\sqrt{2}w) \frac{1}{\sqrt{2\pi\sigma^2}} e^{-w^2} \sigma\sqrt{2}\mathrm{d}w \\
&= \prod_i \int_{-\infty}^{\infty} \prod_{t=1}^{n_i} f(z_{it}|z_{it-1}, \sigma\sqrt{2}w) \frac{1}{\sqrt{\pi}} e^{-w^2} \mathrm{d}w \\
&= \prod_i \pi^{-\frac{n_i}{2}} \int_{-\infty}^{\infty} \prod_{t=1}^{n_i} f(z_{it}|z_{it-1}, \sigma\sqrt{2}w) e^{-w^2} \mathrm{d}w \\
&\approx \prod_i \pi^{-\frac{n_i}{2}} \sum_{k=1}^{q} \prod_{t=1}^{n_i} f(z_{it}|z_{it-1}, \sigma\sqrt{2}s_k) c_k,
\end{aligned}$$

where s_k are quadrature points and c_k are the corresponding weights.

3.2 Predictors

Table 3.1 lists the predictors that were included in the model.

Table 3.1: Predictor variables included and corresponding notation.

Notation	Predictor	# Categories	Range
x_{it}	Age	-	0 - 66
γ_j	Sex	2	1=F, 2=M
τ_k	Group	2	1=Ctrl, 2=Surv
δ_{kl}	Diagnosis	6	1 - 6
ψ_{km}	Treatment modality	3	1 - 3
ϕ_{kn}	Age at diagnosis	2	1 - 2
ω_q	SES quintile	5	1 - 5
ν_r	Affiliated health authority	5	1 - 5
ξ_s	Residential status	2	1 - 2

$$\begin{aligned}
&\text{logit}\left[\mathbb{P}(Z_{i,tjqrsklmn} = 1 | Z_{i,t-1,jqrsklmn} = z_{i,t-1,jqrsklmn}, \boldsymbol{X}_{it} = \boldsymbol{x}_{it}, U_i = u_i)\right] \qquad (3.4) \\
= \;& \mu + \alpha z_{i,t-1} + u_i + \omega_q + \nu_r + \xi_s + \gamma_j + \\
& \beta_1 x_{it} + \beta_2 {x_{it}}^2 + (\gamma\beta)_{j1} x_{it} + (\gamma\beta)_{j2} {x_{it}}^2 + \\
& \tau_k + (\tau\beta)_{k1} x_{it} + (\tau\beta)_{k2} {x_{it}}^2 + \\
& \delta_{kl} + \psi_{km} + \phi_{kn} + \\
& (\delta\beta)_{kl1} x_{it} + (\delta\beta)_{kl2} {x_{it}}^2 + (\psi\beta)_{km1} x_{it} + (\psi\beta)_{km2} {x_{it}}^2 + (\phi\beta)_{kn1} x_{it} + (\phi\beta)_{kn2} {x_{it}}^2
\end{aligned}$$

where $\omega_1 = \nu_1 = \xi_1 = \gamma_1 = \delta_{k1} = \psi_{k1} = \phi_{k1} = (\delta\beta)_{k11} = (\delta\beta)_{k12} = (\psi\beta)_{k11} = (\psi\beta)_{k12} = (\phi\beta)_{k11} = (\phi\beta)_{k12} = 0$, and any parameters with k = 1 in their index(es) are also set to 0. The effect of being on the drug in the previous time point is represented by α. We would expect α to be lower for drug classes that tend to be prescribed often and for shorter periods of time, and higher for drug classes that tend to be prescribed less frequently but for longer periods of time.

To include the survivor-specific predictors diagnosis, treatment modality and age at diagnosis, in the transition probabilities, we include group-by-diagnosis, group-by-treatment-modality and group-by-age-at-diagnosis interaction terms (i.e. parameters in (3.1) with k in their indexes), but omit the main effects of these predictors. By doing so, a single model is sufficient to capture the effects of survivor-specific predictors on prescription drug use compared to the general population and within survivors. Two examples are provided to better explain the parameters for survivor-control and within-survivor comparisons.

3.2.1 Example 1: survivors vs general population

Table 3.2 shows the models assumed for female controls and 3 female survivor categories, where category is defined by diagnosis, treatment modality, and age at diagnosis. For example, "F Survivor (1, 1, 1)" represents a female survivor falling in category 1 of diagnosis, treatment modality, and age at diagnosis. Sociodemographic predictors are omitted for simplicity.

Table 3.2: Assumed models for female control group and female survivor groups, where (l, m, n) represent the categories of diagnosis, treatment modality, and age at diagnosis; and $\mathrm{P} = \mathbb{P}(Z_{itjklmnqrs} = 1 | Z_{it-1,jklmnqrs} = z_{it-1,jklmnqrs}, \boldsymbol{X}_{it} = \boldsymbol{x}_{it}, U_i = u_i)$.

Subject group	Log odds
F Control	$\text{logit(P)} = \mu + \alpha z_{it-1} + u_i + \beta_1 x_{it} + \beta_2 {x_{it}}^2$
F Survivor (1,1,1)	$\text{logit(P)} = \mu + \alpha z_{it-1} + u_i + \tau_2 + [\beta_1 + (\tau\beta)_{21}] x_{it} + [\beta_2 + (\tau\beta)_{22}] {x_{it}}^2$
F Survivor (l,1,1)	$\text{logit(P)} = \mu + \alpha z_{it-1} + u_i + \tau_2 +$ $[(\beta_1 + (\tau\beta)_{21} + (\delta\beta)_{2l1}] x_{it} + [\beta_2 + (\tau\beta)_{22} + (\delta\beta)_{2l2}] {x_{it}}^2$
F Survivor (l, m,1)	$\text{logit(P)} = \mu + \alpha z_{it-1} + u_i + \tau_2 + \delta_{2l} + \psi_{2m} +$ $[\beta_1 + (\tau\beta)_{21} + (\delta\beta)_{2l1} + (\psi\beta)_{2m1}] x_{it} +$ $[\beta_2 + (\tau\beta)_{22} + (\delta\beta)_{2l2} + (\psi\beta)_{2m2}] {x_{it}}^2$
F Survivor (l, m, 2)	$\text{logit(P)} = \mu + \alpha z_{it-1} + u_i + \tau_2 + \delta_{2l} + \psi_{2m} + \phi_{22} +$ $[\beta_1 + (\tau\beta)_{21} + (\delta\beta)_{2l1} + (\psi\beta)_{2m1} + (\phi\beta)_{221}] x_{it} +$ $[\beta_2 + (\tau\beta)_{22} + (\delta\beta)_{2l2} + (\psi\beta)_{2m2} + (\phi\beta)_{222}] {x_{it}}^2$

The odds ratio of going on a prescription for "F Survivors (1,1,1)" vs. female controls for given levels of the other predictors is $\exp[\tau_2 + (\tau\beta)_{21} x_{it} + (\tau\beta)_{22} {x_{it}}^2]$. Note that τ_2, $(\tau\beta)_{21}$ and $(\tau\beta)_{22}$ can not be interpreted as group effects in the normal way. Rather they

represent the effects of being in category 1 of diagnosis, treatment modality, and age at diagnosis relative to a control. Similarly, the odds ratio is $\exp[\tau_2 + (\tau\beta)_{21}x_{it} + (\tau\beta)_{22}{x_{it}}^2 + \delta_{2l} + (\delta\beta)_{2l1}x_{it} + (\delta\beta)_{2l2}{x_{it}}^2]$ for "F Survivors (l, 1, 1)" vs. female controls. The odds ratio for females survivors with diagnosis l, treatment modality m and diagnosed at 15-24 years of age vs. female controls is $\exp[\tau_2 + (\tau\beta)_{21}x_{it} + (\tau\beta)_{22}{x_{it}}^2 + \delta_{2l} + (\delta\beta)_{2l1}x_{it} + (\delta\beta)_{2l2}{x_{it}}^2 + \psi_{2m} + (\psi\beta)_{2m1}x_{it} + (\psi\beta)_{2m2}{x_{it}}^2 + \phi_{22} + (\phi\beta)_{221}x_{it} + (\phi\beta)_{222}{x_{it}}^2]$, for given levels of the other predictors. In other words, the constant and the coefficients of the linear and quadratic functions of age are allowed to vary among survivor categories.

3.2.2 Example 2: within survivors

From assumed models for survivors in Table 3.2, we can make within survivor comparisons.

For example, using the models for "F Survivor (1, 1, 1)" and "F Survivor (l, 1, 1)", we can compute the odds ratio of going on a prescription for survivors with diagnosis l vs 1, for given levels of the other predictors. This odds ratio is $\exp[\delta_{2l} + (\delta\beta)_{2l1}x_{it} + (\delta\beta)_{2l2}{x_{it}}^2]$ and represents the effect of diagnosis l vs. 1 on the odds of going on prescriptions.

3.3 Estimation methods and big data wrangling

We can use the `glmer()` function in the `lme4` package to fit this model under the binary GLMM framework. The major difference between (3.1) and a GLMM for binary data is the dependence on the previous state. By treating the previous state as a covariate and assuming subjects start without being on any prescriptions, the likelihoods under 3.1 and a binary GLMM are equivalent, hence we can use the binary GLMM framework to find the MLEs.

