ABSTRACT

YI, ZINAN. Anticipating U.S. Population-level Health Trends Based on Individual-level Dynamics to Inform Public Policy Decisions. (Under the direction of Dr. Maria Mayorga.)

This dissertation presents two applications of the combination of statistical analysis and discrete-event simulation (DES) to predict population-level health trends based on historical person-level information: (1) A Predictive Model of Smoking Prevalence Based on Individual Dynamics; (2) Predicting Liver Transplant Waiting List in the US Using Discrete Event Simulation.

The first application considers individual adult cigarette smoking trajectories in the US. In the first part, we use the Tobacco Usage Supplement to Current Population Survey (TUS-CPS) 2002-2003 Longitudinal Cohort dataset. A Markov model is built to characterize the transitions between any two of the five smoking states defined as: daily heavy, daily light, non-daily, former and non-smoker. Transition matrices are developed for the different groups (age 18-34 vs. age 35+; non-Hispanic White vs. non-Hispanic Black). By comparing the transition rates from the matrices, we investigate the differences in smoking behaviors between age groups, initial smoking states and race/ethnicities. Based on the Markov model, a discrete event simulation (DES) model is developed to forecast smoking prevalence through 2020. We also propose and test several scenarios for smoking reduction using the DES model. Then, we show how the simulation model can be applied to gain insights into smoking trajectories. Subsequently, we update the results (transition matrices and the comparisons) of the first part using the latest dataset: TUS-CPS 2010-2011 Longitudinal Cohort which became available in August 2015. In the end, we compare the two (8-year apart) longitudinal datasets, and study the changes in cigarette
smoking initiation, cessation, and relapse among U.S. adults.

In the second application, we aim to forecast the liver transplant (LT) waiting list in the US. The data is from the United Network of Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) Dataset Files. First of all, we used database to perform a retrospective cohort study of patients listed for liver transplantation in the US between 2003 and 2014. We examined yearly trends in patient attributes and performed competing risk regression and logistic regression analyses to evaluate factors associated with receiving a transplant versus waitlist removal for other reasons (dropout). We analyzed nationwide data as well as data from UNOS regions 5 and 11. Then, we use and analyze 2003-2014 waitlist data to characterize the demographic and clinical attributes of the patients (age, gender, race, diagnosis, etc). Then, the results from the analysis are used to parameterize a DES model we built to predict future LT waiting list trends through 2025 under different scenarios. Finally, we modeled the patients’ natural history and embedded this into the simulation model to predict the future.

This work contributes to the field of Operations Research in healthcare. We illustrate how mathematical, statistical and simulation methods can be applied to model processes in healthcare. Both projects use US population-level data. Thus, our results are nationally representative and informative to public health researchers and policy makers. While both projects are topic-specific, it is believed that many modules of the models in our study are generic and can be transferred and applied to other health care areas and will aid decision and policy makers in creating and evaluating possible interventions and policies.
DEDICATION

To My Parents
BIOGRAPHY

Zinan Yi was born on October 2nd, 1986, in Nanchang, Jiangxi, China. She received her Bachelor of Science degree in Computing and Information Science from Beijing Jiaotong University, Beijing, China in 2007. She then earned her Master of Science degree in Mathematics from Fudan University, Shanghai, China in 2010. Afterward, she came to North Carolina State University for her doctoral study in Operations Research.
ACKNOWLEDGEMENTS

This dissertation would not have been possible without the help of many people.

First of all, I would like express my sincere gratitude and appreciation to my advisor Dr. Maria Mayorga for her guidance, endless support, and encouragement. I am so grateful for her understanding and patience through out this special phase in my life. For me, she is not only a good advisor, but also set a role model for me as a woman. Her positive attitude toward life and work will continue influencing me as I start my new life. I would also like to thank all my committee members, Dr. Kristen Hassmiller Lich, Dr. Radmila Sazdanovic, and Dr. Javad Taheri. Without their suggestions and help, I would not be able to complete my dissertation.

Secondly, thank you to our wonderful collaborators. Dr. Kristen Hassmiller Lich, Dr. Jennifer Pearson, Dr. Stephanie B. Wheeler, Doctors A. Sidney Barritt IV, Eric S. Orman, and Paul H. Hayashi for being resourceful, initiative and willing to help me to learn.

Last but not least, I want to thank my family. Thank you to my dearest parents for their unconditional love for me in the past thirty years. Thank you to my husband Po-Chen for supporting and encouraging me over the past four years. Thank you to my little boy, Xi-Ao, for giving me another pair of eyes to observe this beautiful world, and for motivating and exploring my potential in every way.
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Chapter 1

Introduction

The application of mathematical modeling in the public health/policy areas has been very popular in recent years. For example, Markov models can be used to represent the discrete states of health, and to estimate the probability of transitioning from one state to another (Sonnenberg and Beck 1993); Markov Decision Processes (MDPs) are used for sequential decision making under uncertainty (Alagoz et al. 2010); Mixed integer programming models can be used for operating room scheduling (Cardoen et al. 2010), etc. Over the last decade, with the vastly increased supply of data, such as clinical trials and medical records, the integration of statistical and analytical modeling techniques has helped to inform public health research. Such methods enable policy decision makers to quantitatively estimate changes in policy, identify driving factors, and customize and recommend actions in several healthcare environments which include disease control and prevention, cost reduction, process optimization, etc. With the data availability, predictive modeling becomes a useful tool to inform the policy makers of possible future trends so that they can take precautions to the possible changes in the future (Toro-Diaz et al. 2014).
In this dissertation, we provide two examples of integrating statistical analysis and predictive modeling for healthcare management: (1) a model to predict future smoking prevalence and estimate the effectiveness of different smoking cessation policies, and (2) a model to predict future liver transplant waitlist size and composition. The two projects with similar methodological approaches are compiled together. The data for both projects are nationally representative. The first one uses the data from the Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2002-2003 and 2010-2011 Longitudinal Cohort and the second one uses the United Network of Organ Sharing Standard Transplant Analysis and Research (UNOS STAR) Dataset Files. Based on these data, we analyze and predict the US population-level health trends.

The remainder of this dissertation is organized as follows. Chapters 2 to 5 focus on project 1 (smoking model). Chapter 6 to Chapter 8 focus on project 2 (waitlist model).

In Chapter 2, we construct a Markov model for smokers’ transitions among five smoking states, defined as: daily heavy, daily light, someday, former and non-smoker, using the TUS-CPS 2002-2003 longitudinal data. We confine our study to people aged 18 to 80 and model younger (18-34) and older (35+) adults separately. Two transition matrices are developed for the two groups, respectively. From the two matrices, meaningful comparisons are made between age groups and smoking states. Based on the Markov model, we build a discrete event simulation model to forecast smoking prevalence through 2020. Then, we show how the simulation model can be applied to gain insights into smoking trajectories. To our knowledge, this is the first work to describe an adult individual’s transition between smoking states using a nationally representative sample.
In Chapter 3, we present an application of the simulation model built in Chapter 2. We propose several scenarios for smoking reduction, such as preventing kids (under age 18) from initiating smoking, stopping daily light smokers from progressing into daily heavy smokers. Though these scenarios are not real, they help us estimate the boundaries of the uncertain future, describing how the future may unfold as we choose different paths. It is also very helpful to public health decision makers who need to set a realistic target for future smoking prevalence. In addition to the hypothetical scenarios, we also examine the effect of a potential 94-cent federal excise tax increase, as proposed by President Obama in his fiscal year 2016 budget plan (www.tobaccofreekids.org).

In Chapter 4, we update the results of Chapter 2 by analyzing a newer dataset: TUS-CPS 2010-2011 Longitudinal Cohort which became available in August 2015, several months after the completion of the previous two chapters.

In Chapter 5, we compared the changes in cigarette smoking initiation, cessation, and relapse among U.S. adults by comparing the two longitudinal samples TUS-CPS 2002-2003 and 2010-2011. We quantified the changes between smoking states (daily-heavy, daily-light, non-daily, former and non-smoker) for the two longitudinal cohorts, and used a series of multivariable logistic regression models to examine the association of socio-demographic attributes and initial smoking states on smoking initiation, cessation, and relapse between waves within each cohort.

In Chapter 6, we used the United Network for Organ Sharing database to perform a retrospective cohort study of patients listed for liver transplantation in the US between 2003
and 2014. We examined yearly trends in patient attributes and performed competing risk regression and logistic regression analyses to evaluate factors associated with receiving a transplant versus waitlist removal for other reasons (dropout). We analyzed nationwide data as well as data from UNOS regions 5 and 11.

Chapter 7, a discrete event simulation (DES) model is built to predict future liver transplant trends through 2025. The model is informed by the characteristics of current patients including demographic (age, race, gender), and clinical (e.g., disease type) attributes and their dependencies upon each other. The data source is the UNOS STAR file, which contains all patient-level information for liver transplant wait list in the US. With the DES model, we predict future wait list size under different possible scenarios by altering the assumptions about the future liver availability, the number of patient arrivals and the effect of time on the time-varying attributes.

In Chapter 8, a modification to the DES model in Chapter 7 is conducted. Instead of using estimated waiting time to control patients’ length of stay on the list, a natural history model (the dynamics of MELD score) is developed and embedded into the simulation model so that when a liver becomes available, the system can assign the liver to the patient with the highest MELD score at the moment in the system. Compared with the DES model in Chapter 7, this model is closer to the real liver allocation system. Using this model, we also predicted future waitlist attributes under the same scenarios as in Chapter 7.
Chapter 2

A Predictive Model of Smoking Prevalence Based on Individual Dynamics

2.1 Introduction

The smoking patterns of individuals are complex and change over time (McClure et al. 2013). A clear understanding of distinct types of smokers is needed if we are going to substantially reduce tobacco use (Krupski et al. 2013). While smoker types are often classified in terms of their current smoking habits (smoking frequency, number of cigarettes smoked, type of cigarette smoked, etc.) (Bricker et al. 2009, Hassmiller et al. 2003, Luo et al. 2009), it is not unusual for the smoking habits of individuals to change over time. However, few studies consider how individuals’ habits change over time, or how they transition between types or statuses.
Tobacco control literature often represents transition between tobacco use states as linear, moving from initiation, to experimentation, to consistent use, to cessation. In literature that examines transition between smoking statuses, the transtheoretical model (TTM) of change is used widely to model the five stages smokers go through until they quit (Andersen 2007, Prochaska et al. 1992, Robinson and Vail 2012). Each stage describes the level of a person’s readiness to take the next step. In the TTM model, the transition among the stages usually only goes in one direction. Another popular model type is the Markov chain model (Killeen 2011, Yeh et al. 2012), which allows for transitions to occur between statuses. In a first-order Markov model, these transitions depend only on the current status and are independent of the past. In Markov chain models, a probability is given for each potential transition. Additionally, several papers (Fergusson and Horwood 1995, Mathur et al. 2014, White et al. 2009) have applied latent transition analysis developed from a more simplified Markov chain model to study more complex transitions. However, all of the above papers have focused solely on adolescent smokers except (Yeh et al. 2012) which focused on heavy smokers in rural areas. The simulation model SimSmoke (Levy et al. 2010, 2011) has been used to analyze the potential future effects of policy interventions. This model was informed by a first-order discrete time Markov chain model. However, the transitions probabilities used in the SimSmoke model are based on one year’s worth of data and are not reported explicitly by the authors.

In this study, we classified adult smokers’ smoking patterns by smoking intensity and developed a first-order Markov chain model for an individual’s transitions between smoking statuses. Previous studies describing transition probabilities were limited to adolescent smokers (Fergusson and Horwood 1995, White et al. 2009) or were not based on a nationally representative sample (Bondy et al. 2013, Yeh et al. 2012) or did not differentiate
age groups (Bondy et al. 2013). To our knowledge, our study is the first to describe the likelihood of an adult individual transitioning between current smoking statuses using a nationally representative sample. Killeen [2011] conceptualizes a three state Markov model which he uses to show long term abstinence rates when transition probabilities are estimated from previously published quit and relapse rates. Killeen states that “the Markov model embodies the dynamic nature of the cessation/relapse process; it permits stronger inference to long-term abstinence rates, provides measures of treatment efficacy, describes the outcomes of new quit attempts, and suggests mechanisms for the survival process” (pg.15549).

In this chapter, we provide such a Markov model that considers five smoking statuses and transitions that are age dependent. Based on the Markov model, we build a simulation model to predict future smoking prevalence in the U.S. through 2020. In the last part of the chapter, we show three applications of the Markov model to highlight how it can be used to gain insights into long term smoking trajectories.

2.2 Data and measures

Data for this analysis were drawn from the partial sample overlap from the 2002 Tobacco Use Supplement to the Current Population Survey (TUS-CPS) and the 2003 Tobacco Use Special Cessation Supplement (TUSCS-CPS) (N = 15,846) (William et al. 2007). Detailed information on survey methods is available elsewhere (Census Bureau 2004, National Cancer Institute 2006). Briefly, the purpose of these surveys is to monitor tobacco use behavior, attitudes, and norms at the national, state, and sub-state levels. Both surveys are nationally representative of the civilian, non-institutionalized U.S. population.
aged 15 years and older at the time the sample was collected. The sample was collected via address-based sampling and the majority of interviews were via telephone, with a smaller proportion collected in person (National Cancer Institute 2013).

To obtain our final sample of 15,410, first, we excluded 502 observations from respondents under 18 years of age to confine our analyses to adults. Second, we excluded an additional 78 participants from analysis because their smoking status in 2002 TUS-CPS or 2003 TUSCS-CPS could not be determined. A participant’s smoking status was deemed “undetermined” if he answered “refused” or “don’t know” to “Have you ever smoked more than 100 cigarettes in your entire life?”, or if he answered “don’t know,” “refused” or “no response” to “Are you currently smoking?” Third, for those who reported “yes” to “Have you ever smoked more than 100 cigarettes in your entire life?” in year 2002 but then reported “no” to the same question in 2003, we manually changed their smoking status in 2003 to “former smokers” which is explained in the next paragraph.

We created five statuses to represent distinct current smoking patterns: everyday heavy, everyday light, someday, former and non smokers. Non smokers had not smoked 100 lifetime cigarettes. All daily heavy, daily light, someday, and former smokers smoked at least 100 cigarettes in their lifetime. Both daily heavy and light smokers smoked “every day,” with light and heavy smokers consuming < 10 cigarettes and ≥ 10 cigarettes per day, respectively. All current smokers who reported non-daily smoking were grouped as “someday” smokers regardless of the number of cigarettes consumed on the days they smoke. Former smokers had smoked at least 100 cigarettes in their life but were not currently smoking. Using ages reported in the 2002 dataset, we further divided each smoking group into young adult (ages 18-34) and older adult (age 35+) subcategories, because
we believe that young and old adults exhibit different smoking behavior. The differences between younger and older adults is well documented in the literature. For example, Hassmiller et al. [2003] found that smokers aged 15 to 25 were more likely to be someday smokers than any of the older age groups. Furthermore, someday smokers on average were slightly younger than daily smokers. We want to further study this difference between age groups in this chapter.

The final sample was primarily female (59.2%), non-Hispanic White (82.2%), and had completed at least some college or had some degree (53.5%). Most of them were above age 35 (79.3%). The majority were non smokers in both 2002 (55.8%) and 2003 (52.7%) (Table 2.1).

2.3 Markov chain model

A Markov model is a very useful tool to model the changing dynamics of a system. In our case, it naturally embodies the dynamics of transitioning between different smoking stages. In addition, it can be used to predict future stages and the proportion of a cohort or population in each stage. Based on the data discussed above, we built a discrete time, first-order Markov chain model to estimate the probabilities of transitioning in any given year from one smoking state to another: daily heavy smoker (DHS), daily light smoker (DLS), non-daily smoker (SS), former smoker (FS), and non smoker (NS). This was done separately for each of the two age categories, resulting in two sets of 25 transition probabilities. Transition probabilities and the 95% confidence intervals (CI) of each proportion were estimated using SAS (Version 9.3) Procedure PROC FREQ. Table 2.2 shows the transition matrices we derived for the two age categories (young adult:
Table 2.1: Descriptive statistics of the TUS-CPS data used in the analysis

<table>
<thead>
<tr>
<th></th>
<th>2002 (%, SD)</th>
<th>2003 (%, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-</td>
<td>48.2(0.07)</td>
</tr>
<tr>
<td>Female</td>
<td>-</td>
<td>51.8(0.07)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-34</td>
<td>-</td>
<td>31.0(0.12)</td>
</tr>
<tr>
<td>35+</td>
<td>-</td>
<td>69.0(0.12)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>-</td>
<td>70.5(0.07)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>-</td>
<td>11.4(0.05)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>-</td>
<td>12.3(0.06)</td>
</tr>
<tr>
<td>Asian/Other</td>
<td>-</td>
<td>5.74(0.04)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>18.6(0.20)</td>
<td>16.6(0.21)</td>
</tr>
<tr>
<td>high school</td>
<td>29.3(0.25)</td>
<td>29.6(0.28)</td>
</tr>
<tr>
<td>Some college/associates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>degree/some other degree</td>
<td>26.6(0.28)</td>
<td>27.9(0.29)</td>
</tr>
<tr>
<td>Bachelor’s degree or higher</td>
<td>25.6(0.25)</td>
<td>25.9(0.26)</td>
</tr>
<tr>
<td><strong>Smoker Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily heavy smoker</td>
<td>4.9(0.15)</td>
<td>4.9(0.14)</td>
</tr>
<tr>
<td>Daily light smoker</td>
<td>9.9(0.15)</td>
<td>9.2(0.15)</td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td>4.2(0.12)</td>
<td>3.4(0.10)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>22.2(0.23)</td>
<td>27.2(0.25)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>58.7(0.32)</td>
<td>55.3(0.32)</td>
</tr>
</tbody>
</table>

18-34; older adult: 35+) separately. The values in the matrices represent the one year transition probabilities. For example, the probability of transitioning from DLS to SS is 0.45 for young adults. In both age groups, statistically equivalent proportions of non smokers remained non smokers between 2002 and 2003 (94.6% vs. 94.3%; p = 0.6448). However, a greater proportion of young adult non smokers transitioned to someday (1.35% vs 0.43%; p < 0.0001) or daily light smoking (0.87% vs 0.33%; p = 0.0015) than older adult non smokers. Further comparisons are provided in the applications section.
2.4 Simulating population dynamics

2.4.1 Baseline simulation model

Using the transition probabilities from the Markov chain model, we developed a simulation model to project smoking prevalence from 2002 - 2020. Figure 2.1 provides a conceptual overview of the model. We populated the model with 100,000 people using age and gender distributions based on the US demographic characteristics of people aged 18-80 from the 2000 US Census population tables (Census Bureau 2012, 2014). The smoking status distribution for each age by gender (e.g. 20-year-old females) is determined by the distribution of the same group in February 2002 TUS-CPS. New 18-year-olds enter the model each year, beginning in 2003. The number of male (female) 18 year-olds added to the model each year is equal to the multiplication of the current population size in the simulation model and the ratio of the number of male (female) 17 year-olds to the number of age 18-80 U.S. population in the previous year (Census Bureau 2012, 2014). Individuals enter the model with a smoking status given as either daily heavy smoker or non smoker. The probability of being assigned as an daily heavy smoker was equal to 18-year-olds’ mean smoking prevalence from 2002-2012 (NYTS) (CDC 2014e). The reason we used this discrete distribution between daily heavy smoker and non smoker is that NYTS did not provide the same smoking statuses as TUS-CPS. NYTS only has data for 2002, 2004, 2006, 2009, 2011 and 2012. The rest of the years (2003, 2005, 2007, 2008 and 2010) used the average value of the two closest years among 2002, 2004, 2006, 2009, 2011 and 2012. Each individual cycles among the five smoking statuses according to the Markov chain. People leave the model for two reasons: aging out, or death. We assumed that people aged 80+ were unlikely to transition between tobacco use states. So when people reach the age of 81, they leave the system. For death, we used age-specific,
gender-specific, all-cause mortality data from the 2002-2009 National Center for Health Statistics (NCHS) life tables to inform leaving the model due to mortality (CDC 2014d). For all circumstances in which future data were not available, we used linear prediction to project youth smoking prevalence and mortality data through 2020. We used Arena version 14.0 (Kelton W.D., Sadowski R.P., Sturrock D.T. 2014,?) to build the simulation. Using these parameters, our base model yields a smoking prevalence of 19.5% in the base year 2002, compared with 19.1% in 2002 TUS-CPS.

![Conceptual overview for the simulation model](image)

**Figure 2.1:** Conceptual overview for the simulation model

### 2.4.2 Calibrated simulation model

The smoking prevalence in 2002 from the CDC is 22.5% (CDC 2004), which was higher than 19.5%, the smoking prevalence in 2002 from our base simulation model. This may be due to several differences between the two surveys, including different sample frames, different data collection modes, and differential non-response bias (Schneider et al. 2012).
We wanted to calibrate our model to match the CDC in 2002 because the CDC result is more widely used. To accomplish this, we adjusted the initial population smoking status distribution proportionally which raised smoking prevalence to 22.5% without changing the total population size. In addition, to make the simulation more realistic, we allow for variation in the transition probabilities in the sense that the probability for every single transition of every single individual is sampled uniformly between the upper and lower bounds of each transition probability estimate and its 95% CI (Table 2). We ran the calibrated simulation model for five replications from which we obtained the average smoking prevalence in each year and their 95% CIs. Five replications were chosen because it was sufficient to achieve a 95% CI half-width about smoking prevalence of 0.5% for all years (Law AM, Kelton DW 2000). The results from the simulation model are discussed next.

### 2.4.3 Smoking prevalence from the calibrated simulation model and surveys

In Figure 2, we show the smoking prevalence from four different surveys: CDC (CDC 2004, 2005a,b, 2007, 2008, 2009, 2010, 2012, 2014c, BRFSS (CDC 2014b,e), NSDUH (CDC 2014e, NSDUH 2014b,c,d,e,f,g,a); , TUS-CPS 2002, TUSCS-CPS 2003 (??) from 2002 up to 2013, when available, and two simulation model predictions through 2020. CIs of the smoking prevalence from the two simulation models along with the available CIs from CDC are also shown in Figure 2. The other three surveys do not have CIs available. Please refer to Table 1 in the Appendix for the detailed values associated with Figure 2.2.

The trends of the four surveys are declining from 2002 to 2012, though they also experi-
enced increases in some years; such as NSDUH from 2011 to 2013. The CDC and BRFSS used the results from identical questions with TUS-CPS to define current smokers, while NSDUH used a different question: “have you smoked part or all of a cigarette in the past 30 days?” as the criterion (Ryan et al. 2012). This may explain why the CDC and BRFSS have similar values to each other but which differ greatly from NSDUH. The two points for TUS-CPS are the weighted smoking prevalence in year 2002 and 2003, calculated from the February 2002 TUS-CPS and February 2003 TUSCS-CPS data. 2011 is the first year BRFSS started using landlines and cell phones. Thus, data after 2011 is not comparable to previous years. Hence, the line connecting 2010 and 2011 is absent in the figure.

In both the base and calibrated simulation models the smoking prevalence quickly decreases in the first few years and then becomes stable, with a slight increase after year 2009. As we mentioned previously, in the calibrated model, we manually increased the initial smoking prevalence in 2002 to match the CDC value. The prevalence in 2012
of the calibrated model matched again with CDC. The two simulation models’ prediction for smoking prevalence in 2020 is 18.1% and 18.2%. The continuous pattern of our simulation is due to the assumption that smoking transitions do not change over time. New data could inform updated transition probabilities, as discussed in the limitations section. However, the simulation model framework is generalizable and can be rerun as new transition probabilities become available. Furthermore, the results of our simulation model provide more detail than CDC model estimates, such as the proportion of smokers in each category any given year (Figure 2.3).

Figure 2.3: Proportions of the five smoking states from 2002-2020 under the calibrated model
2.5 Applications of the Markov and simulation models

2.5.1 Comparison between age categories and smoking statuses

From the transition matrices estimated for younger adults and older adults, some meaningful observations can be drawn. We investigated differences in behaviors between age categories and between smoking statuses. The calculations were done by SAS (Version 9.3) Procedure PROC FREQ. We will use “younger” and “older” to stand for people in the 18-34 and 35+ age categories. “Relapse” is defined as a former smoker returning to any active smoking status (daily heavy, daily light or non-daily smoker). “Quit rate” is the probability for an active smoker becoming a former smoker.

The first three comparisons are made between the two age categories. As shown in the top panel of Table 2.3, from left to right are the results for the comparison of relapse rates between younger and older former smokers; the comparison of the quit rates between younger someday smokers and older someday smokers; and the comparison of the probabilities for a someday smokers to fall into more intensive smoking (DLS or DHS) between younger and older age categories.

Take the first comparison for example; the relapse rates for younger and older former smokers are 15.23% and 4.65% respectively. The difference of the two relapse rates and the corresponding 95% CI are 10.6% and (7.0%, 14.2%) with $p < 0.0001$. Then, we obtain the odds ratio (OR) which is 3.7 with its 95% CI being (3.0, 5.1). This means that the odds that a younger former smoker will relapse instead of stay quit is 3.7 times greater
than the odds that an older former smoker will relapse instead of stay quit. The rest of the table is interpreted in the same way. The odds for a younger non-daily smoker to quit instead of stay as a non-daily smoker is 2.1 times greater than the odds that an older non-daily smoker to quit instead of stay as a non-daily smoker (OR = 2.1, 95% CI: (1.5, 3.0), \(p < 0.0001\)). The odds for an older someday smokers to transition into more intense smoking instead of stay as a non-daily smoker is 3.0 times greater than the odds for a younger non-daily smoker transitioning into more intense smoking instead of stay as a non-daily smoker (OR = 3.0, 95% CI: (1.3, 3.0), \(p = 0.0014\)).

From these three comparisons, we can see that young smokers are more likely to quit and relapse, however, they are less likely to develop heavier smoking habits. The results seem to imply that young smokers have not developed as permanent smoking habits and are more likely to experiment than their older peers.

The bottom panel in Table 2.3 shows another four comparisons between smokers in different smoking statuses. First, we compared the quitting behavior between DLS and DHS. We found that DLS are more likely to quit than DHS in both age groups. In the 18-34 age category, OR is 2.15 (95% CI: (1.34, 3.45), \(p = 0.0012\)). In the 35+ age category, OR = 1.59 (95% CI: (1.21, 2.09), \(p = 0.0007\)). Second, we compared the likelihood of becoming someday smokers between DLS and DHS. The results show that DLS are more likely than DHS in both age groups. In the 18-34 age category, OR = 3.62 (95% CI: (1.45, 9.04), \(p = 0.0035\)). In the 35+ age category, OR = 3.01 (95% CI: (2.06, 4.40), \(p < 0.0001\)). The above four comparisons shed light on the differences between daily light and daily heavy smokers. While both types smoke every day, the number of cigarettes they consume per day has a big influence on their smoking behavior. Daily light smokers
have a much greater potential to switch to someday smoking or even quit smoking.

2.5.2 Investigating individual-level trajectories to understand smokers’ long-term smoking behavior

As we can see from the above comparisons, smokers have different smoking behaviors in terms of their smoking intensity and their smoking behaviors change over time. Understanding this changing mechanism is crucial to the public policy and clinical treatment area. One way to do this is to investigate the trajectories of smokers over time; our simulation model can provide this information.

As an illustration, we looked at the trajectory of 5000 18-year-old male non-smokers in 2002 through 2020. We ran the simulation once. Because there are thousands of different trajectories, it is necessary to put them into groups. Thus, we divided all the trajectories into four types. Type I: stay as non smoker; Type II: start smoking and continue for several years and then quit (become former smokers) for good through 2020; Type III: start smoking and continue smoking without ever quitting; Type IV: start smoking, then quit and relapse several times throughout the rest of the process. Trajectories for those who die during 2002 to 2020 are not considered, and this results in 4874 valid trajectories in 2020. Figure 2.4 shows the distribution of the trajectory types in the upper left chart. The other three charts show two trajectory examples for type II, III and IV. Type I trajectory is trivial and is thus omitted.