Large administrative datasets present challenges in terms of finding efficient ways to wrangle the data, and in fact, data wrangling may be the most time consuming task in the data analysis. In our case, the data required heavy transformation to achieve the desired structure for analysis. `R` is adequate at handling "medium" data ($<$ 1 million rows), but for "big data", we often run into insufficient memory usage errors or spend a good amount of time waiting for computations to complete. The `dplyr` package, along with other packages bundled in the `tidyverse` package, provide useful and user-friendly functions to perform most wrangling tasks. However, since we are working with longitudinal data with repeated observations from subjects, do-by-group operations are key manipulation commands and can be expensive when the number of groups becomes large. The `data.table` package provides fast data aggregation and other functionality particularly useful for large datasets due to `data.table`'s enhanced memory efficiency. In addition to using `data.table`, we also saved data objects as `RDS` or `Rdata` formats (which are much more compressed than `csv` files), avoided for-loops, and vectorized whenever possible.

Chapter 4

Results

In this section, we present the results of our analysis, emphasizing the effects of the predictors on the trends of prescription use over the course of an individual's lifetime. Results for antiinfectives and CNS agents, the two most used drug classes, are presented. Results for other drug classes that were analyzed are provided in Appendix A and Appendix B.

Since the only difference between the odds of starting vs. staying on a prescription is the multiplicative factor e^{α}, we present only the odds ratios related to starting a prescription. The odds ratios related to staying on a prescription at each age will exhibit the same ranking, with only the scale differing.

We present estimated odds ratios in §4.1 and §4.2 and discuss formal tests of predictor variable effects in §4.3.

4.1 Survivors vs. General Population

Figures 4.1 and 4.2 show the odds ratios of going on antiinfectives and CNS agents by attained age for survivors vs. the general population. Since the model in (3.4) is formulated in such a way to allow each survivor category (defined by diagnosis, treatment modality, and age at diagnosis cohort) to be compared to the general population, separate curves are shown for each survivor categories.

For example, panel 1 in Figure 4.1 shows the odds ratios of going on antiinfectives for survivors of different cancer types, diagnosed at age 0-14, and who received any radiation vs. controls, for fixed levels of the other predictors.

In general, all survivor groups have higher odds of going on antiinfectives than the general population over the course of their lifetime. Survivors diagnosed at 0-14 vs. 15-24 years of age exhibit very similar trends in the odds of going on antifectives by attained age. The odds of going on antiinfectives appear to be decreasing with age for survivors who have had CNS cancer, regardless of treatment modality and age at diagnosis, and for survivors of other cancers who had surgery and chemotherapy. In contrast, survivors of other cancers

who either received any radiation or surgery only, show an increasing trend in the odds of going on antiinfectives compared to the general population.

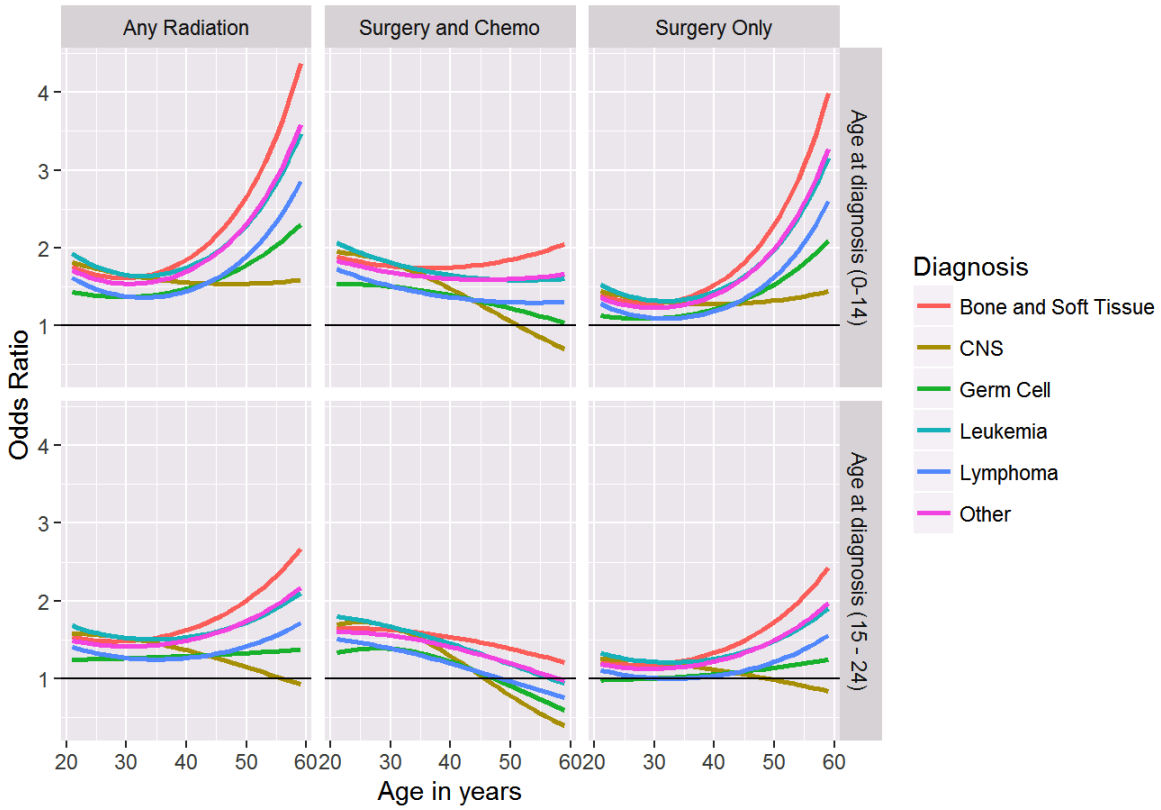


Figure 4.1: Odds ratios of going on antiinfectives for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

Overall, survivors tend to have higher odds of going on CNS agents compared to the general population at each age. The odds of going on CNS agents for survivors who had CNS cancer exhibit a declining trend with age. Nonetheless, compared to other cancer types, CNS survivors appear to have the highest odds of going on CNS agents until around age 45.

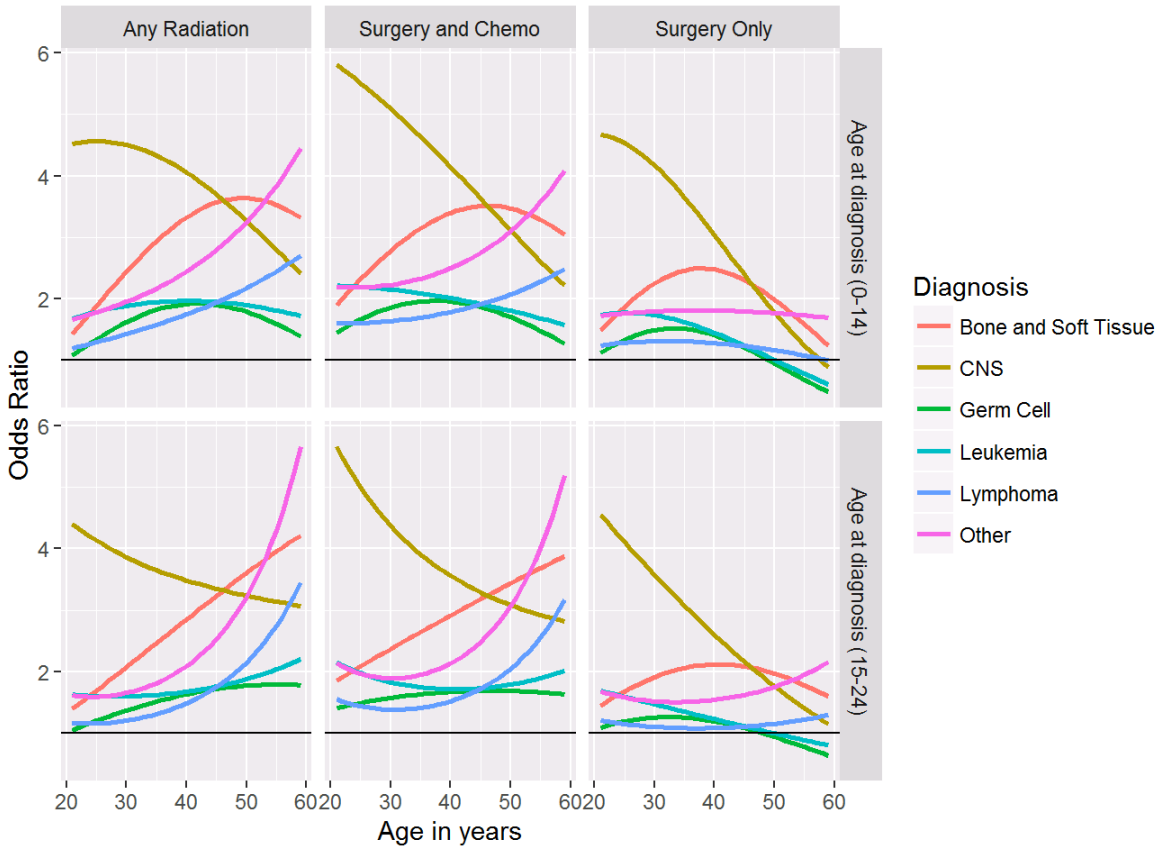


Figure 4.2: Odds ratios of going on CNS agents for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

4.2 Among survivors

In 4.1, we discussed the odds of starting a drug for survivors in different groups relative to those for controls. In this section, we assess the effects of diagnosis, treatment modality, and age at diagnosis separately by comparing these odds relative to those for other survivor groups. This approach also allows us to assess the effects of sex, socioeconomic status, affiliated health authority, and urban/rural residential status.