From the histogram of the trajectory types, we noticed that the two most common types are type I and type IV and each takes up nearly 40% of the total population. Type I
(stay a non smoker) is common, and this is no surprise because the probability for a non smoker staying as a non smoker is much higher than the probability of becoming a smoker. A large proportion of type IV smokers indicate that although people who begin to smoke are likely to attempt to quit, many are unsuccessful. The two examples for type IV show that the time spent as abstinent can vary.

For type II trajectories, the individual in example 2 stays as a non smoker from 2002 to 2005. In 2016, he/she reports as a former smoker. This means, between 2005 and 2006, he/she started smoking and then quit afterward. We don’t know what type of smoker the individual was when he/she was a smoker. In example 1 of type II, the individual first becomes an daily light smoker (DLS) in 2007 and stays as an DLS until 2009. At that
time, he/she smokes more and becomes an DHS. After this, he/she switches back and forth between DLS and DHS until 2019 when the individual becomes a former smoker. As discussed in the previous paragraph, the time spent as a former smoker can vary greatly between individuals. So, it is highly likely that type II and type IV are equivalent in the long run.

From these trajectory examples, we see that smokers do change and change often. From a public health perspective, we are not only interested in smokers’ current smoking intensity, but the length time they have been smokers is also very important. “Pack-years” is a useful measurement which takes into account both smoking intensity and time spent smoking, e.g., 1 pack-year means smokers smokes the equivalent one pack for one year, or two packs for 6 months, etc. Janjigian et al. [2010] showed that as the number of pack-years increased, the median overall survival of stage IIIB/IV non-small cell lung cancer decreased. Therefore, understanding the individual’s long term behavior, illustrated by this trajectory analysis, is another important aspect in the public health arena.

### 2.5.3 Time-to-event insights

In addition to predicting smoking prevalence, the simulation model allows us to conduct other types of analysis regarding the smoking patterns. We provide two examples here. First, we can investigate the mean time to events, such as mean time to cessation $T^C$ for daily light (heavy) smokers, defined as the average time it takes to transition from the daily light (heavy) state to the former state for the first time. e.g., a 45-year-old male daily light smoker needs 4.7 years on average to quit, and a 45-year-old male daily heavy smoker needs 5.3 years. A second example is mean time to initiation $T^I$, defined as the
average time spent in state NS (non smoker) before making a transition to any other smoking state. e.g., an 18-year-old male non smoker will move to another state in 5.8 years on average, and a 45-year-old male non smoker will do so in 5.2 years.

2.6 Conclusion

In this study, the change of individuals’ smoking patterns was modeled using a first-order Markov chain model which describes an individual’s transition between smoking statuses in terms of annual probabilities. Based on this, we developed a simulation model to predict future smoking prevalence through 2020. The simulation model can provide many insights about smoking prevalence and patterns beyond the year 2002. For example, we can obtain population level statistics: smoking prevalence in each year, proportion of smokers in each class in each year, average time to quit for each smoker type, and average time to initiate for a non smoker. The model also enables us to collect individual level statistics, such as individual smoking pattern trajectories, as shown in the application section.

As with any model, there are limitations to our study. One limitation is that the data we used is dated, but this is the latest longitudinal data available to us. Therefore, it may not be representative of current smoking patterns. However, the model in itself is a contribution, and model inputs can easily be updated as new data becomes available. Another limitation is that, although the smoking prevalence from our calibrated simulation model in year 2002 and 2012 matches the CDC values it neither matches those values from years 2003 to 2011, nor does it match those values found in other surveys. This raises further questions regarding other factors affecting tobacco use.
This study enables much future work. For example, given more extensive data, a more comprehensive model could be developed to account for other tobacco use characteristics that we did not account for in this model, such as menthol use. Secondly, time-inhomogeneous transitions could be considered, that is transition probabilities could change with time. Furthermore, the simulation model can be used to explore the future effects of different interventions aimed at impacting individual smoking patterns.
Table 2.2: Transition Matrices between all states, young adults (15-34) and older adults (35+) shown

### Transition probabilities — ages 18 – 34 (unweighted n = 3,002)

<table>
<thead>
<tr>
<th>2002 Smoking States</th>
<th>2003 Smoking States</th>
<th>Daily heavy smoker</th>
<th>Daily light smoker</th>
<th>Non-daily smoker</th>
<th>Former smoker</th>
<th>Non-smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily heavy smoker</td>
<td>70.1 (66.3, 74.0)</td>
<td>18.2 (14.4, 22.0)</td>
<td>1.7 (0.78, 2.5)</td>
<td>10.0 (7.8, 12.3)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Daily light smoker</td>
<td>18.1 (14.4, 21.8)</td>
<td>50.3 (44.7, 55.9)</td>
<td>6.7 (4.7, 8.6)</td>
<td>25.0 (20.6, 29.4)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td>5.3 (3.4, 7.2)</td>
<td>15.3 (10.9, 19.8)</td>
<td>24.5 (21.0, 28.0)</td>
<td>54.9 (50.3, 54.5)</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>3.9 (2.1, 5.7)</td>
<td>4.2 (2.9, 5.4)</td>
<td>7.7 (6.0, 9.31)</td>
<td>84.3 (81.9, 86.7)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>0.4 (0.3, 0.5)</td>
<td>1.0 (0.8, 1.2)</td>
<td>2.1 (1.5, 2.6)</td>
<td>2.4 (2.0, 2.7)</td>
<td>94.2</td>
<td></td>
</tr>
</tbody>
</table>

### Transition probabilities — ages 35+ (unweighted n = 12,408)

<table>
<thead>
<tr>
<th>2002 Smoking States</th>
<th>2003 Smoking States</th>
<th>Daily heavy smoker</th>
<th>Daily light smoker</th>
<th>Non-daily smoker</th>
<th>Former smoker</th>
<th>Non-smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily heavy smoker</td>
<td>71.8 (70.4, 73.2)</td>
<td>9.9 (8.9, 10.9)</td>
<td>4.8 (4.0, 5.6)</td>
<td>13.5 (12.3, 14.7)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Daily light smoker</td>
<td>21.5 (19.2, 23.7)</td>
<td>45.6 (43.2, 48.1)</td>
<td>11.6 (9.5, 13.8)</td>
<td>21.3 (19.1, 23.5)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td>13.0 (10.9, 15.0)</td>
<td>17.9 (15.5, 20.3)</td>
<td>31.4 (28.6, 34.2)</td>
<td>37.7 (34.7, 40.8)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.7 (1.5, 1.9)</td>
<td>1.1 (0.9, 1.3)</td>
<td>2.1 (1.8, 2.3)</td>
<td>95.1 (94.8, 95.5)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>0.5 (0.4, 0.6)</td>
<td>0.3 (0.2, 0.4)</td>
<td>0.7 (0.5, 0.9)</td>
<td>4.4 (4.1, 4.8)</td>
<td>94.1</td>
<td></td>
</tr>
</tbody>
</table>

23
<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Proportions (%)</th>
<th>Odds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>age</td>
<td>age</td>
</tr>
<tr>
<td></td>
<td>18-34</td>
<td>35+</td>
</tr>
<tr>
<td>1. Former smoker to active smoker&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15.7</td>
<td>4.9</td>
</tr>
<tr>
<td>2. Non-daily smoker to former smoker</td>
<td>54.9</td>
<td>37.7</td>
</tr>
<tr>
<td>3. Daily light smoker to former smoker</td>
<td>25.0</td>
<td>21.3</td>
</tr>
<tr>
<td>4. Daily heavy smoker to former smoker</td>
<td>10.0</td>
<td>13.5</td>
</tr>
<tr>
<td>5. Daily light smoker to non-daily smoker</td>
<td>6.7</td>
<td>11.6</td>
</tr>
<tr>
<td>6. Daily heavy smoker to non-daily smoker</td>
<td>1.7</td>
<td>4.8</td>
</tr>
<tr>
<td>7. Non-daily smoker to daily light smoker/daily heavy smoker</td>
<td>20.6</td>
<td>30.9</td>
</tr>
<tr>
<td>8. Non-daily smoker to daily light smoker</td>
<td>15.3</td>
<td>17.9</td>
</tr>
<tr>
<td>9. Non-daily smoker to daily heavy smoker</td>
<td>5.3</td>
<td>13</td>
</tr>
<tr>
<td>10. Daily light smoker to daily heavy smoker</td>
<td>18.1</td>
<td>21.5</td>
</tr>
<tr>
<td>11. Non-smoker to ever smoker&lt;sup&gt;b&lt;/sup&gt; among Non-Hispanic Whites</td>
<td>6.4</td>
<td>5.9</td>
</tr>
<tr>
<td>12. Non-smoker to ever smoker&lt;sup&gt;b&lt;/sup&gt; among Non-Hispanic Blacks</td>
<td>6.3</td>
<td>8.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Active smokers are: daily light, daily heavy and non-daily smokers.

<sup>b</sup>Ever smokers are daily light, daily heavy, non-daily and former smokers.
Chapter 3

Predicting Smoking Prevalence
Target for Healthy People 2030:
Exploring Scenarios by a Simulation Model

3.1 Introduction

Today, smoking prevalence is around 20% in the US adult population. Although it has declined by one half since 1964 when the first surgeon general’s report on smoking and health was released (?), it is decreasing at a much slower rate in recent years (CDC [2009]) and is far behind the ambitious healthy people 2020 target of 12% (Office of Disease Prevention and Health Promotion). Thus, smoking reduction is still a very important as it is known to cause tremendous harm to people’s health (?World Health Organization 2008). As efforts to reduce smoking prevalence have stagnated, new efforts are needed to
understand current trends and analyze the potential impact of different policies. In this chapter, smoking is defined as the use of cigarettes only, in other words, the use of cigar, e-cigarettes, or the other types of tobacco products is not considered.

We propose several scenarios for smoking reduction. Though these scenarios are not realistic, they help us estimate the boundaries of the uncertain future, describing how the future may unfold as we choose different paths. It’s also very helpful to public health decision makers who need to set a realistic target for future smoking prevalence. Previous works have studied or proposed some scenarios/interventions on smoking. For example, some studies include the effect of home smoking bans in smoking behavior during emerging adulthood (Mathur et al. 2014), the effect of a menthol ban on smoking prevalence (Levy et al. 2011), targeted efforts for special populations or raise smoking age to reduce smoking prevalence (Institute for Alternative Futures). Our scenarios target more general populations and do not specify the intervention details (e.g., home smoking ban), but rather, specify the possible outcomes of “interventions” (e.g., imagine some intervention that would result in all kids reaching the age 18 as non-smokers). In addition to the hypothetical scenarios, we also examined the effect of a potential 94-cent federal excise tax increase proposed by President Obama (www.tobaccofreekids.org).

We tested the performance of each scenario in terms of smoking prevalence in 2030 by a discrete event simulation (DES) model. DES is a useful tool in understanding the potential scenarios and in evaluating the effect of such policies. Méndez and Warner [2008], Warner and Méndez [2012] used a simulation model to predict the smoking prevalence from 2005 through 2020. In their model, they used initiation and cessation rates estimated from National Health Interview Surveys 1965-1993 data to forecast the smoking
prevalence in 2020. Levy et al. [2010] Levy et al. used a so-called SimSmoke model to
test three scenarios for dramatically reducing smoking prevalence through 2010. The
SimSmoke model has three smoking states: current smoker, never smoker and former
smoker. The dynamics among the three types of smokers are controlled by initiation rate
(never to current smoker), cessation rate (current to former smoker) and relapse rate
(former to current smoker). These rates are calculated from various surveys. Our simu-
lation model is built upon a first-order Markov Chain Model. To our knowledge, this is
the first chapter to predict the 2030 US adult smoking prevalence.

3.2 Method

3.2.1 Data

In this chapter, we use the data drawn from the partial sample overlap from the 2002
Tobacco Use Supplement to the Current Population Survey (TUS-CPS) and the 2003
Tobacco Use Special Cessation Supplement (TUSCS-CPS) (N=15,846) (William et al.
2007). Detailed information on survey methods is available elsewhere (Census Bureau
2004, National Cancer Institute 2006). Briefly, the purpose of these surveys is to mon-
itor tobacco use behavior, attitudes, and norms at the national, state, and sub-state
levels. Both surveys are nationally representative of the civilian, non-institutionalized
U.S. population aged 15 years and older at the time data was collected. The sample
was constructed through address-based sampling, and the majority of interviews were
via telephone, with a smaller proportion collected in person (National Cancer Institute
2013).
We used three questions from the survey to create five mutually exclusive smoking states: daily heavy smoker (DHS), daily light smoker (DLS), non-daily smoker (NDS), former smoker (FS) and non-smoker (NS). Please refer to Figure 3.1 for the details.

To obtain the final sample of 15,410. First, we exclude 358 observations from respondents under 18 years of age in 2003 to confine our analyses to adults. We will explain why we used responses from 2003 instead of 2002 in the next paragraph. Second, we exclude an additional 78 “indeterminate” participants because their smoking states in 2002 TUS-CPS or 2003 TUS-CPS are “indeterminate” (please see figure 1 for the definition). Third, for those respondents responded “yes” to Q1 in 2002 but then reported “no” to the same question in 2003 (n=1,020), we regard their answers as inconsistent during the two years and manually change their smoking states in 2003 to “former smokers (FS)”.

Figure 3.1: Flow of the survey questions
The reason we assign “FS” to them is due to the fact that, in 2002, about 70% of these people reported themselves as “FS”, remaining 30% were either someday or daily light smokers in 2002. Alternatively, if we labeled them as non-smokers in 2002, the smoking prevalence in 2002 would be 16.79% which is too low to be real. The impact that the above two assumptions have on our results is reported in Chapter 2.

In order to make our analysis representative of the US population, weights are applied to all the analysis in this chapter. Since the weights for this overlap sample are derived from February 2003 TUSCS-CPS weights, and only by using the responses in 2003 can we get the same demographic statistics as the official numbers (William et al. 2007), we decide to use the response from 2003 to divide the sample into different age groups. This is also why we use the ages from 2003 when we confine our study to adults, as mentioned in the above paragraph. Using ages reported in 2003, we further divided each smoking state group into young adult (ages 18-34) and older adult (age 35+).

### 3.2.2 The simulation model

The model we used to test different scenarios is the calibrated model described in detail in chapter Chapter 2.

### 3.2.3 Scenario analyses

In this section, we explore all the possible scenarios that might help decrease the smoking prevalence in the future through 2030. The first six “big” scenarios describe some extreme strategies because we want to know the lowest smoking prevalence that could be reached if we achieved the scenario. The last scenario is a real world situation where
we estimate the effect of the 94 cents increase in federal excise tax proposed by president Obama in his fiscal year 2016 budget plan.

Scenario 1: Kids never start. Scenario 1 is an ambitious plan which enables all 18-year-olds to enter their adulthood as non-smokers. Imagine we have very limited access to tobacco purchase, increase legal tobacco purchase age, or major national media campaign and changes in social norms. All these will help prevent adolescent smoking and thus make this scenario possible. To fulfill this in the simulation, instead of using the smoking prevalence from NYTS to assign a smoking status to every 18-year old, we will set all of them to be non-smokers when they enter the simulation system.

Scenario 2: Raise barrier to adult initiation. We want to see the effect if we control the adult initiation in age category 18-34 and 35+, respectively. We want to control this in a way that non-smokers in the corresponding age category will not initiate smoking, but non-smokers outside of the age interval are free. This ban will prevent non-smokers aged 18-34 or 35+ from initiating (scenario 2a and scenario 2b). That means, all 18 to 34-year-olds non-smokers will not start smoking and thus entering one of the other four smoking statuses. We have no restriction on those who are not non-smokers.

Scenario 3: Stop progression. There are two different sub-scenarios that we test, each controlling the transitions of someday smokers. First, we consider the 18-34 age category (scenario 3a), in which we prevent someday smokers from becoming daily smokers. In other words, we prevent someday smokers from becoming daily light and daily heavy smokers. This is accomplished in the simulation by setting the transition probability $p_{NDS,DLS}$ and $p_{NDS,DHS}$ equal to zero at the same time. We then repeat this same process
with the 35+ age category (scenario 3b), resulting in a total of two unique sub-scenarios.

**Scenario 4**: Directing initiation. This scenario models the hypothetical situation that we could control the movement of non-smokers, to discourage them away from daily heavy (scenario 4a and 4b) only and discourage them away from both daily light and daily heavy (scenario 4c and 4d). Then scenario 4 is tested by looking at four different sub-scenarios. First, we consider the 18-34 age category, in which we complete two independent runs of the model by applying scenario 4a and 4c ($p_{NS,DHS} = 0$ and $p_{NS,DHS} = 0$, $p_{NS,DLS} = 0$), respectively. We repeat this same process with the 35+ age category (scenario 4b and 4d), resulting in a total of four unique sub-scenarios.

**Scenario 5**: Redirecting heavy smokers. In our model, daily heavy smokers are the most intensive smoking group in terms of daily cigarette consumption. If we must have a high smoking prevalence, we would prefer more daily light or non-daily smokers instead of daily heavy smokers. Therefore, scenario 5 redirects daily heavy smokers to less intensive smoking statuses. This could be done by imposing a strict smoking policy in public, such that daily heavy smokers have less chance to smoke and their daily consumption will decrease to daily heavy smoker quantities. In the simulation, we set $p_{DHS,DHS} = 0$ to implement this. The scenario is tested in 18-34 and 35+ age group separately. They are labeled as scenarios 5a and 5b, respectively.

**Scenario 6**: Increase quit rate. Increasing quit rate is a very popular strategy in decreasing smoking prevalence. In this scenario, we are trying to promote cessation percentages from three smoking statuses, (daily heavy, daily light and non-daily) to former - by an absolute amount of 10% and deduct the same amount from transitioning to itself. This
strategy is tested in 18-34 and 35+ age group separately (scenarios 6a and 6b). After this, we increased the amount 10% to 20% and do a similar thing to the two age groups separately (scenarios 6c and 6d).

The above 6 big scenarios result in 15 different settings. Each is added to the base model independently so that we can examine the effect of a single change. Besides this, we also test the effect of the combination of any two of the 15 settings. This adds another 93 possible experiments (not all the combination make sense. For example scenario 2 implies scenario 4.). All the experiments are put into effect from the year 2015 forward to 2030. The smoking prevalence in year 2030 are collected and compared in the result section.

Scenario 7: A real-life scenario. Since all the above scenarios are not real interventions themselves, but rather represent some optimistic outcomes of potential interventions. We would like to use our simulation model to test the impact of one real life intervention. In President Obama’s fiscal year 2016 budget plan, he proposed increasing the federal excise tax on cigarettes by 94 cents per pack (www.whitehouse.gov). We would like see the effect of this potential increase. Price elasticity of smoking prevalence is defined as the percentage change of smoking prevalence resulting from 1% increase in price. The price elasticity reported in the literature is quite consistent. Most report that a 10% increase in cigarette prices reduces overall consumption by 2.5% to 5%; about half of this impact is on prevalence (impact of prevalence is from increasing smoking cessation, decreasing initiation and reinitiation (Chaloupka et al. 2002) and the rest is on the consumption of continuing smokers (Chaloupka et al.). Also, Levy et al. [2010] found that a 10% increase in price reduces prevalence by 3% for those ages 18 to 24; by 2% for those age 25-34; and by 1% for age 35+ . This is consistent with the finding by Tauras [2004] who found a
10% increase in price results in the increase of cessation probability (one way to reduce prevalence) by 3.5% in 18-32 year-olds. While the literature also mentions that a price increase has a larger effect in the long run than in the short run (Becker and Murphy 1988), we will not consider the time effect of price elasticity in this model.

These effects discussed above can be translated to our simulation in the following way: (i) The increase in the probability of cessation is from the increase of the following three probabilities: \( p_{DHS,FS} \), \( p_{DLS,FS} \), and \( p_{NDS,FS} \). (ii) Reduction in initiation is related to the increase of \( p_{NS,NS} \). (iii) Reduction of re-initiation is controlled by \( p_{FS,FS} \). (iv) The reduction of the consumption of the current smoker which can be reflected from the decreasing of \( p_{DHS,DLS} \), \( p_{DLS,NDS} \) and \( p_{DHS,NDS} \).

Figure 3.2 shows the breakdown of the price effect to the simulation model. Now, we need to decide the percentage change for each of the impacted probabilities, shown in the ellipses in Figure 3.2. From left to right, (i) \( p_{DHS,FS} \), \( p_{DLS,FS} \) and \( p_{NDS,FS} \) will increase by 3.5%. This is directly from the literature. For (ii) & (iii), we tested the percentage that \( p_{NS,NS} \) and \( p_{FS,FS} \) need to increase in order to results in a 1% - 2% increase in the smoking prevalence, using our simulation model. We found that 1% increase of the two probabilities is enough. For (iv), we assume that \( p_{DHS,DLS} \), \( p_{DLS,NDS} \) and \( p_{DHS,NDS} \) will also increase by the 3.5% as in (i).

Next, we need to determine the amount of the percentage change of these probabilities if there is a 94 cents increase in cigarette price. The latest average cigarette retail price in US we can find is $6.25 in 2015 (Campaign for Tobacco-Free Kids 2015). Thus, a 94 cents increase will result in a 15.04% increase in price. Then, (i) The probabilities of cessation
$p_{DHS,FS}$, $p_{DLS,FS}$ and $p_{SS,FS}$ will increase by $3.5\% \times 1.504 = 5.264\%$; (ii) Reduction in initiation, $p_{NS,NS}$, will increase by $1\% \times 1.504 = 1.504\%$; (iii) Reduction of re-initiation, $p_{FS,FS}$, will increase by $1\% \times 1.504 = 1.504\%$; (iv) The three probabilities $p_{DHS,DLS}$, $p_{DLS,NDS}$ and $p_{DHS,NDS}$ related to the reduction of consumption will increase by $3.5\% \times 1.504 = 5.264\%$.

By implementing these changes in the simulation model, we will be able to know the impact of this tax increase.

Figure 3.2: Decomposition of the total effect of a 10% increase in cigarette price. (All the values in the figure are from the literature)
3.3 Results

Table 3.1 shows the results for the base simulation model and the results under seven different scenarios. Smoking prevalence in 2030 is shown, along with the smoking type distribution in 2030. The base simulation has a 19.23% smoking prevalence in 2030. This means, if the current situation continues, the smoking prevalence in 2030 will be as high as 19.23%, which is not very optimistic. For the first 6 scenarios (a total of 15 sub-scenarios), the top five are colored in blue in Table 3.1. They are 6d, 5b, 2a, 6b, and 6c in the order from low to high prevalence in the result. Three of them are from scenario 6: increasing quit rate. Three out of the top five target the older age group: 35+. And the lowest smoking prevalence we can get for 2013 is scenario 6d: increase quit rate in age 35+ group by 20%.

For the rest of the scenarios, though scenario 1 appears to be very ambitious, it only helps reduce the smoking prevalence to 17.55% in 2030. It does not produce as much effect as other scenarios. However, trying to reduce adolescent smoking is still a very important task in public health. Scenario 2 has a better effect if targeted the age 18-34 category (scenario 2a, the 3rd best scenario), while scenario 3 has a better effect in age 35+ group (scenario 3b). This result confirmed an important message: different strategies should be applied to different age groups because they exhibit different smoking behaviors. Indeed, after combining the two scenarios (2a & 3b) in the simulation model, the smoking prevalence in 2030 reduces to 13.03%. Scenario 4 doesn’t seem to have much effect on reducing smoking prevalence. This may be due to the fact that transition probabilities of going from non-smoking to daily smoking are already very low (0.3% to 1%), so reducing them to zero does not have a large impact. Therefore, trying to guide the initiation of
Table 3.1: Results of the simulation model and under the seven scenarios

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>no.</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>1</td>
<td>The base simulation model</td>
</tr>
<tr>
<td>1</td>
<td>Kids never start</td>
</tr>
<tr>
<td>2a</td>
<td>Raise barrier to adult initiation</td>
</tr>
<tr>
<td>2b</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>Stop progression</td>
</tr>
<tr>
<td>3b</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>Direct initiation</td>
</tr>
<tr>
<td>4b</td>
<td>No daily heavy smoker</td>
</tr>
<tr>
<td>4c</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>No daily smoker</td>
</tr>
<tr>
<td>4d</td>
<td></td>
</tr>
<tr>
<td>5a</td>
<td>Redirect daily heavy smoker</td>
</tr>
<tr>
<td>5b</td>
<td></td>
</tr>
<tr>
<td>6a</td>
<td>Increase quit rate by 10%</td>
</tr>
<tr>
<td>6b</td>
<td></td>
</tr>
<tr>
<td>6c</td>
<td>Increase quit rate by 20%</td>
</tr>
<tr>
<td>6d</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>94 cents increase in federal excise tax</td>
</tr>
</tbody>
</table>

non-smokers is not an effective and efficient way to reduce smoking prevalence. Scenario 5 is similar to scenario 3. Both have a better performance when they are applied to the older age group, but scenario 5 produces an overall lower smoking prevalence than scenario 3. Therefore, if we combine scenario 2a with 5b, instead of 2a with 3b as discussed previously, the smoking prevalence drops to 11.14% in 2030, much lower than 13.03%. In fact, the combination of 2a and 5b is the best in all the combinations which are discussed in the next paragraph.

Next, we look at the results of the combination experiments. The best four scenarios’ results are plotted in Figure 3.3. Intuitively, the good combinations (those that result
in lower smoking prevalence in 2030) are from the combinations of two good single sub-scenarios. Although the blue line (Scenario 2a+5b) has the lowest smoking prevalence in 2030, the second best (red line: scenario 6c+6d) has lower smoking prevalence throughout the years. The third best (green line: scenario 1+6d) also has lower smoking prevalence than the blue line in most of the years. The last one (purple line: 2a+6b) may also be a good choice, if scenario 6b is easier to be implemented than other scenarios in real life. Therefore, all the four combinations could be potential prevalence reduction policies.

![Simulation results for the top 4 combination scenarios](image)

**Figure 3.3**

Lastly, the real tax intervention scenario is discussed. In the simulation model, the 94 cents increase in the federal excise tax will result in a smoking prevalence of 17.57% (half width: 0.20%) in 2030, compared with the predicted 2030 smoking prevalence of 19.23% (half width 0.39%) in the original base model. This means, the 94 cents increase will decrease the smoking prevalence by almost an extra of 2% in 2030. Actually, In June 2012, the Congressional Budget Office (CBO) studied the effect of a hypothetical 50-cent federal excise tax increase per pack of cigarettes. Adjusting this prediction for the 94
cents increase, it would result in a reduction in number of adult smokers by 2.6 million over 10 years (www.tobaccofreekids.org). In order to interpret this 2.6 million reduction, we did the following calculation. The adult smoking population in 2012 is 42.1 million (US Census Bureau). We assume that adult smoking population in 2015 is the same as 2012. Therefore, according to CBO, if a 94 cents increase were applied, the smoking population would become 42.1-2.6 =39.5 (million) in 2025. The official prediction for adult population in 2025 is 268.22 million (US Census Bureau). Thus, 2025 smoking prevalence would be 39.5/268.22=14.73%. This is 3% lower than our prediction. There are several possible reasons for the gap. First, it is possible that the official prediction overestimates the effect. Second, from our side, the transition matrices used to determine changing dynamics of smoker’s smoking states are derived from the 2002-2003 data. Thus, it may not reflect the actual behaviors of smokers in 2015. Third, the price elasticities from the literature maybe not accurate. Fourth, the population dynamics (the predicted demographic attributes (e.g., mortality rate by age)) in the simulation model may be different from the official prediction. Even though there is a gap between the two predictions, both agree on the positive impact of the tax increase on smoking prevalence reduction.