Of survivors with fixed sociodemographic and clinical covariates (i.e. diagnosis, treatment modality, age at diagnosis, etc), females generally have higher odds of being prescribed antiinfectives and CNS agents than males. Both drug classes exhibit similar trends over age, namely the magnitude of the differences seems to increase until 35 - 40 years old and decline afterwards.

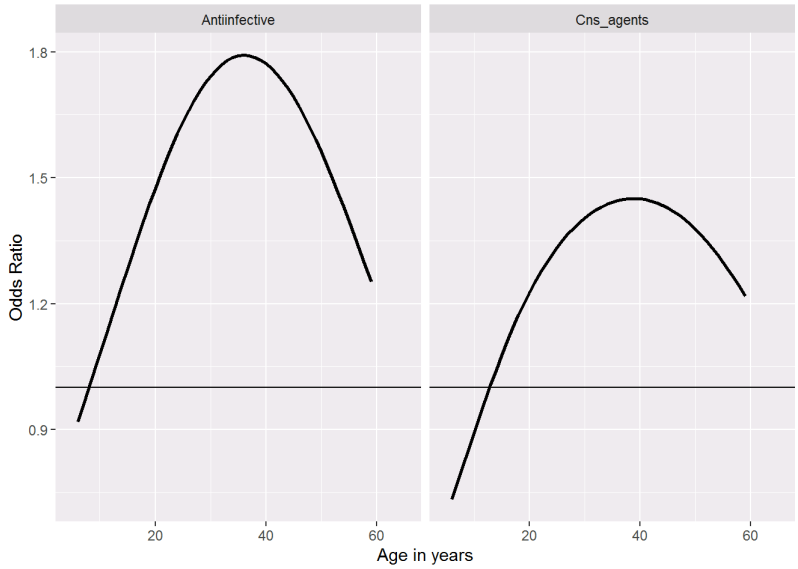


Figure 4.3: Odds ratios of going on prescriptions for female vs. male survivors for given levels of the other predictors.

Figure 4.4 shows the odds ratios of going on antiinfectives and CNS agents for survivors of various cancer types compared to survivors of bone and soft tissue cancer (our chosen reference category). Overall, there appears to be a gradual decreasing trend in the odds ratio of going on antiinfectives for the different cancer types vs. bone and soft tissue cancer. On the other hand, survivors diagnosed with CNS cancer have the highest odds of going on CNS drugs, compared survivors of other cancer types.

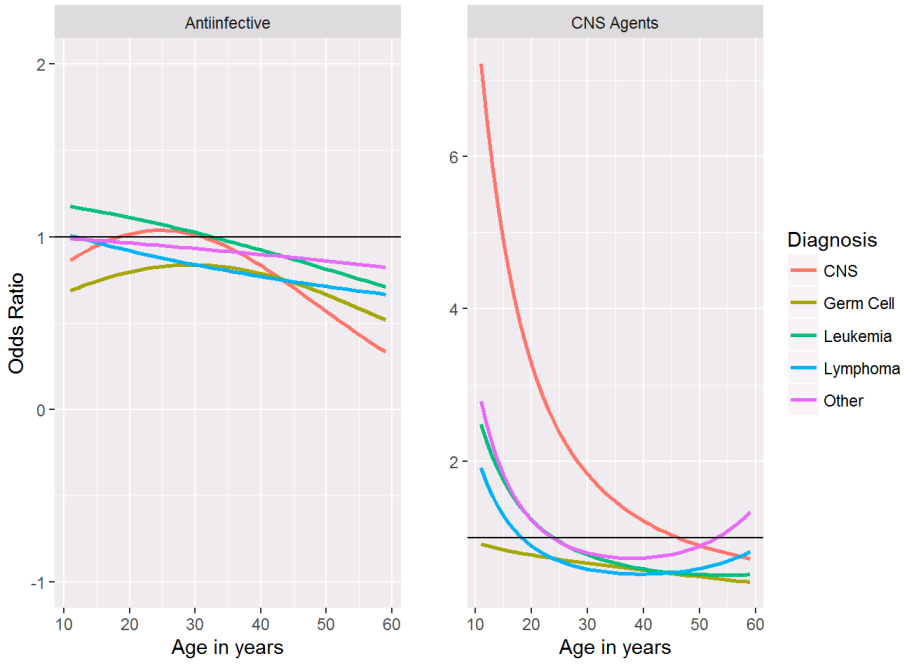


Figure 4.4: Odds ratios of going on prescriptions for survivors of each cancer type vs. bone and soft tissue cancer, for given levels of the other covariates.

In general, survivors who received surgery and chemotherapy or any radiation show higher odds of going on antiinfectives and CNS agents, compared to survivors who received surgery only. The odds of going on antiinfectives exhibit a gradual decreasing trend for survivors who received any radiation. In contrast, for survivors who received surgery and chemotherapy, the odds of going on antiinfectives seem to first increase with age but decrease after age ∼30, compared to survivors who received surgery only. The odds of going on CNS agents for survivors who received any radiation seems to increase with time. Furthermore, the odds of going on CNS agents after age ∼40 for survivors who received any radiation and those who received surgery and chemotherapy appear very similar.

Compared to survivors diagnosed at 0-14 years of age, survivors diagnosed at 15-24 years of age seem to exhibit lower and decreasing odds of going on antiinfectives by attained age, and increasing odds of going on CNS agents by attained age.

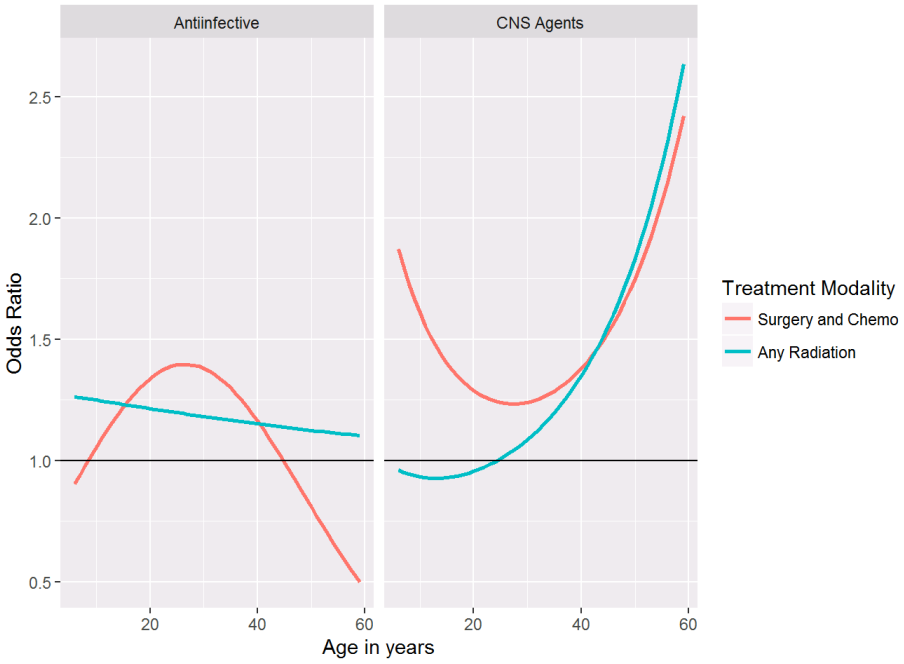


Figure 4.5: Odds ratios of going on prescriptions for survivors in each treatment modality vs. surgery only, given fixed levels of the other covariates.

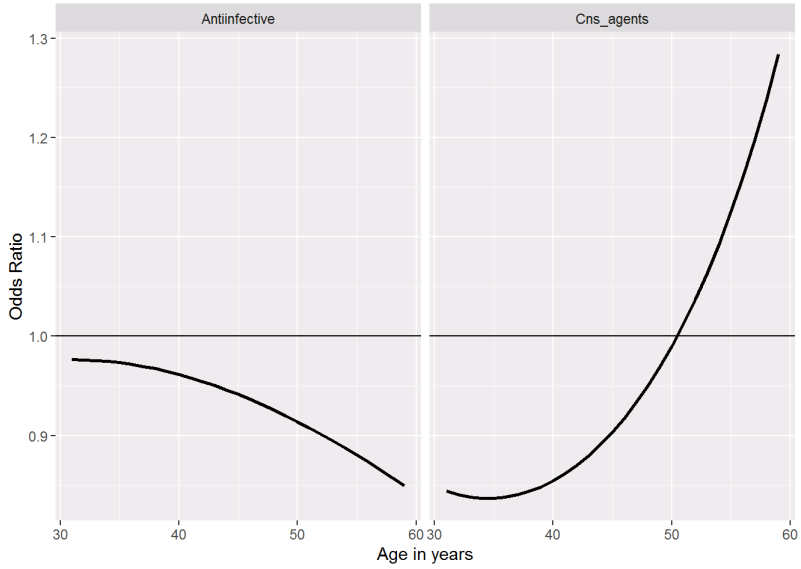


Figure 4.6: Odds ratios of going on prescriptions for survivors diagnosed at age 15-24 vs. 0-14, given fixed levels of the other covariates.

4.3 Likelihood ratio tests

Tables 4.2 and 4.3 show the estimated coefficients from the fitted models for the antiinfective and CNS agents drug classes, respectively. To test for differences between controls and all survivors on the probability of starting prescriptions, we fit a reduced model where we include only sociodemographic predictors. The likelihood ratio tests for antiinfectives and CNS agents suggest that there is indeed a difference between controls and survivors in terms of prescription usage (p-value $<<$ 0.0001).

We also conducted likelihood ratio tests to assess whether there are diagnosis, treatment modality or age at diagnosis effects within survivors on prescription usage. Table 4.1 shows the likelihood ratio test results. The diagnosis and treatment modality effects are statistically significant among survivors for antiinfectives and CNS agents. There is not enough evidence to suggest that the effect of age at diagnosis on antiinfective usage is different among survivors, which agrees with the observed trend in Figure 4.6.

Table 4.1: p-values from likelihood ratio tests for survivor-specific predictors.

Drug Class	Diagnosis	Treatment Modality	Age at diagnosis
Antiinfectives	0.0001	<0.0001	0.6534
CNS Agents	<0.0001	<0.0001	<0.0001

Table 4.2: Estimated parameters of model of antiinfective drug use patterns.

	Predictor	Estimate	Std. Error	z value	Pr(>|z|)
1	Intercept	-3.44758	0.04948	-69.67119	0.00000
2	Previous State on drug	0.01210	0.01006	1.20301	0.22897
3	Sex (vs. female)	0.41562	0.04513	9.20936	0.00000
4	Age	-0.01386	0.00227	-6.11405	0.00000
5	Age^2	0.00043	0.00004	10.62464	0.00000
	Affiliated Health Authority (vs. Interior)				
6	Fraser	0.10774	0.03416	3.15359	0.00161
7	Vancouver Coastal	-0.16737	0.03516	-4.76008	0.00000
8	Island	0.03873	0.03736	1.03692	0.29977
9	Northern	0.07252	0.04413	1.64338	0.10030
	SES (vs. low)				
10	SES 2	-0.04860	0.03152	-1.54185	0.12311
11	SES 3	0.03407	0.03191	1.06754	0.28573
12	SES 4	-0.01017	0.03224	-0.31533	0.75251
13	SES 5	-0.06020	0.03253	-1.85079	0.06420
14	Urban (vs. Rural)	-0.10243	0.03280	-3.12241	0.00179
15	Group	0.48227	0.28510	1.69156	0.09073
16	Sex:Age	-0.05798	0.00313	-18.55034	0.00000
17	$Sex:Age^2$	0.00078	0.00006	13.78352	0.00000
18	Group:Age	-0.00001	0.00002	-0.46237	0.64382
19	$Group:Age^2$	0.00038	0.00033	1.15088	0.24978
	Diagnosis (vs. Bone and Soft Tissue)				
20	CNS	-0.62724	0.30119	-2.08256	0.03729
21	Germ Cell	-0.74555	0.72254	-1.03185	0.30214
22	Leukemia	0.22690	0.27501	0.82504	0.40935
23	Lymphoma	0.14285	0.33263	0.42944	0.66760
24	Other	0.02114	0.26409	0.08005	0.93620
	Treatment Modality (vs. surgery only)				
25	Surgery and Chemo	-0.44111	0.20809	-2.11981	0.03402
26	Any Radiation	0.28644	0.20783	1.37823	0.16813
27	Age at diagnosis (15-24) (vs. 0-14)	-0.23521	0.28634	-0.82144	0.41139
28	CNS:age	0.00005	0.00002	2.63649	0.00838
29	Germ Cell:Age	0.00004	0.00004	0.92084	0.35713
30	Leukemia:Age	-0.00000	0.00002	-0.12163	0.90319
31	Lymphoma:Age	-0.00001	0.00002	-0.60702	0.54384
32	Other:Age	-0.00000	0.00002	-0.14740	0.88282
33	$CNS:Age^2$	-0.00109	0.00035	-3.14309	0.00167
34	$Germ\ Cell:Age^2$	-0.00063	0.00055	-1.13547	0.25618
35	$Leukemia:Age^2$	-0.00014	0.00039	-0.35616	0.72172
36	$Lymphoma:Age^2$	0.00004	0.00033	0.11966	0.90475
37	$Other:Age^2$	-0.00003	0.00030	-0.08871	0.92931
38	Surgery and Chemo:Age	0.00006	0.00001	4.50799	0.00001
39	Any Radiation:Age	-0.00000	0.00001	-0.28010	0.77940
40	$Surgery\ and\ Chemo:Age^2$	-0.00116	0.00023	-5.11727	0.00000
41	$Any\ Radiation:Age^2$	0.00001	0.00021	0.07018	0.94405
42	Age at diagnosis(15-24):Age	0.00001	0.00002	0.80815	0.41900
43	$Age\ at\ diagnosis(15\text{-}24):Age^2$	-0.00022	0.00025	-0.86417	0.38749
44	Subject-level random effect SD	1.20029			

Table 4.3: Estimated parameters of model of CNS agents use patterns.

	Predictor	Estimate	Std. Error	z value	Pr(>|z|)
1	(Intercept)	-7.39435	0.08238	-89.76340	0.00000
2	Previous State on drug	1.16622	0.00695	167.81193	0.00000
3	Sex (vs. female)	0.67440	0.07425	9.08256	0.00000
4	Age	0.16535	0.00324	50.99670	0.00000
5	Age^2	-0.00129	0.00005	-25.73321	0.00000
	Affiliated Health Authority				
6	Fraser (vs. Interior)	-0.10070	0.05717	-1.76132	0.07818
7	Vancouver Coastal	-0.57300	0.05897	-9.71726	0.00000
8	Island	0.04571	0.06217	0.73522	0.46221
9	Northern	0.00511	0.07382	0.06925	0.94479
	SES (vs. low)				
10	SES 2 (vs. low)	-0.04848	0.05302	-0.91445	0.36048
11	SES 3	-0.01727	0.05371	-0.32164	0.74773
12	SES 4	-0.12100	0.05442	-2.22344	0.02619
13	SES 5	-0.11967	0.05474	-2.18623	0.02880
14	Urban (vs. Rural)	-0.21053	0.05470	-3.84909	0.00012
15	Group	-2.67620	0.43127	-6.20533	0.00000
16	Sex:Age	-0.06256	0.00439	-14.25575	0.00000
17	$Sex:Age^2$	0.00078	0.00007	11.25288	0.00000
18	Group:Age	0.00021	0.00003	7.90064	0.00000
19	$Group:Age^2$	-0.00266	0.00041	-6.49994	0.00000
	Diagnosis (vs. Bone and Soft Tissue)				
20	CNS	3.60710	0.42626	8.46218	0.00000
21	Germ Cell	0.17826	0.79678	0.22372	0.82297
22	Leukemia	2.32394	0.42819	5.42737	0.00000
23	Lymphoma	2.34940	0.47623	4.93335	0.00000
24	Other	2.91658	0.41163	7.08549	0.00000
	Treatment Modality (vs. surgery only)				
25	Surgery and Chemo	1.03074	0.28079	3.67087	0.00024
26	Any Radiation	0.05859	0.26748	0.21904	0.82662
27	Age at diagnosis (15-24) (vs. 0-14)	1.18860	0.30295	3.92347	0.00009
28	CNS:Age	-0.00011	0.00003	-4.14801	0.00003
29	Germ Cell:Age	-0.00003	0.00004	-0.58230	0.56037
30	Leukemia:Age	-0.00012	0.00003	-4.44917	0.00001
31	Lymphoma:Age	-0.00017	0.00003	-5.96056	0.00000
32	Other:Age	-0.00018	0.00002	-7.17419	0.00000
33	$CNS:Age^2$	0.00064	0.00040	1.58683	0.11255
34	$Germ\ Cell:Age^2$	-0.00002	0.00060	-0.03757	0.97003
35	$Leukemia:Age^2$	0.00113	0.00047	2.39505	0.01662
36	$Lymphoma:Age^2$	0.00204	0.00041	4.97602	0.00000
37	$Other:Age^2$	0.00232	0.00038	6.17703	0.00000
38	Surgery and Chemo:Age	-0.00006	0.00002	-3.39901	0.00068
39	Any Radiation:Age	-0.00002	0.00002	-1.45630	0.14531
40	$Surgery\ and\ Chemo:Age^2$	0.00106	0.00025	4.30583	0.00002
41	$Any\ Radiation:Age^2$	0.00082	0.00023	3.58018	0.00034
42	Age at diagnosis(15-24):Age	-0.00008	0.00002	-4.80038	0.00000
43	$Age\ at\ diagnosis(15\text{-}24):Age^2$	0.00118	0.00026	4.53195	0.00001
44	Subject-level random effect SD	1.99034			

Chapter 5

Simulation Study

We conducted a simulation study to assess the bias, standard errors and confidence intervals (CIs) produced by the model fits.

For each iteration, we generated data using our fitted model from (3.4) and our subjects' covariate values. To accomplish this task, we first simulated each subject's random effect, u_i from a $N(0, \hat{\sigma}_u)$ distribution. Then, the transition probabilities were computed for each attained age t using (3.4), u_i, and the regression coefficient estimates from (3.4). Under the assumption that all subjects start without being on any prescriptions, the subjects' first responses (the z_{i1}'s) were generated from Bin(1, $P_{1,01}$). All subsequent responses were generated from either Bin(1, $P_{t,01}$) or Bin(1, $P_{t,11}$) depending on the previous occupied state. The model was then refit to the simulated data, and the resulting parameter estimates and standard errors were recorded. We repeated this procedure 200 times.

Due to the expensive computation time required to fit the model, instead of using Gaussian quadrature to find the MLEs, we used the `nagq = 0` option in `glmer()`. This option uses a more efficient fitting algorithm based on Laplace approximation of the likelihood. Our assumption is that our parameter estimates in §4 (which are based on Gaussian quadrature) are at least as well-behaved as those we investigate in this section. Further details may be found in the package vignette and on a blurb written by the package author[1].