3.4 Discussion

In this chapter, we proposed six hypothetical scenarios for smoking prevalence reduction, and tested them along with another real-world intervention by the simulation model described in Chapter 2. The results shows that (1) The best intervention is to increase the quit rate; (2) The same strategy has different impact on different age groups; and (3) For the real-world intervention (scenario 7), both the simulation model and the official prediction showed a big decrease in smoking prevalence if the policy is applied.
The limitation of this work is the same as Chapter 2, i.e., the inherent model of the DES is a time-homogeneous Markov model. With the availability of the newer dataset which will be discussed in the next chapter, we will be able to produce more convincing results in terms of the absolute value. However, the current DES model is still a very useful tool to test whether an intervention is effective in decreasing the smoking prevalence.
Chapter 4

Individual Adult Cigarette Smoking Trajectories in the US: Results from the TUS-CPS Longitudinal Cohort

4.1 Introduction

Up until recently, tobacco control literature often represented an individuals’ smoking history as a one-way path, with transitions between distinct cigarette smoking patterns moving from initiation, to light smoking, to heavy smoking. This implicit model does not reflect actual smoking behavior and has recently fallen out of favor as research has highlighted the importance of light and non-daily smoking (Shiffman and Paty 2006, Klemperer and Hughes 2015). Evidence suggests that there is a significant amount of “churn” between current and former smoking states, with 48% of recent former smokers relapsing within 24 hours of their cessation attempt (Hughes et al. 2014, Borland et al. 2012) and approximately 62% relapsing within two weeks of quitting (Garvey et al.
1992). Additionally, there is significant movement between levels of smoking intensity, with smokers shifting from daily heavy, daily light, and occasional smoking statuses throughout their smoking careers (Bondy et al. 2013, McDermott et al. 2007). To date, these patterns have not been examined holistically using a U.S. national dataset.

The likelihood of occupying a certain smoking status or of moving between smoking statuses varies not only within a person’s lifetime, but also between groups of people. For example, young adults are more likely than older adults to quit smoking successfully (Messer et al. 2008), and non-Hispanic Blacks start smoking later than non-Hispanic Whites (Sterling and Weinkam 1989, Kandel et al. 2004). While non-Hispanic Black smokers make more attempts to quit, non-Hispanic White smokers are more successful at staying quit (Fu et al. 2008, Royce et al. 1993). These population-level averages suggest that the implicit model of escalating smoking with increasing age to a plateau is more complex than previously assumed. Few studies have comprehensively reported how individuals’ smoking states change over time. Examination of the rate of transition between smoking states is a first step in constructing a model to project the effect of tobacco use or tobacco control policies on long-term population-level outcomes.

The purpose of this study was to estimate transition rates between five smoking states reflecting variation in the intensity of smoking among US adults: daily heavy smoker, daily light smoker, non-daily smoker, former smoker and non-smoker. A secondary objective was to study the transitions between smoking states in younger (18-34 year olds) compared to older (35+ years old) adults and in non-Hispanic White (NHW) compared to non-Hispanic Black (NHB) adults. Previous studies describing the transitions between smoking states have been limited to adolescent smokers, White et al. [2009], Fergusson
and Horwood [1995], Mannan and Koval [2003], Mathur et al. [2014] are not based on a nationally representative sample (Yeh et al. 2012, Bondy et al. 2013), are focused on a subset of transitions and reported only odds ratios as a measure of differences (Hassmiller et al. 2003), or did not differentiate between age or race/ethnicity groups (Bondy et al. 2013). To our knowledge, this is the first study to describe the likelihood of individuals transitioning between a broad set of smoking states across the adult life course and by race/ethnicity using a nationally representative sample.

4.2 Methods

4.2.1 Data and sample

This secondary data analysis was conducted in 2015, using data from the Tobacco Use Supplement to the Current Population Survey (TUS-CPS) May 2010-11 TUS-CPS Longitudinal Cohort (N=28,153). Detailed information on survey methods is available elsewhere (US Department of Commerce 2015). Briefly, the purpose of the TUS-CPS is to monitor tobacco use behavior, attitudes, and norms at the national, state, and sub-state levels. It is nationally representative of the civilian, non-institutionalized U.S. population. The sample was constructed through address-based sampling, and the majority of interviews were via telephone, with a smaller proportion collected in person (National Cancer Institute 2013).

To obtain the final sample of 18,393, we first excluded 9,654 observations from proxy respondents because full information about the target respondent (e.g. number of cigarettes smoked per day) was not collected. Second, we excluded an additional 106 participants
from analyses because their smoking states in the 2010 or 2011 TUS-CPS could not be determined. A participant’s smoking state was deemed “indeterminate” if he/she answered “refused” or “don’t know” to “Have you ever smoked more than 100 cigarettes in your entire life?”, or if he/she answered “don’t know,” “refused” or “no response” to “Are you currently smoking?” In total, 0.5% of the adult population was excluded from our analyses because their smoking status could not be determined. Finally, a proportion of respondents had inconsistent smoking status reports between the 2010 and 2011 observations. “Inconsistent” responders were defined as individuals who responded “yes” to “Have you ever smoked more than 100 cigarettes in your entire life?” in 2010 but reported “no” to the same question in 2011 (n=1,041). In 2010, about 75% of these participants identified themselves as former smokers, with the remaining 25% identifying as either non-daily, daily light, or daily heavy smokers. Because these participants had previously identified themselves as some form of smoker, we assumed that their 2010 response to lifetime smoking was correct and changed their 2011 smoking state to “former.” In sensitivity analyses we compare this classification approach with results from an analysis where we excluded these inconsistent responders, our qualitative findings were not sensitive to this assumption.

4.2.2 Measures

The overlap sample included adults age 18 and over; four race/ethnicity groups (Hispanic, non-Hispanic White, non-Hispanic Black, and non-Hispanic Other); and 18 educational attainment categories (e.g. less than 1st grade, 2st grade, 12th grade, high school grad-diploma or GED, some college but no degree, bachelor’s degree, professional degree, etc.) (William et al. 2007). We defined young adulthood as 18-34 because prior research
has shown that quitting smoking by age 35 significantly reduces the risk of smoking- attributable death (Prabhat et al. 2013). While young adulthood may also be defined as 18-24, we included 25-34 as transitional years that capture the shift from early young adulthood experimentation to older adult stability and to increase sample size to allow comparisons between young and older adults (Green et al. 2007). Educational attainment was aggregated into four categories: less than high school (any grade up to 12th grade with no diploma), high school degree/GED (high school grad-diploma or GED), some college/associates degree/some other degree (some college but no degree, associate degree, associate degree-academic), and bachelor’s degree or higher (bachelor’s degree, master’s degree, professional degree, doctorate degree).

We created five states to represent mutually exclusive smoking patterns: daily heavy smoker, daily light smoker, non-daily smoker, former smoker, and non-smoker. Respondents who had not consumed 100 lifetime cigarettes were classified as non-smokers. All the other four smoker types are restricted to respondents who had smoked at least 100 cigarettes in their lifetime. Both daily heavy and daily light smokers reported that they smoked daily, with daily light smokers consuming ≤ 10 cigarettes and daily heavy smokers consuming > 10 cigarettes per day. To be consistent with other literature, we chose ≤10 cigarettes/day as the criterion for light smoking. All current smokers who reported non-daily smoking were grouped regardless of the number of cigarettes they consumed on the days they smoked. Former smokers had smoked at least 100 lifetime cigarettes, but were not currently smoking. We further divided each smoking state based on age (young adults [ages 18-34] and older adults [age 35+]), and race/ethnicity (non-Hispanic Whites [NHW] and non-Hispanic Blacks [NHB]); we did not examine smoking dynamics among Hispanic or Non-Hispanic “other” race/ethnicities due to a limited sample of smokers in
4.2.3 Statistical analysis

We quantified transitions between smoking states at two time points (2010 and 2011) that were 12 months apart, overall and by age (young adults vs older adults) and race/ethnicity (non-Hispanic White vs non-Hispanic Black). For each group (age or race/ethnicity by initial smoking state), we report the proportion that transition to each of the five smoking states in 2011.

We estimated each proportion that transitioned between states and corresponding 95% confidence intervals around our estimates (CI) using the PROC SURVEYFREQ procedure in SAS (Version 9.3, SAS Institute, Cary, NC). To account for the complex survey study design and response rate, we employed the main and replicate weights provided with the data as recommended for the TUS-CPS overlap sample (US Department of Commerce 2015). Consistent with similar analyses, the replicate weights for this overlap sample were derived using balanced repeated replication (BRR) (William et al. 2007).

4.3 Results

Table 4.1 presents descriptive statistics for the weighted analytical sample. The weighted sample was primarily female (51.7%), aged 35+ (69.2%), and non-Hispanic White (68.0%). In 2010, 28.0% completed at least some college and 30.3% had at least a bachelor’s degree. The majority of participants were non-smokers (64.8%), followed by former smokers (19.6%), daily heavy smokers (7.1%), daily light smokers (5.1%), and non-daily smokers (3.4%). Between 2010 and 2011, there was no change in the proportion of daily light smok-
ers, but there were decreases in the proportion of daily heavy smokers (-0.6%, \( p < 0.0148 \)), non-daily smokers (-0.7%, \( p = 0.0093 \)), and non-smokers (-4.8%, \( p < 0.0001 \)). Additionally, 6% more individuals in the cohort identified as former smokers in 2011 as compared to 2010 (\( p < 0.0001 \)).

Table 4.1: Descriptive statistics for the TUS-CPS 2010-2011 weighted sample

<table>
<thead>
<tr>
<th>Time-invariant sociodemographic characteristics</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48.3 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51.7 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-34</td>
<td>30.7 (0.02)</td>
<td></td>
</tr>
<tr>
<td>35+</td>
<td>69.2 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>68.0 (0.02)</td>
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</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>11.4 (0.01)</td>
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<tr>
<td>Hispanic</td>
<td>13.9 (0.02)</td>
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<tr>
<td>Other</td>
<td>6.6 (0.01)</td>
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<th>Time-varying sociodemographic characteristics</th>
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<tbody>
<tr>
<td>Education</td>
<td></td>
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<tr>
<td>Less than high school</td>
<td>13.1 (0.17)</td>
<td>11.7 (0.16)</td>
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<tr>
<td>High school degree/GED</td>
<td>28.6 (0.21)</td>
<td>27.9 (0.23)</td>
</tr>
<tr>
<td>Some college/associates degree/some other degree</td>
<td>28.0 (0.22)</td>
<td>29.7 (0.21)</td>
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<tr>
<td>Bachelor’s degree or higher</td>
<td>30.3 (0.22)</td>
<td>30.8 (0.23)</td>
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<table>
<thead>
<tr>
<th>Smoking states</th>
<th>2010</th>
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<tr>
<td>Daily light smoker</td>
<td>5.1 (0.11)</td>
<td>5.0 (0.12)</td>
</tr>
<tr>
<td>Daily heavy smoker</td>
<td>7.1 (0.12)</td>
<td>6.6 (0.11)</td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td>3.4 (0.09)</td>
<td>2.7 (0.08)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>19.6 (0.15)</td>
<td>25.8 (0.19)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>64.8 (0.23)</td>
<td>60.0 (0.25)</td>
</tr>
</tbody>
</table>

\( ^a \)SD: standard deviation
Young adults vs. older adults - transitions between smoking states

In 2010, daily light and non-daily smoking were more common among young adults (6.2% and 4.8%) than older adults (4.6% and 2.8%; \( p < 0.001 \) for all comparisons). Conversely, daily heavy smoking was more prevalent among older adults (7.8% versus 5.7%). Among young adults 73.3% were non-smokers, compared to 61.0% older adults, while fewer young adults than older adults were former smokers (10.1% vs. 23.7%; \( p < 0.0001 \)).

Table 4.2 presents the proportion of individuals transitioning between smoking states in 2010 and 2011, stratified by age. In both adult age groups, the majority of individuals who were non- and former smokers in 2010 remained non- and former smokers in 2011. Among smoking states, daily heavy smoking was the most difficult state to escape for all adults, with 53.7% of young adult heavy smokers and 67.2% of older adult heavy smokers remaining heavy smokers in 2011. The most common pathway out of daily heavy smoking for young adults was transitioning to quitting (25.3%), followed by daily light smoking (18.1%), and transitioning to non-daily smoking (2.9%). Similarly, as a pathway out, the largest percentage of older adult heavy smokers quit smoking (15.9%), followed by transitioning to daily light (13.8%) or non-daily smoking (3.1%).

Table 4.3 presents comparisons of smoking state transition probabilities. Overall, the odds of smoking relapse (from former smoking to any current active smoking state) were higher among young adults than older adults (OR=3.36; \( p < 0.001 \)), while the odds of cessation were higher for young adult smokers than their older adult counterparts, in both daily heavy (OR=1.79, \( p < .0001 \)) and daily light (OR=1.47, \( p < 0.0001 \)) smokers. Daily light smokers were more likely to quit than daily heavy smokers in both age categories (young adults: OR=1.16, \( p > 0.5 \); older adults: OR=1.41, \( p < 0001 \)). Furthermore, daily
light smokers were more likely to become non-daily smokers than daily heavy smokers in both age categories (young adults: \( \text{OR}=3.17, p < 0.0001 \); older adults: \( \text{OR}=3.82, p < 0.0001 \)).