We examine the bias and the sample standard deviation of the parameter estimates, along with the coverage probability of the associated CIs. Figures 5.1 and 5.2 show the sample bias and sample standard deviation of the parameter estimates. Most of the parameter estimates appear unbiased. The intercept and previous state estimates were poorly behaved and omitted from the figures. Note, however, that these estimates do not affect estimates of odds ratios, which are of primary interest. Survivor-specific parameter estimates appear to exhibit noise relative to the rest of the parameter estimates, perhaps due to only 200 replicates.

[1] https://github.com/dmbates/MixedModelsinJulia/blob/master/nAGQ.ipynb

Coverage probability results in Figure 5.3 show that for most parameters, the coverage probability of 95% CIs is above 90%. However, some parameters appear to exhibit low coverage probabilities. We suspect that the magnitude of the true parameter estimates may be associated with the poor coverage probabilities. Upon examination of the size of the true parameter estimates and corresponding coverage probabilities, consistent patterns were not apparent. With more replicates we expect greater precision in these results.

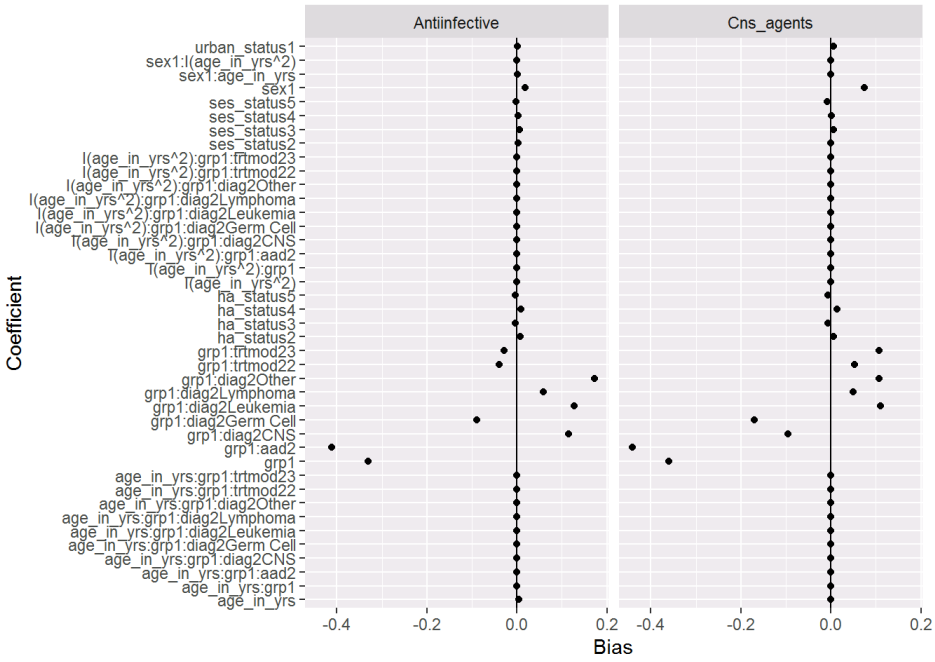


Figure 5.1: Bias of parameter estimates for antiinfectives and CNS agents models (based on 200 replicates)

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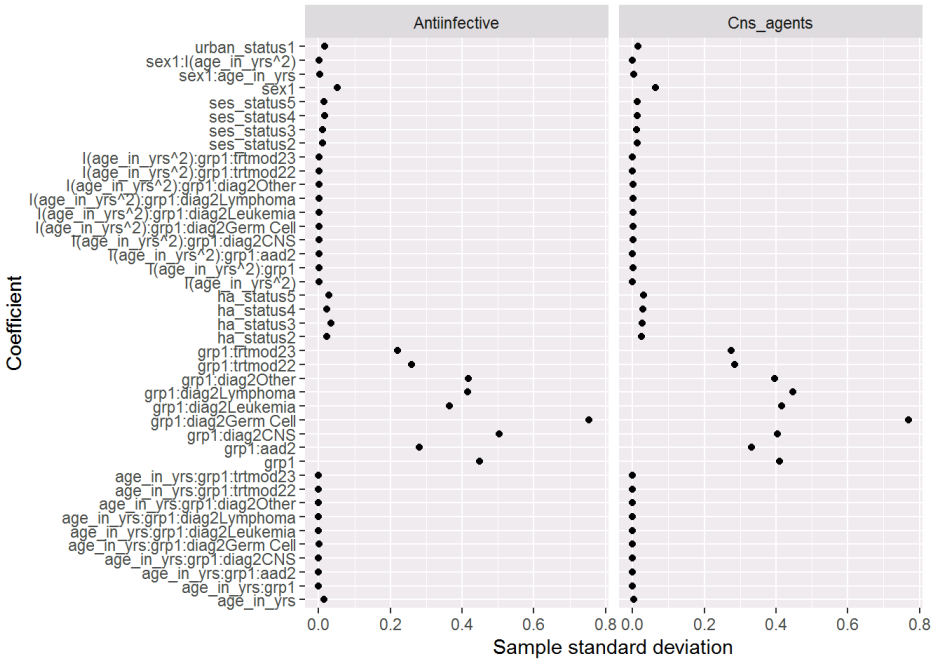

Figure 5.2: Sample standard deviation of parameter estimates for antiinfectives and CNS agents models. (based on 200 replicates)

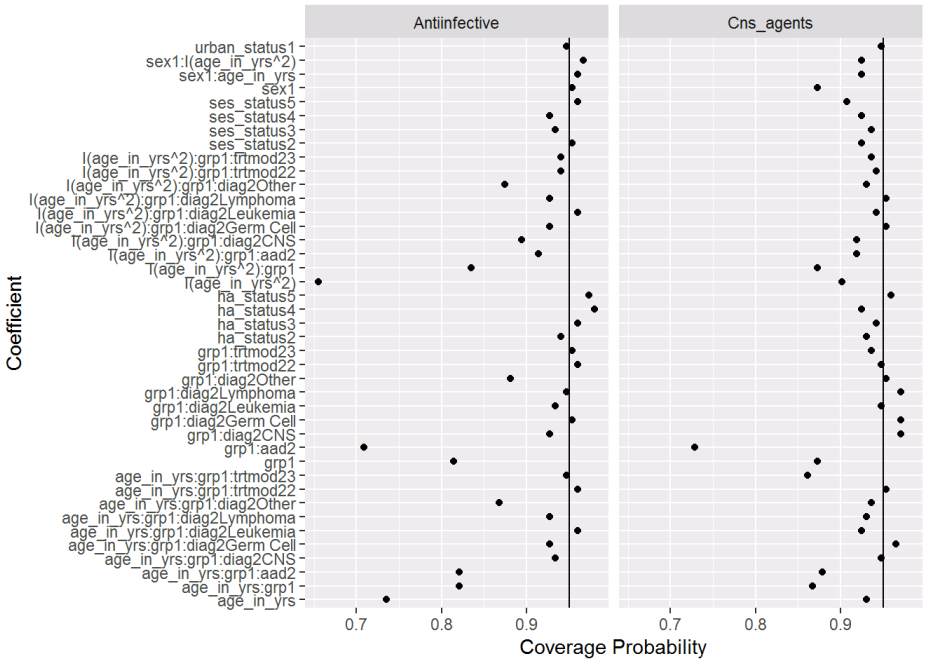

Figure 5.3: Coverage probability of 95% CI of parameter estimates for antiinfectives and CNS agents models. (based on 200 replicates)

Chapter 6

Discussion

In a preliminary attempt to characterize the on-off process of being on prescriptions, our results show that the employed methods are feasible and have reasonable performance. However, in the process, we have made a number of assumptions that require further exploration and assessment.

Firstly, we considered only the inclusion of a single random effect to capture each subject's propensities both to go on and to stay on prescriptions. Another random effect could be added such that one random effect captures a subject's tendency to go on prescriptions while the other captures a subject's tendency to stay on prescriptions. In addition, these random effects could be correlated.

Similarly, our model assumes that the effects of the covariates do not depend on the previous state, meaning for example, that the effect of sex is the same whether or not a subject was on or off a prescription in the previous month. This assumption could tested by the inclusion of an interaction of the previous state with the explanatory variables as shown in Diggle (2002).

We could also perform a more thorough examination of the first-order Markov assumption. In an exploratory analysis, we examined the distributions of time on and time off prescriptions for each drug class and found that clustering occurred at around 30 and 90 days. By coarsening the data and using months as the unit of time, these distributions were closer to a continuous mixture of geometric distributions, a necessary condition of our model. We could formally test the first-order Markov assumption by fitting a model of higher order, such as second order, and performing a likelihood ratio test.

Previous longitudinal analyses of physician visits and costs by Wang (2015) found that female survivors see physicians more frequently especially during pregnancy periods, and survivors receiving radiation therapy compared to the other treatment modalities, are at a higher risk of seeing physicians later on in life. Similarly, our results show that the probability of going on prescriptions is higher for females and this difference is highest during late reproductive and pre-menopausal years. Moreover, in general, survivors who

received any radiation tend to go on prescriptions more than survivors of other treatment modalities in the later years of an individual's life.

The benefit of a longitudinal analysis is that we can assess the estimated effects of predictors at each age, which cannot be achieved by a cross-sectional analysis. Our analysis provides insight into the prescription needs of childhood and AYA cancer survivors over the course of their lifetime. Prescription drugs are a substantial component of health service utilization, thus it is important to understand the prescription needs of this large survivor population in order to improve health care planning.