**Non-Hispanic Whites vs. Non-Hispanic Blacks - transitions between smoking states**

Table 4.4 presents the proportion of individuals transitioning from a given smoking state in 2010 to a given smoking state in 2011, stratified by race/ethnicity (non-Hispanic White and non-Hispanic Black). Overall, statistically equivalent proportions of non-Hispanic Black and non-Hispanic White participants initiated smoking between 2010 and 2011 (8.0% vs. 7.5%, \( p = 0.3295 \)). However, significantly more non-Hispanic Black non-smokers became daily light smokers than non-Hispanic White non-smokers between 2010 and 2011 (1.0% vs. 0.6%, \( p = 0.0007 \)). Daily heavy smoking was “stickier” among non-Hispanic White than non-Hispanic Black smokers (\( \text{OR}=2.17; p < 0.0001 \)). Among individuals who were daily heavy smokers in 2010, there was more movement towards daily light smoking (26.4% vs. 13.9%, \( p < 0.0001 \)) and quitting (23.0% vs. 17.3%, \( p = 0.0158 \)) among non-Hispanic Blacks than Whites. A higher proportion of non-Hispanic White non-daily smokers remained in this state in 2011 compared to non-Hispanic Black non-daily smokers (33.2% vs. 23.8%, \( p = 0.003 \)); however, transition from non-daily to daily light smoking was more common among non-Hispanic Blacks than non-Hispanic White participants (33.0% vs. 19.8%, \( p < 0.0001 \)).
4.4 Discussion

Overall within the cohort, this study reveals positive trends in smoking patterns, with daily heavy smoking decreasing as the proportion of former smokers increased. We found that daily heavy smoking is a more difficult state to escape compared to daily light smoking and that non-daily smokers are more likely to quit than daily smokers. This was consistent between age categories and findings are similar to those from other studies. For example, Yeh et al. found that among daily smokers, those who smoked fewer cigarettes were more likely to quit (Yeh et al. 2012). In another study, Bondy et al. [2013] analyzed transitions between daily, non-daily and former smoking over three six-month follow-ups. They found that those transitioning from daily to non-daily smoking (between time points one and two) were more likely to become former smokers (in time point three) than those who remained daily smokers. However, transitioning from daily to non-daily smoking also carries a greater risk of returning to daily smoking compared to those who transitioned from daily directly for former.

We observed some differences in smoking transitions by age group. As expected, we found that non-daily and daily light smoking were more common among young adults than older adults. Similar to our findings, Hassmiller et al. [2003] found that smokers aged 15 to 25 were more likely to be non-daily smokers than any older age group. We also observed that young adult smokers were more likely to quit (transition from active to former smoker) and relapse (transition from former to active smoker) than older smokers. Similarly, revealed an inverse association between quit attempts and age, as young adults had the highest prevalence of attempting to quit (48.5%) and those 65 years of age or older had the lowest prevalence (34.6%). These data support the understanding that young adults
are in a critical developmental phase when they are developing lifetime smoking patterns, and highlight the potential for targeted prevention and smoking cessation interventions to make a significant impact on public health.

We also considered differences in smoking transitions by race/ethnicity. We found that daily heavy and non-daily smoking states were stickier for non-Hispanic White than non-Hispanic Black smokers. We also observed that non-Hispanic Black daily heavy smokers were more likely to quit or become daily light smokers than non-Hispanic White smokers. Our conclusions contradict findings from previous studies suggesting that non-Hispanic White smokers are more likely to stay quit (Fu et al. 2008, Royce et al. 1993) and have a higher quit ratio than non-Hispanic Black smokers (?). This may be due to our definition of smoking states, which disaggregates daily from non-daily smoking and stratifies by smoking intensity; different age distributions in the non-Hispanic White and Black smoker populations; greater use of non-cigarette tobacco products among non-Hispanic Blacks; or an actual recent narrowing in the disparity in successful quitting between non-Hispanic White and Black smokers. Replication in other datasets with different smoking definitions and a holistic assessment of non-cigarette tobacco use is necessary to assess whether these findings are indicative of a narrowing in the previously observed disparity in cessation by race/ethnicity.

**Limitations**

As with any study, our study has several limitations that deserve attention. First, we did not consider forms of tobacco use other than cigarette smoking. Complex tobacco use profiles that include products such as cigars, e-cigarettes, and hookah are likely more reflective of individuals’ actual tobacco use behaviors; unfortunately, the NHIS
only includes questions on cigarette smoking. Second, our definition of never smokers is somewhat imprecise, as it includes a small number of recent initiates who had not yet consumed 100 lifetime cigarettes, but reported that they smoked some days or every day. Third, certain assumptions were made in data cleaning and reducing our data set to the final analytical sample. These assumptions included: (A) removing those with “indeterminate” answers in either 2010 or 2011; and, (B) recoding smoking statuses for those respondents who claimed lifetime consumption of 100 or more cigarettes in 2010, but not in 2011. We tested the effect of these assumptions by conducting the same analysis under different assumptions. We first tested the effect of assumption A by: 1) listwise deleting those participants whose smoking status could not be determined in both years; and 2) matching both years’ smoking statuses to whichever year’s smoking status could be determined, then re-running analyses. Second, we tested the effect of assumption B by listwise deleting all those participants with inconsistent lifetime cigarette consumption responses, maintaining assumption A, then re-running analyses. Finally, we combined our tests of assumption A and B and re-ran analyses. We found that our results did not change the direction of comparisons, and statistically significant findings remained significant in all but one case (comparison 13 in Table 4.3 became insignificant when testing assumptions 1 and 3 independently).

Conclusions
This study highlights the complex and shifting nature of adult cigarette smoking patterns in the US, and reveals patterns in smoking by age and race/ethnicity that have not been studied in a large, national longitudinal sample. Future work will explore these patterns by menthol use, and compare transition probabilities observed in this dataset to patterns observed almost 10 years earlier in the 2002-2003 TUC-CPS. This study will also be
informative of computer simulation work to understand the effect of local, state, and federal policy interventions on individual transition dynamics, tobacco use prevalence, and associated health consequences.
Table 4.2: Transitions between smoking states for young and older adults from the 2010-2011 TUS-CPS survey

<table>
<thead>
<tr>
<th>2010 Smoking States</th>
<th>2011 Smoking States</th>
<th>Daily heavy smoker</th>
<th>Daily light smoker</th>
<th>Non-daily smoker</th>
<th>Former smoker</th>
<th>Non-smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily heavy smoker</td>
<td>Daily heavy smoker</td>
<td>53.7, 57.9</td>
<td>18.1, 20.7</td>
<td>2.9, 3.4</td>
<td>25.3, NA</td>
<td>NA</td>
</tr>
<tr>
<td>Daily light smoker</td>
<td>Daily light smoker</td>
<td>17.4, 14.1</td>
<td>45.9, 41.1</td>
<td>8.6, 10.9</td>
<td>28.2, NA</td>
<td>NA</td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td>Non-daily smoker</td>
<td>11.5, 7.9</td>
<td>21.9, 11.2</td>
<td>28.4, 24.1</td>
<td>38.2, NA</td>
<td>NA</td>
</tr>
<tr>
<td>Former smoker</td>
<td>Former smoker</td>
<td>1.3, 0.7</td>
<td>5.5, 3.9</td>
<td>5.6, 4.4</td>
<td>87.6, NA</td>
<td>NA</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>Non-smoker</td>
<td>0.8, 0.6</td>
<td>8.8, 0.6</td>
<td>1.2, 0.9</td>
<td>3.6, 93.6</td>
<td>92.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2010 Smoking States</th>
<th>2011 Smoking States</th>
<th>Daily heavy smoker</th>
<th>Daily light smoker</th>
<th>Non-daily smoker</th>
<th>Former smoker</th>
<th>Non-smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily heavy smoker</td>
<td>Daily heavy smoker</td>
<td>67.2, 65.6</td>
<td>13.8, 12.6</td>
<td>3.1, 2.5</td>
<td>15.9, 14.6</td>
<td>NA</td>
</tr>
<tr>
<td>Daily light smoker</td>
<td>Daily light smoker</td>
<td>21.3, 19.7</td>
<td>46.6, 44.6</td>
<td>11.0, 9.7</td>
<td>21.1, 19.2</td>
<td>NA</td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td>Non-daily smoker</td>
<td>10.4, 8.6</td>
<td>22.3, 19.9</td>
<td>31.3, 28.6</td>
<td>36.0, 33.4</td>
<td>NA</td>
</tr>
<tr>
<td>Former smoker</td>
<td>Former smoker</td>
<td>1.1, 0.9</td>
<td>1.4, 1.2</td>
<td>1.6, 1.3</td>
<td>96.0, 95.6</td>
<td>NA</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>Non-smoker</td>
<td>0.6, 0.5</td>
<td>0.5, 0.4</td>
<td>0.6, 0.5</td>
<td>6.3, 6.1</td>
<td>92.0</td>
</tr>
</tbody>
</table>
Table 4.3: Comparisons of smokers between age categories and smoking states

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Proportions (%)</th>
<th>Odds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>age 18-34</td>
<td>age 35+</td>
</tr>
<tr>
<td>1. Former smoker to active smoker(^a)</td>
<td>12.4</td>
<td>4.0</td>
</tr>
<tr>
<td>2. Non-daily smoker to former smoker</td>
<td>38.2</td>
<td>36.0</td>
</tr>
<tr>
<td>3. Daily light smoker to former smoker</td>
<td>28.2</td>
<td>21.1</td>
</tr>
<tr>
<td>4. Daily heavy smoker to former smoker</td>
<td>25.3</td>
<td>15.9</td>
</tr>
<tr>
<td>5. Daily light smoker to non-daily smoker</td>
<td>8.6</td>
<td>11</td>
</tr>
<tr>
<td>6. Daily heavy smoker to non-daily smoker</td>
<td>2.9</td>
<td>3.1</td>
</tr>
<tr>
<td>7. Non-daily smoker to daily light smoker/daily heavy smoker</td>
<td>33.4</td>
<td>32.7</td>
</tr>
<tr>
<td>8. Non-daily smoker to daily light smoker</td>
<td>21.9</td>
<td>22.3</td>
</tr>
<tr>
<td>9. Non-daily smoker to daily heavy smoker</td>
<td>11.5</td>
<td>10.4</td>
</tr>
<tr>
<td>10. Daily light smoker to daily heavy smoker</td>
<td>17.4</td>
<td>21.3</td>
</tr>
<tr>
<td>11. Non-smoker to ever smoker(^b) among Non-Hispanic Whites</td>
<td>6.9</td>
<td>8.3</td>
</tr>
<tr>
<td>12. Non-smoker to ever smoker(^b) among Non-Hispanic Blacks</td>
<td>7.3</td>
<td>9.11</td>
</tr>
</tbody>
</table>

Comparisons between smoking states:

| Comparisons                                                                 | Proportions (%) | Odds   |
|                                                                            | DL\(^c\) in 2010 | DH\(^c\) in 2010 | Difference (%) | 95% CI | DL in 2010 | DH in 2010 |
| 13. Become a former smoker in 2011                                          | 28.2     | 25.3    | 2.9 (-2.7, 8.5)   | 1.16   | Ref       |
| age 18-34                                                                   | 21.1     | 15.9    | 5.2 (3.0, 7.4)**  | 1.41   | Ref       |
| 14. Become a non-daily smoker in 2011                                        | 8.6      | 2.9     | 5.7 (3.1, 8.3)**  | 3.17   | Ref       |
| age 18-34                                                                   | 11.0     | 3.1     | 7.9 (6.4, 9.4)**  | 3.82   | Ref       |
| age 35+                                                                      |           |         |                   |        |           |

\* ** *** **** indicated statistical significance level (*p < 0.05, **p < 0.01, ***p < 0.0001).

\(^a\) Active smokers are: daily light, daily heavy and non-daily smokers.

\(^b\) Ever smokers are daily light, daily heavy, non-daily and former smokers.

\(^c\) DL and DH are for daily light and daily heavy smokers.
Table 4.4: Transitions between smoking states for young and older adults from the 2010-2011 TUS-CPS survey

<table>
<thead>
<tr>
<th>2010 Smoking States</th>
<th>2011 Smoking States</th>
<th>Daily heavy smoker</th>
<th>Daily light smoker</th>
<th>Non-daily smoker</th>
<th>Former smoker</th>
<th>Non-smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Daily heavy smoker</td>
<td></td>
<td>66.0 (64.2, 67.8)</td>
<td>13.9 (2.5, 15.2)</td>
<td>2.9 (2.3, 3.4)</td>
<td>17.3 (15.6, 18.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Daily light smoker</td>
<td></td>
<td>24.2 (22.2, 26.3)</td>
<td>46.0 (43.5, 48.4)</td>
<td>8.9 (7.6, 10.2)</td>
<td>20.9 (18.7, 23.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td></td>
<td>11.4 (9.3, 13.5)</td>
<td>19.8 (16.9, 22.6)</td>
<td>33.2 (30.0, 36.3)</td>
<td>35.6 (32.8, 38.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Former smoker</td>
<td></td>
<td>1.1 (0.9, 1.3)</td>
<td>2.0 (1.7, 2.4)</td>
<td>1.9 (1.6, 2.1)</td>
<td>95.0 (94.5, 95.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Non-smoker</td>
<td></td>
<td>0.8 (0.7, 1.0)</td>
<td>0.6 (0.4, 0.7)</td>
<td>0.6 (0.5, 0.7)</td>
<td>6.0 (5.7, 6.3)</td>
<td>92.0</td>
</tr>
</tbody>
</table>

Transition probabilities — Non-Hispanic Whites (unweighted $n = 13,934$)

<table>
<thead>
<tr>
<th>2010 Smoking States</th>
<th>2011 Smoking States</th>
<th>Daily heavy smoker</th>
<th>Daily light smoker</th>
<th>Non-daily smoker</th>
<th>Former smoker</th>
<th>Non-smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Daily heavy smoker</td>
<td></td>
<td>47.2 (40.4, 53.9)</td>
<td>26.4 (20.8, 32.0)</td>
<td>3.4 (1.0, 5.9)</td>
<td>23.0 (18.0, 28.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Daily light smoker</td>
<td></td>
<td>13.8 (10.4, 17.1)</td>
<td>49.3 (44.2, 54.4)</td>
<td>12.6 (9.2, 16.0)</td>
<td>24.4 (20.3, 28.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td></td>
<td>10.5 (5.1, 15.9)</td>
<td>33.0 (26.3, 39.8)</td>
<td>23.8 (18.7, 28.8)</td>
<td>32.7 (26.5, 38.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Former smoker</td>
<td></td>
<td>1.9 (0.5, 3.3)</td>
<td>1.7 (0.8, 2.5)</td>
<td>3.4 (2.0, 4.8)</td>
<td>93.1 (91.0, 95.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Non-smoker</td>
<td></td>
<td>0.4 (0.2, 0.5)</td>
<td>1.0 (0.7, 1.3)</td>
<td>1.5 (1.1, 1.9)</td>
<td>4.6 (3.9, 5.3)</td>
<td>92.5</td>
</tr>
</tbody>
</table>

Transition probabilities — Non-Hispanic Blacks (unweighted $n = 1,712$)

<table>
<thead>
<tr>
<th>2010 Smoking States</th>
<th>2011 Smoking States</th>
<th>Daily heavy smoker</th>
<th>Daily light smoker</th>
<th>Non-daily smoker</th>
<th>Former smoker</th>
<th>Non-smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Daily heavy smoker</td>
<td></td>
<td>47.2 (40.4, 53.9)</td>
<td>26.4 (20.8, 32.0)</td>
<td>3.4 (1.0, 5.9)</td>
<td>23.0 (18.0, 28.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Daily light smoker</td>
<td></td>
<td>13.8 (10.4, 17.1)</td>
<td>49.3 (44.2, 54.4)</td>
<td>12.6 (9.2, 16.0)</td>
<td>24.4 (20.3, 28.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td></td>
<td>10.5 (5.1, 15.9)</td>
<td>33.0 (26.3, 39.8)</td>
<td>23.8 (18.7, 28.8)</td>
<td>32.7 (26.5, 38.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Former smoker</td>
<td></td>
<td>1.9 (0.5, 3.3)</td>
<td>1.7 (0.8, 2.5)</td>
<td>3.4 (2.0, 4.8)</td>
<td>93.1 (91.0, 95.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Non-smoker</td>
<td></td>
<td>0.4 (0.2, 0.5)</td>
<td>1.0 (0.7, 1.3)</td>
<td>1.5 (1.1, 1.9)</td>
<td>4.6 (3.9, 5.3)</td>
<td>92.5</td>
</tr>
</tbody>
</table>
Chapter 5

Changes in Cigarette Smoking
Initiation, Cessation, and Relapse
among U.S. Adults: a Comparison of
Two Longitudinal Samples

5.1 Introduction

Over the past 50 years, the cigarette smoking epidemic in the U.S. has matured thanks to changing tobacco control policy and smoking-related norms (U.S. Department of health and Human Services 2014). Over the last decade, youth and adult cigarette smoking has decreased significantly (U.S. Department of health and Human Services 2014, Jamal et al. 2015, Warner 2015). There has been a shift toward lighter smoking, with increasing prevalence of non-daily smoking (Schane et al. 2010, Shiffman and Paty 2006) and a decrease in cigarette consumption.(CDC 2014a) Despite this, smoking continues to be
the leading cause of preventable disease and death in the U.S., accounting for more than 480,000 deaths every year (U.S. Department of health and Human Services 2014). Smoking, especially daily-heavy smoking, has become concentrated among those with the least education and lowest incomes (Lawrence et al. 2007, Asfar et al. 2016). As the nature of the U.S. smoking epidemic continues to change, it is important to understand dynamic smoking behaviors (initiation, cessation, and relapse) by sub-population to provide effective tobacco control.

Most first experiences with cigarette smoking occur in adolescence, with about 90% of smokers taking their first puff by age 18 (U.S. Department of health and Human Services 2014, US Department of Health and Human Services 2012). However, recent studies suggest that the average age of initiation has increased (Asfar et al. 2016). Race/ethnicity also plays a role in age of first puff, with non-Hispanic blacks first smoking later than non-Hispanic whites (Sterling and Weinkam 1989, Kandel et al. 2004). Studies and developmental theory suggest that establishment of regular, lifelong smoking patterns occurs not in adolescence, but after age 18, when individuals often move away from family influences and gain legal access to tobacco products (Richard et al. 2015). Examination of trends beyond never to ever cigarette smoking in adolescence, to transitions of established cigarette smoking patterns in adulthood can inform efforts to prevent smoking escalation and dependence.

Difficulty quitting and the high rate of relapse are continued challenges for tobacco control. Recently the Centers for Disease Control and Prevention found that while more than half of adult smokers reported past-year quit attempts, only 6.2% were not smoking one year later (Center of Disease Control and Prevention 2011) with the majority of relapses
occurring within the first week after quitting (Piasecki 2006). Young adults are more likely than older adults to try to quit, and to quit successfully (Messer et al. 2008). While non-Hispanic black smokers make more attempts to quit, non-Hispanic white smokers are more successful at staying quit (Fu et al. 2008, Royce et al. 1993). To fully understand the smoking behavior dynamics which may lead to health disparities in the U.S. adult population, examining trends in initiation, cessation, and relapse is essential.

Few studies have assessed smoking transitions using prospective data, which decreases problems of recall or temporality common in cross sectional data (Bondy et al. 2013, McWhorter et al. 1990, Weinberger et al. 2014). In an analysis from 1990, McWhorter et al. examined predictors of smoking cessation and relapse (McWhorter et al. 1990). In a more recent analysis of Canadian adult smokers, Bondy et al. [2013] examined the correlates of transitions between daily, non-daily and former smoking over three six-month follow-ups. Recently, Weinberger et al. [2014] examined smoking stability among U.S. adults between 2001-2005 with a focus on transitions between daily and non-daily smoking.

Each of these studies present essential data on population-level smoking dynamics, but each has drawbacks that limit generalizability, including: 1) old data gathered before the rise of e-cigarettes and other non-traditional tobacco products (Bondy et al. 2013, McWhorter et al. 1990, Weinberger et al. 2014, Regan et al. 2013); 2) lack of comprehensive information on all possible smoking transitions (initiation, cessation, and relapse) (Bondy et al. 2013, McWhorter et al. 1990); and 3) exclusion of heaviness of smoking from analyses. The 2002-2003 and 2010-2011 longitudinal datasets from the Tobacco Use Supplement to the Current Population Survey (TUS-CPS) provide an opportunity
to examine changes in cigarette smoking including changes in non-daily, daily-heavy, and daily-light smoking among two large, nationally representative samples of the U.S. The primary aim of this study was to examine changes in smoking transitions across an 8-year period, based on smoking assessments among two cohorts of individuals in which data was collected at two time points (waves) each, one year apart. Secondary aims of this study included: 1) describing changes in cigarette smoking initiation, cessation, and relapse by sociodemographic characteristics; and 2) describing changes in cessation and relapse by individuals with different patterns of cigarette smoking; comparing differences across cohorts. Illuminating changes in the smoking epidemic and identifying groups that are at elevated risk of initiation or relapse will inform prevention and treatment efforts.

5.2 Method

5.2.1 Dataset

This analysis employs two longitudinal datasets from the Tobacco Use Supplement to the Current Population Survey (TUS-CPS) from 2002-2003 (N=15,846)(William et al. 2007) and 2010-11 (N=28,153)(TUS). Detailed information on survey methods is available elsewhere(TUS). Briefly, the purpose of the TUS-CPS is to monitor tobacco use behavior, attitudes, and norms at national and lower levels. The data are nationally representative of the civilian, non-institutionalized U.S. population and is collected using telephone and in person interviews(National Cancer Institute 2013).

To obtain our final samples of N=15,410 (2002-2003) and N=18,393 (2010-2011), we used the following exclusion criteria. First, we excluded N=358 participants from the 2002-
2003 dataset who were <18 years old in 2002 to confine our analyses to adults, as the 2010-2011 TUS-CPS did not enroll individuals <18. Second, we excluded participants (N=78 in 2002-2003, N=106 in 2010-2011) because their smoking state was indeterminate. Smoking state was “indeterminate” if a participant answered “refused” or “don’t know” to any of the following questions: “Have you ever smoked more than 100 cigarettes in your entire life?”, “Are you currently smoking?” in either wave. In total, 2.8% of the 2002-2003 and 0.6% of the 2010-2011 original samples were excluded due to these procedures. N=9,654 observations were excluded from proxy respondents in the 2010-2011 dataset because the 2002-2003 dataset did not collect information by proxy; and full information about the target participant (e.g. number of cigarettes smoked per day) was not collected via proxy.

Some participants also reported inconsistent smoking state changes between survey waves. “Inconsistent” responses were defined as individuals who responded “yes” to “Have you ever smoked more than 100 cigarettes in your entire life?” in wave 1 but reported “no” to the same question in wave 2 (N=1,020 in 2002-2003, N=1,041 in 2010-2011). Among “inconsistent” responders, 70-75% self-reported as former smokers at wave 1, with the remaining 25-30% self-reporting as either non-daily or daily-light smokers at wave 2. Because most of these participants had identified as former smokers in 2002 or 2010, we assumed that their wave 1 response was correct and changed all their wave 2 smoking state to “former”. In sensitivity analyses (data not shown), we compared this reclassification approach with results from an analysis where we excluded inconsistent responders and found no qualitative difference.
5.2.2 Measures

Socio-demographics
We grouped participants into three age groups: 18-29, 30-44 and 45+ to be consistent with similar studies (Weinberger et al. 2014). Educational attainment was aggregated from 18 categories into three categories: less than high school (any with no diploma), high school degree/GED (high school grad-diploma or GED), and higher than high school (any college and higher). Marriage status was aggregated into two categories: currently married (married-spouse present or absent), and currently unmarried.

Smoking states
We created five mutually exclusive smoking states: daily-heavy, daily-light, non-daily, former, and non-smokers. Respondents who had not consumed 100 lifetime cigarettes were considered non-smokers. The other four smoker types were restricted to respondents who had smoked at least 100 lifetime cigarettes. Daily-heavy and daily-light smokers reported that they smoked every day, with daily-light smokers consuming $\leq 10$ cigarettes (consistent with prior definitions of light smoking (Warner 2015, Schane et al. 2010)) and daily-heavy smokers consuming $>10$ cigarettes per day. Non-daily smokers were grouped regardless of the number of cigarettes they consumed on the days they smoked. Former smokers reported not currently smoking.

Smoking transitions
We examined changes in these smoking states with a focus on initiation, cessation and relapse, defined as moving between the following smoking states between waves 1 and 2: “Initiation”: from non-smoking to any current smoking; “Cessation”: from any current
to former smoking; “Relapse”: from former to any current smoking.

5.2.3 Statistical analysis

To account for the complex survey design and response rate, we used the main and replicate weights provided with the data as recommended for the TUS-CPS overlap samples in all analyses (TUS), with replicate weights derived using balanced repeated replication (William et al. 2007).

We estimated the proportion of participants that transitioned between smoking states from wave 1 to wave 2 and corresponding 95% confidence intervals (CI) around each estimate using PROC SURVEYFREQ in SAS (Version 9.3, SAS Institute, Cary, NC).

Then, a series of multivariable logistic regression models were estimated to examine the association of socio-demographic attributes and initial smoking states with smoking transitions between waves for both cohorts using the PROC SURVEYLOGISTIC procedure in SAS. Each model included the primary independent variables of gender, age group, race/ethnicity, marital status and education. Results are presented as adjusted odds ratios (aOR) with corresponding 95% CIs. An association is considered to be statistically significant if the corresponding p-value is less than 0.05. All analysis was conducted in 2016.

5.3 Results

Results focus on comparisons between cohorts; beginning with descriptive statistics followed by changes in smoking states and finally correlates of initiation, cessation and
relapse.

Table 5.1 presents weighted descriptive sociodemographic and smoking statistics for the analytic samples. Overall, the distribution of sex, age, and race/ethnicity were similar between the two cohorts. We observed a few differences in marital status, education and smoking state. In 2010 compared to 2002, a larger proportion of individuals were currently married and had completed at least some college, a smaller proportion had not completed a high school degree; there were more non-smokers and fewer former and daily-heavy smokers.

Table 5.2 presents the prevalence of smoking states and transitions in smoking states between waves for each cohort overall and by age and race group. For the three age groups in both cohorts, as age increases, the proportion of former smokers increases while the proportions of daily-light, non-daily and non-smokers decrease. The age group with the highest proportion of daily-heavy smokers in 2002-2003 was the 30-44 year olds. This is the same birth cohort (now 45+) who also had the highest proportion of daily-heavy smokers in 2010-2011. Also, the older age groups had lower percentages of initiation, cessation and relapse than younger age groups in both cohorts.

For race groups, in both cohorts, non-Hispanic whites had the highest proportion of daily-heavy and former smokers. Non-Hispanic blacks had the highest proportion of daily-light smokers, and Hispanics had the highest proportion of non-daily and non-smokers. Regarding changes in smoking state, there is evidence of low but non-trivial initiation in all race groups, with initiation highest among non-Hispanic blacks and cessation highest among Hispanics in both cohorts. Patterns of relapse by race change across cohorts.
Figure 5.1 illustrates transitions between smoking states between waves in the two cohorts. We observed no statistically significant change ($p > .05$) in initiation patterns between the cohorts at the overall population level, with 2.2% and 2.1% of non-smokers in wave 1 initiating smoking in wave 2 in 2002-2003 and in 2010-2011, respectively, though some non-smokers initiated and quit within the year (3.7% and 5.4% in 2002-2003 versus 2010-2011). The largest changes in cessation were observed among non-daily smokers; 37.0% (95%CI:34.4%-39.5%) of non-daily smokers stopped smoking in 2010-2011, while 44.9% (95%CI:42.1%-47.8%) of non-daily smokers stopped smoking in 2002-2003. In contrast, for daily-heavy smokers, the proportion quitting in 2010-2011 was higher than in 2002-2003; 18.2% (95%CI:16.7%-19.8%) and 12.6% (95%CI:11.5%-13.6%), respectively. For daily-light smokers, the difference in cessation between the two cohorts was not statistically significant. Finally, no significant differences were observed in terms of relapse among former smokers between the two cohorts.