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Appendix A

Survivors vs. General Population

Figure A.1: Odds ratios of going on antihistamines for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

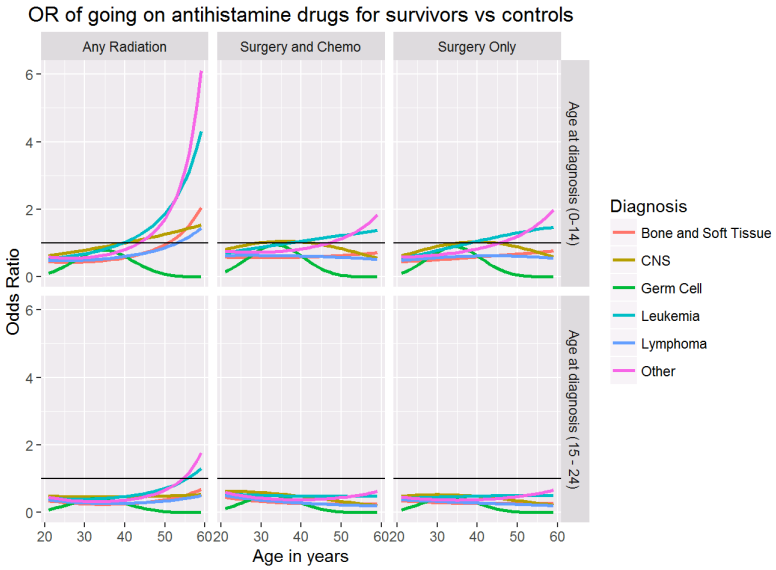


Figure A.2: Odds ratios of going on autonomic drugs for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

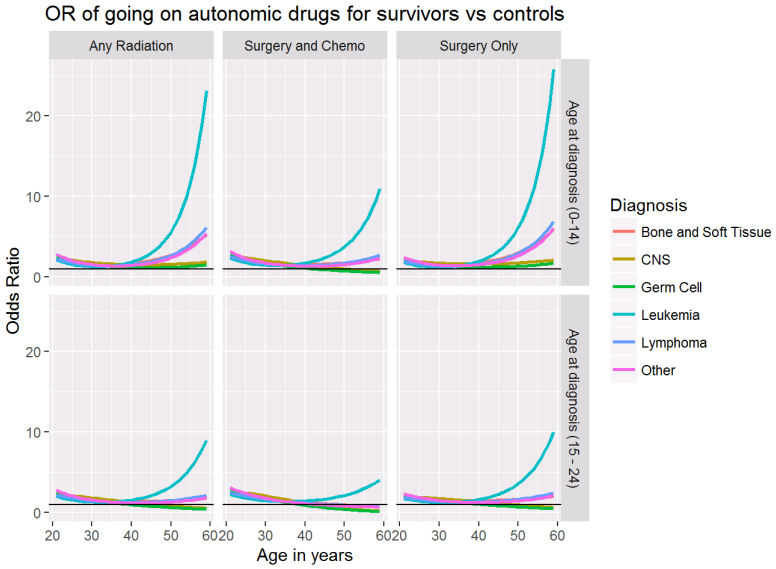


Figure A.3: Odds ratios of going on bloodformation drugs for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

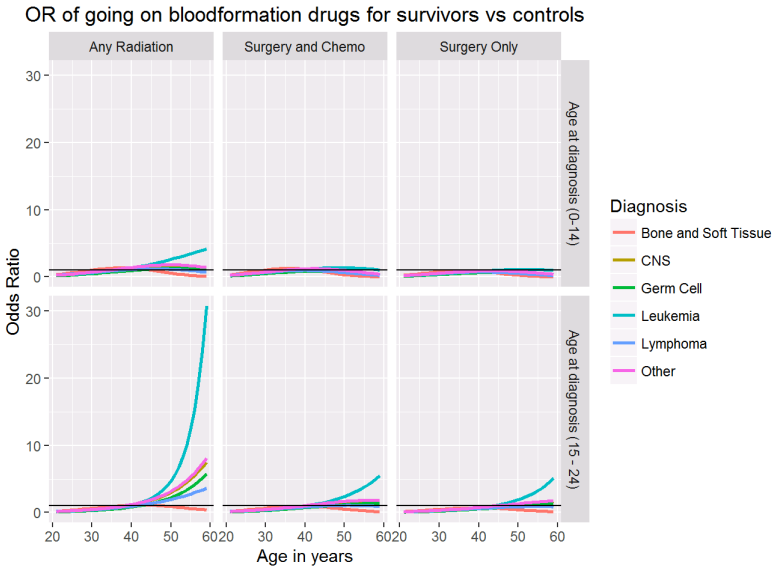


Figure A.4: Odds ratios of going on cardiovascular drugs for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

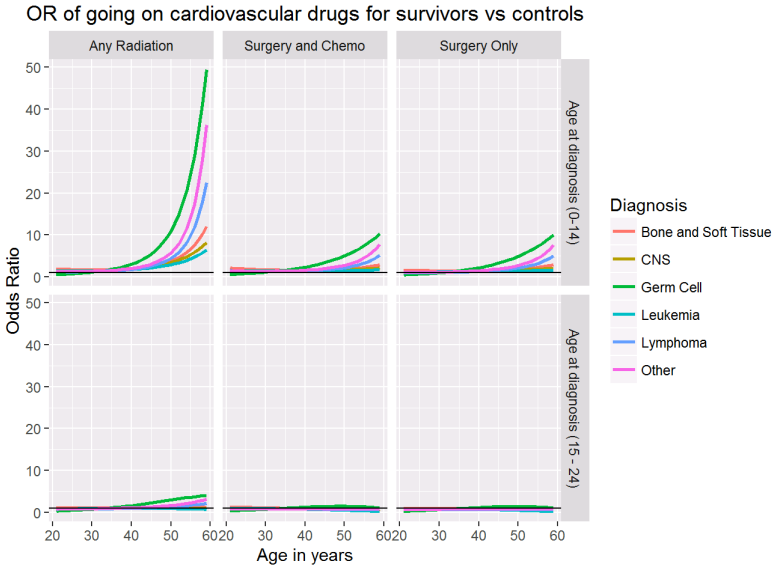


Figure A.5: Odds ratios of going on EENT drugs for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

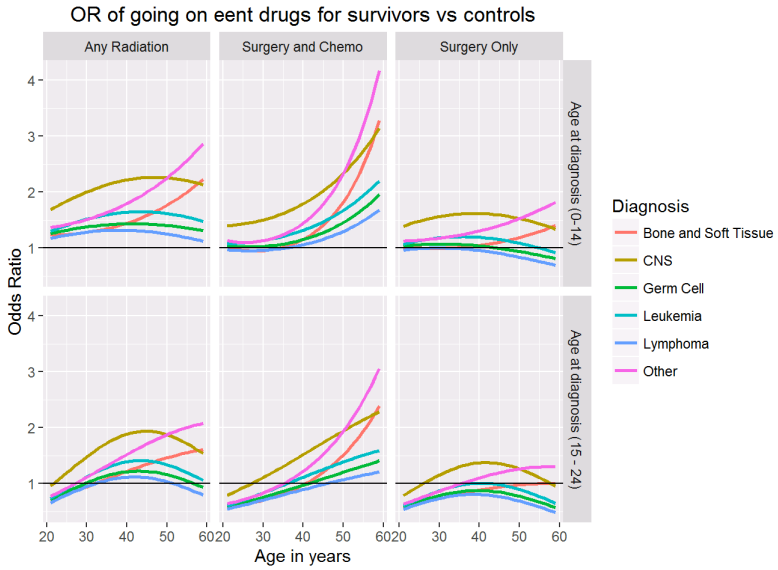


Figure A.6: Odds ratios of going on electrolytic drugs for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

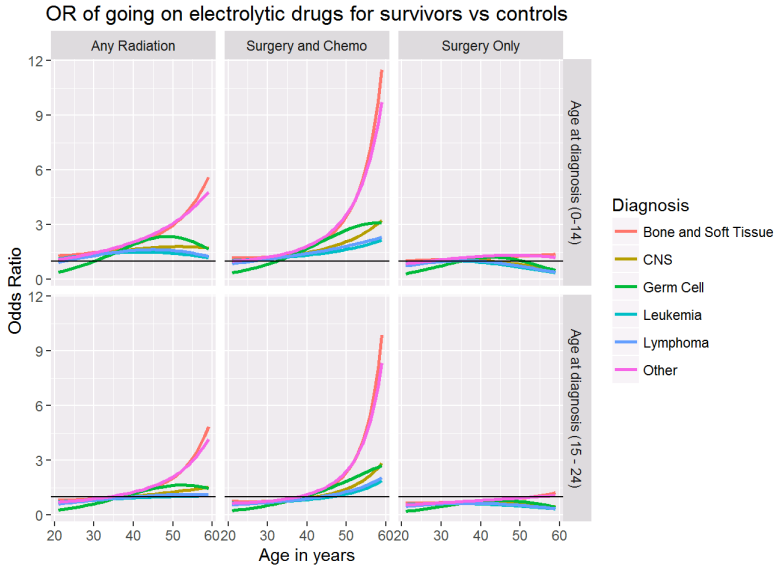


Figure A.7: Odds ratios of going on gastrointestinal drugs for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

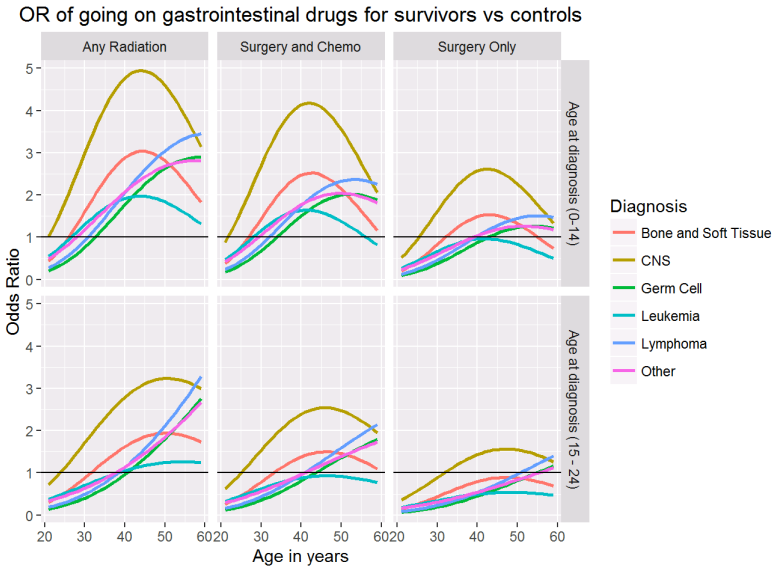


Figure A.8: Odds ratios of going on adrenal hormones for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

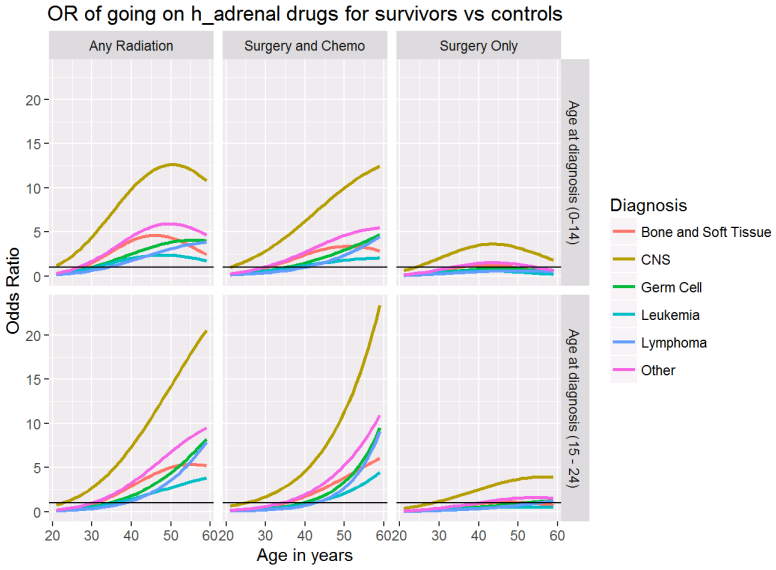


Figure A.9: Odds ratios of going on antidiabetic hormones for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

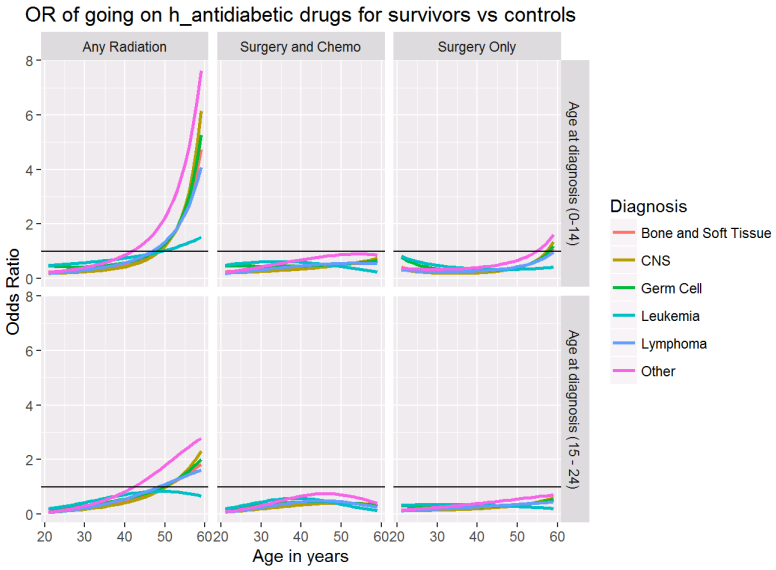


Figure A.10: Odds ratios of going on estrogen hormones for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

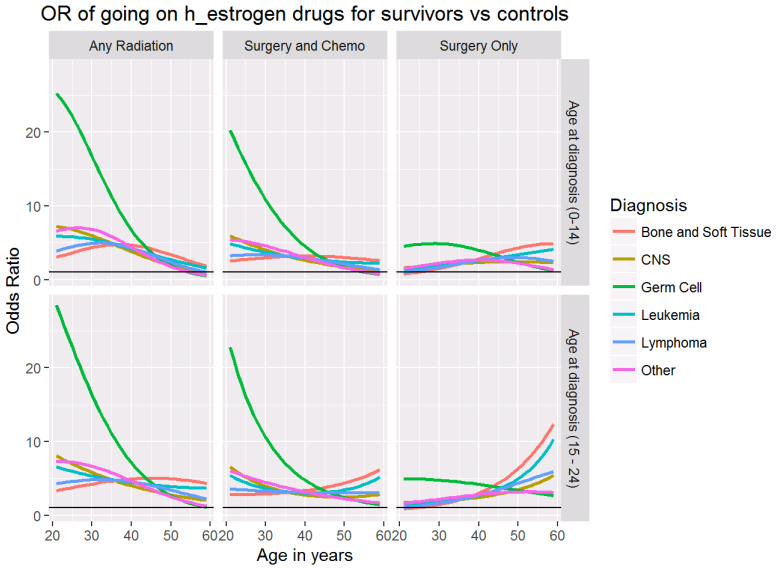


Figure A.11: Odds ratios of going on thyroid hormones for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

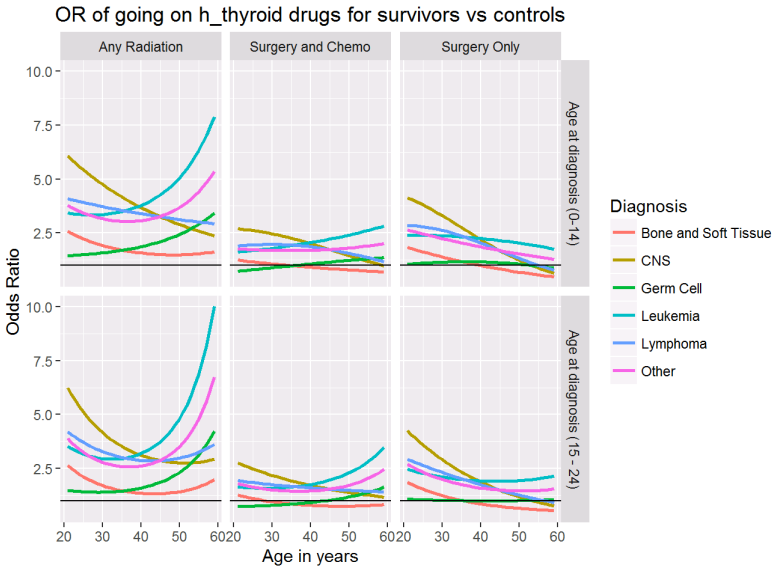


Figure A.12: Odds ratios of going on respiratory tract drugs for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

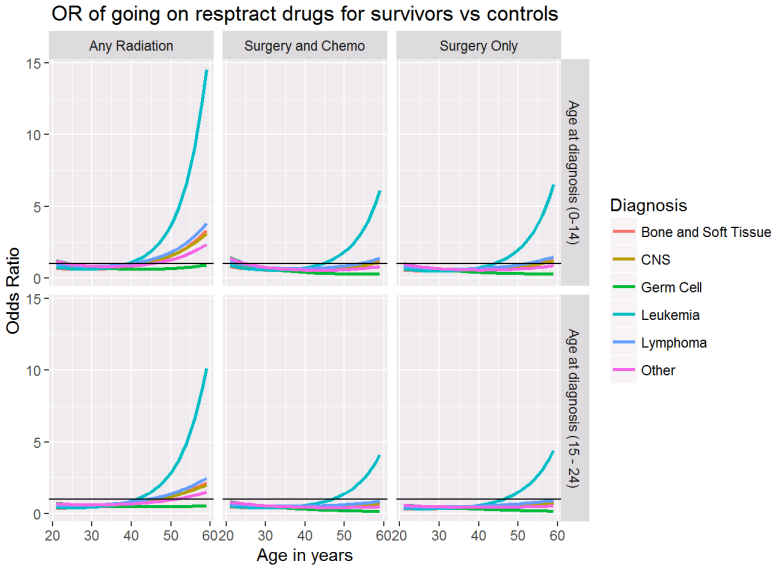


Figure A.13: Odds ratios of going on skin drugs for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.

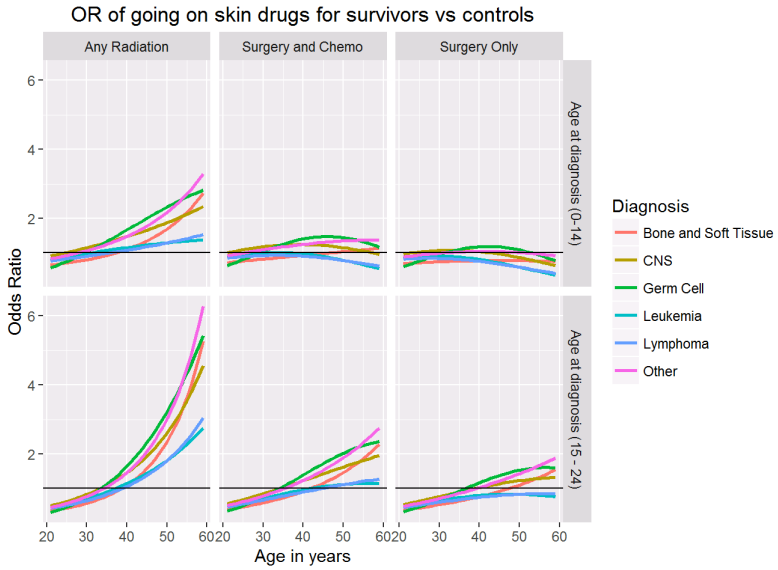
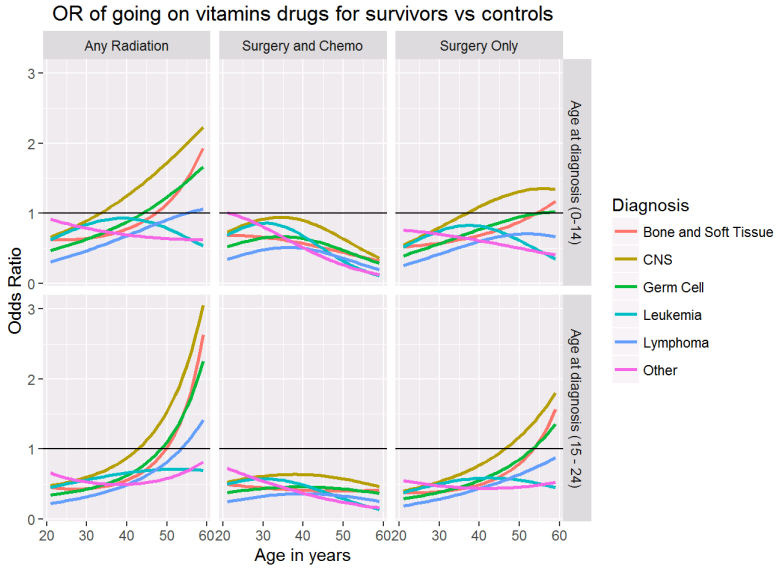


Figure A.14: Odds ratios of going on vitamins for survivors of each diagnosis, treatment modality, and age at diagnosis vs. the general population for given levels of the other predictors.



Appendix B

Among Survivors

Figure B.1: Odds ratios of going on prescriptions for female vs. male survivors for given levels of the other predictors.

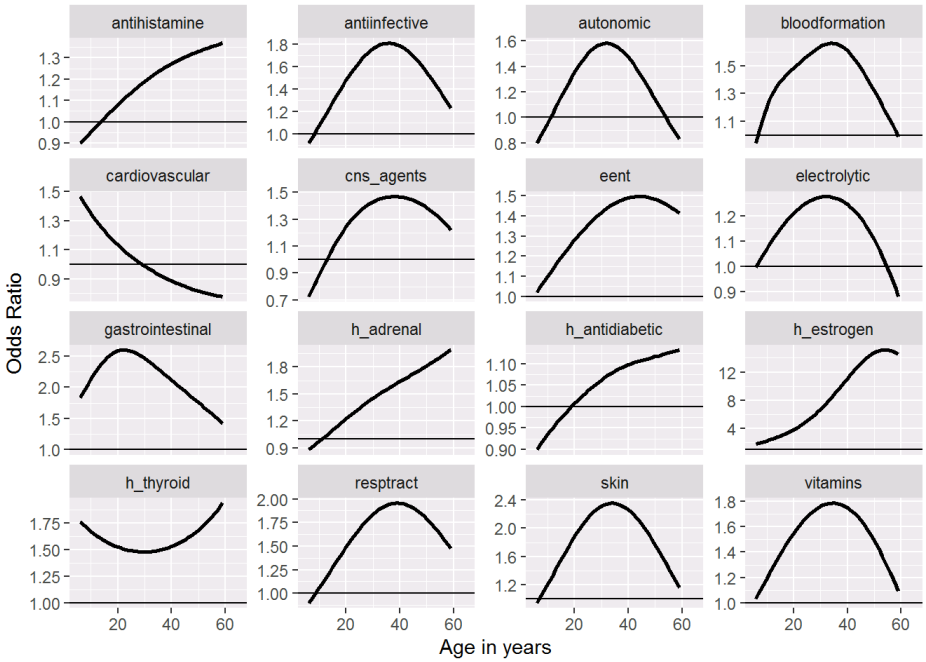


Figure B.2: Odds ratios of going on prescriptions for survivors of each cancer type vs. bone and soft tissue cancer, for given levels of the other covariates.

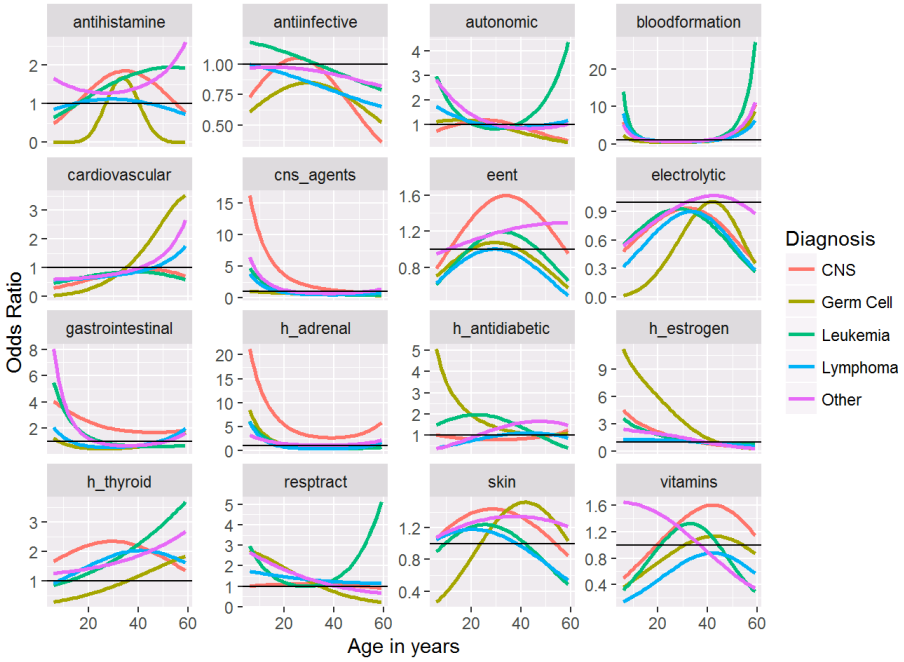


Figure B.3: Odds ratios of going on prescriptions for survivors in each treatment modality vs. surgery only, given fixed levels of the other covariates.

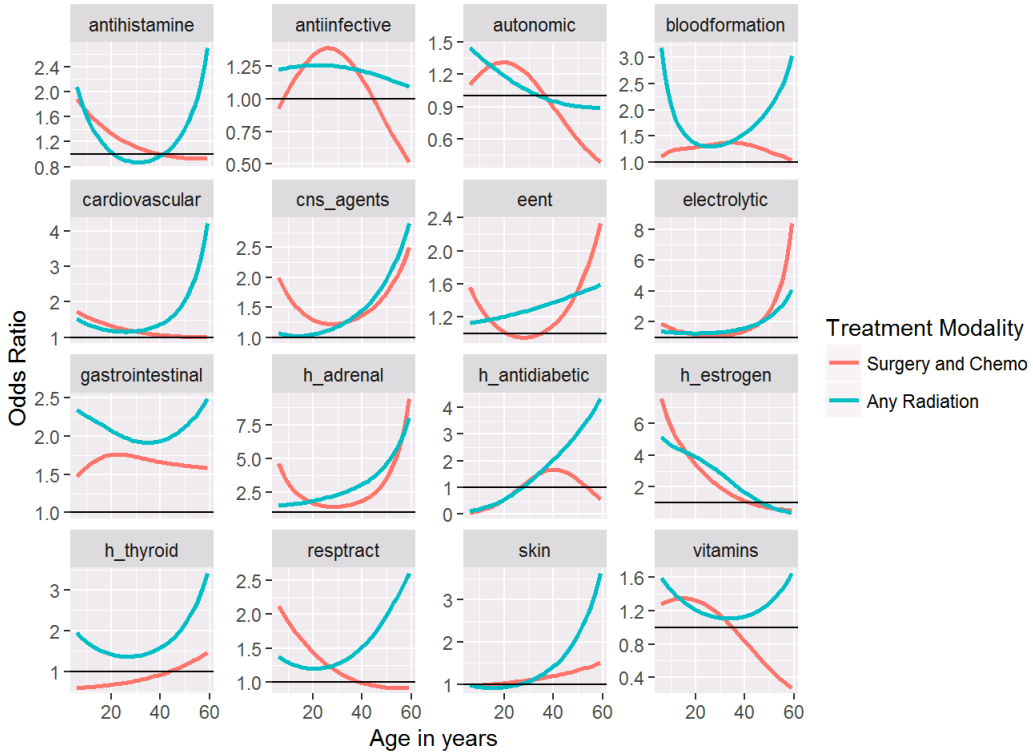


Figure B.4: Odds ratios of going on prescriptions for survivors diagnosed at age 15-24 vs. 0-14, given fixed levels of the other covariates.