By gender, age, and marital status, the odds of smoking initiation remained similar between the two cohorts, with men, younger adults (compared to adults over age 45), and unmarried adults having higher odds of cigarette smoking initiation (Table 5.3). However, compared to 2002-2003, the relationship in 2010-2011 between race/ethnicity, education, and smoking initiation changed. In 2002-2003, non-Hispanic blacks had greater odds of smoking initiation than non-Hispanic whites (aOR:1.42, 95%CI:1.04-1.93); in 2010-2011, there was no statistically significant difference. Additionally, relative to non-Hispanic whites, the odds of initiation for Hispanics decreased between 2002-2003 (aOR:1.19, 95%CI: 0.81-1.74) and 2010-2011 (aOR:0.69, 95%CI: 0.50-0.96). By education, we observed a widening of the effect of education on smoking initiation. In 2002-2003, adults
Figure 5.1: Bars indicate proportion of individual who transition from a smoking status in wave 1 to a smoking status in wave 2 in TUS-CPS 2002-2003 and 2010-2011 cohorts (Percentages < 3% not shown numerically).

with less than a high school education had 1.5 (95%CI:1.17,2.13) times greater odds of initiation than adults with more than a high school education, and there was no difference in initiation comparing adults with a high school degree/GED to those with more than a high school degree. In 2010-2011, adults with the least education had nearly 3.4 times the odds (aOR: 3.39, 95%CI:2.52-4.56) of initiating smoking compared to those with the most education. Additionally, the association between initiation and having a high school degree/GED was significant (aOR:2.85,95%CI:2.34-3.48).

The relationship between socio-demographics and smoking cessation were similar in the 2002-2003 and 2010-2011 cohorts (Table 5.3). Gender was not related to smoking cessation, age was inversely related to cessation, and unmarried adults had lower odds of cessation in both cohorts. By race/ethnicity, the odds of cessation were the highest among
Hispanics compared to non-Hispanic whites in both cohorts. By smoking state, the odds of cessation were the highest among non-daily smokers and lowest among daily-heavy smokers. The only difference observed between the two cohorts was by education. In 2002-2003, adults with less than a high school degree had a greater odds of cessation (aOR: 1.59, 95%CI:1.35-1.87) than those higher levels of education. There was no observed difference in cessation comparing adults with a high school degree/GED to those who had more than a high school degree. In 2010-2011, this relationship had flipped, with lower odds of cessation associated with having less than a high school degree (aOR:0.68, 95%CI:0.56-0.82) or a high school degree/GED (aOR:0.62, 95% CI: 0.55-0.71) compared to those with the highest level of education.

Younger age was associated with an elevated odds of relapse to smoking in both cohorts. Lower education also had a similar association with relapse in both cohorts, though the strength of the association was attenuated in 2010-2011 cohort compared to 2002-2003. The association between marital status, race/ethnicity, and relapse were different in 2010-2011 and 2002-2003. The odds of relapse were 2.11 times higher (95% CI:1.77-2.51) for unmarried than married adults in 2010-2011. While there was no relationship between race/ethnicity and relapse in 2002-2003, Hispanics had a higher odds of relapse compared to non-Hispanic whites (aOR:1.54, 95%CI:1.16-2.04); non-Hispanic blacks also showed an increased but non-significant odds of relapse in 2010-2011. Gender was not associated with relapse in either cohort.
5.4 Discussion

This study compared smoking prevalence overall and by type of smoking (heavy/light and daily/non-daily) as well as transitions in smoking states, by age and race/ethnicity subgroups over approximately a decade using a set of large nationally-representative longitudinal datasets. Consistent with other research, we have found a decrease in overall smoking (U.S. Department of Health and Human Services 2014, Jamal et al. 2015, Warner 2015), and a shift toward lighter smoking. We observed a substantial decrease in daily-heavy smoking, and a modest decrease in daily-light smoking. An increase in non-daily smoking, consistent with previous studies (Schane et al. 2010, Shiffman and Paty 2006), partially offset reductions in daily smoking for an overall decrease in smoking from 19.0% in 2002 to 15.6% in 2010. Studying transitions over time across the two cohorts provides further insights into these statistics. First, daily-heavy smoking is less stable in the more recent cohort; daily-heavy smokers in 2010 were less likely to remain daily-heavy smokers in the next year, with greater movement to daily-light and former smoking (less movement to non-daily smoking). This is consistent with existing evidence and adds insight to why average cigarette consumption is decreasing. While we observed reduction in smoking among daily-heavy smokers, we also observed escalation among non-daily smokers across the cohorts, with increases in transition from non-daily to all other current-smoking states. Future research should examine the reason for observed progress among daily-heavy smokers and escalation among non-daily smokers.

In terms of the association to changes in smoking initiation, cessation, and relapse, most of the results showed consistencies between the two cohorts. Gender, age group, and smoker types exhibit the same pattern in terms of their association to the odds of
initiation, cessation and relapse between the two cohorts. For example, gender seems to play a significant role in initiation, but not in cessation or relapse, with females being less likely to initiate than males. Younger age groups, having a higher odd of changing, are more active than the older groups (CDC 2008). Specifically, age 19-29 has a very high odds ratio of relapse which may be related to young adults social-smoking behavior causing difficulty in cessation and in staying abstinent (Song and Ling 2011). The impact of marital status on smoking behavior has been relatively unchanged between the two cohorts. Currently married adults showed “better” smoking habits, having lower odds of initiation and relapse, and higher odds of cessation; implying that marriage may have a positive impact on smoking behavior (Broms et al. 2004, Lindström 2010, Umberson and Liu 2006). Education groups showed some inconsistent results between the two cohorts regarding the odds of cessation. In both cohorts, lower education level shows a higher odds of initiation/relapse than higher education level, possibly because differences in education may result in differences in understanding of the health hazards of smoking and in receptivity to smoking-related health information (CDC 2009).

Limitations

While complex tobacco use profiles that include products such as cigars, e-cigarettes, and hookah are likely more reflective of individuals’ tobacco use behaviors, the TUS-CPS 2002-2003 only includes detailed questions on cigarette smoking. While the TUS-CPS 2010-2011 collects more information on the use of new products, such as e-cigarettes, we were not able to compare the differences of other tobacco products’ usage between the two cohorts, thus we only study cigarette smoking.
Conclusions

Our analysis can help inform targeted interventions. In line with other studies, we show prevention of initiation efforts should target boys and young men (Weinberger et al. 2014, Freedman et al. 2011), who are unmarried (McKee et al. 2003), non-Hispanic black, and less educated (Weinberger et al. 2014), as these groups are at higher risk of initiating smoking. Interventions to encourage more cessation should target older and non-Hispanic white adults (Weinberger et al. 2014), unmarried individuals, those with only high school degree/GED, and heavier smoking groups because these individuals are less likely to make a quit attempt. Prevention of relapse should focus on younger, married and less educated groups that are most likely to relapse, consistent with other studies (Weinberger et al. 2014, Augustson et al. 2008, Herd et al. 2009). Further research should investigate the extent to which these transitions in smoking are offset or bolstered by other forms of tobacco use. While the direction of change is good, efforts to sustain changes made over the past decade should be bolstered.
Table 5.1: Socio-demographic characteristics and cigarette smoking state among participants in TUS-CPS 2002-2003 & 2010-2011.

<table>
<thead>
<tr>
<th>Time-invariant sociodemographic characteristics</th>
<th>2002-2003(%, SD)</th>
<th>2010-2011(%, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=15,410 N=18,393</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48.2 (0.07)</td>
<td>48.3 (0.02)</td>
</tr>
<tr>
<td>Female</td>
<td>51.8 (0.07)</td>
<td>51.7 (0.02)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>21.1 (0.13)</td>
<td>21.1 (0.10)</td>
</tr>
<tr>
<td>30-44</td>
<td>31.2 (0.10)</td>
<td>27.2 (0.10)</td>
</tr>
<tr>
<td>45+</td>
<td>47.6 (0.05)</td>
<td>51.7 (0.02)</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently married</td>
<td>44.9 (0.24)</td>
<td>48.3 (0.22)</td>
</tr>
<tr>
<td>Currently not married</td>
<td>55.1 (0.25)</td>
<td>51.7 (0.22)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>70.5 (0.07)</td>
<td>68.0 (0.02)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>11.4 (0.05)</td>
<td>11.4 (0.01)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12.3 (0.06)</td>
<td>13.9 (0.02)</td>
</tr>
<tr>
<td>Other</td>
<td>5.7 (0.04)</td>
<td>6.6 (0.01)</td>
</tr>
<tr>
<td>Time-varying socio-demographic characteristics</td>
<td>2002</td>
<td>2003</td>
</tr>
<tr>
<td>N=15,410 N=18,393</td>
<td>(%, SD)</td>
<td>(%, SD)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>18.6 (0.20)</td>
<td>16.6 (0.21)</td>
</tr>
<tr>
<td>High school degree/GED</td>
<td>29.3 (0.25)</td>
<td>29.6 (0.28)</td>
</tr>
<tr>
<td>Higher than high school</td>
<td>52.1 (0.30)</td>
<td>53.8 (0.32)</td>
</tr>
<tr>
<td>18-year-old smoking prevalence</td>
<td>Non-smoker</td>
<td>87.8 (1.48)</td>
</tr>
<tr>
<td>Smoking state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily-heavy smoker</td>
<td>9.9 (0.15)</td>
<td>9.2 (0.15)</td>
</tr>
<tr>
<td>Daily-light smoker</td>
<td>4.9 (0.15)</td>
<td>4.9 (0.14)</td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td>4.2 (0.12)</td>
<td>3.4 (0.10)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>22.2 (0.23)</td>
<td>27.2 (0.25)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>58.7 (0.32)</td>
<td>55.3 (0.32)</td>
</tr>
</tbody>
</table>
Table 5.2: Prevalence of smoking status and changes in smoking status between waves, by age and race.

<table>
<thead>
<tr>
<th>Smoking States</th>
<th>Age 18-29</th>
<th>Age 30-44</th>
<th>Age 45+</th>
<th>NHW</th>
<th>NHB</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily-heavy smoker</td>
<td>7.8(0.4)</td>
<td>9.9(0.2)</td>
<td>9.3(0.1)</td>
<td>11.3(0.2)</td>
<td>5.0(0.3)</td>
<td>2.7(0.3)</td>
</tr>
<tr>
<td>Daily-light smoker</td>
<td>7.6(0.4)</td>
<td>4.7(0.2)</td>
<td>3.8(0.1)</td>
<td>4.6(0.1)</td>
<td>7.8(0.4)</td>
<td>4.7(0.4)</td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td>4.4(0.3)</td>
<td>3.8(0.2)</td>
<td>2.7(0.1)</td>
<td>3.0(0.1)</td>
<td>4.6(0.4)</td>
<td>5.0(0.4)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>15.0(0.5)</td>
<td>22.2(0.4)</td>
<td>35.9(0.3)</td>
<td>30.4(0.2)</td>
<td>21.4(0.7)</td>
<td>18.0(0.6)</td>
</tr>
<tr>
<td>Non smoker</td>
<td>65.3(0.7)</td>
<td>59.3(0.4)</td>
<td>48.2(0.3)</td>
<td>50.8(0.3)</td>
<td>61.2(0.7)</td>
<td>69.6(0.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Changes in Smoking States</th>
<th>% Initiation</th>
<th>% Cessation</th>
<th>% Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUS-CPS 2002-2003 (%) SD</td>
<td>3.8(0.4)</td>
<td>26.9(1.6)</td>
<td>19.6(1.8)</td>
</tr>
<tr>
<td>TUS-CPS 2010-2011 (%) SD</td>
<td>3.2(0.3)</td>
<td>30.4(1.6)</td>
<td>15.0(1.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking States</th>
<th>Age 18-29</th>
<th>Age 30-44</th>
<th>Age 45+</th>
<th>NHW</th>
<th>NHB</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily-heavy smoker</td>
<td>5.7(0.4)</td>
<td>6.9(0.3)</td>
<td>7.9(0.2)</td>
<td>9.0(0.2)</td>
<td>4.0(0.2)</td>
<td>2.3(0.3)</td>
</tr>
<tr>
<td>Daily-light smoker</td>
<td>6.1(0.4)</td>
<td>5.6(0.2)</td>
<td>4.4(0.1)</td>
<td>4.9(0.1)</td>
<td>6.5(0.3)</td>
<td>4.5(0.4)</td>
</tr>
<tr>
<td>Non-daily smoker</td>
<td>5.1(0.4)</td>
<td>4.0(0.2)</td>
<td>2.4(0.1)</td>
<td>3.0(0.1)</td>
<td>4.4(0.3)</td>
<td>4.9(0.4)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>7.7(0.4)</td>
<td>14.7(0.4)</td>
<td>27.0(0.3)</td>
<td>23.3(0.2)</td>
<td>11.7(0.4)</td>
<td>11.0(0.5)</td>
</tr>
<tr>
<td>Non smoker</td>
<td>75.3(0.7)</td>
<td>68.9(0.5)</td>
<td>58.3(0.3)</td>
<td>59.8(0.3)</td>
<td>73.4(0.6)</td>
<td>77.2(0.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Changes in Smoking States</th>
<th>% Initiation</th>
<th>% Cessation</th>
<th>% Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUS-CPS 2002-2003 (%) SD</td>
<td>3.2(0.3)</td>
<td>30.4(1.6)</td>
<td>15.0(1.6)</td>
</tr>
<tr>
<td>TUS-CPS 2010-2011 (%) SD</td>
<td>3.2(0.3)</td>
<td>30.4(1.6)</td>
<td>15.0(1.6)</td>
</tr>
</tbody>
</table>
Table 5.3: Multivariable logistic regression analysis of the association of smoker’s characteristics to initiation, cessation and relapse.

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Initiation aOR(^a) (95% CI)</th>
<th>Cessation aOR(^a) (95% CI)</th>
<th>Relapse aOR(^a) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2002-2003 (n=146)</td>
<td>2010-2011 (n=203)</td>
<td>2002-2003 (n=596)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Women</td>
<td>0.66(0.53,0.84)* 0.53(0.44,0.64)*</td>
<td>1.07(0.93,1.23) 1.01(0.91,1.12)</td>
<td>1.14(0.96,1.35) 0.98(0.82,1.16)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>2.11(1.66,2.67)* 1.90(1.53,2.35)*</td>
<td>1.38(1.17,1.63)* 1.71(1.42,2.06)*</td>
<td>5.66(4.49,7.14)* 4.42(3.36,5.82)*</td>
</tr>
<tr>
<td>30-44</td>
<td>1.61(1.29,2.02)* 1.66(1.35,2.04)*</td>
<td>1.26(1.09,1.46)* 1.38(1.22,1.56)*</td>
<td>1.65(1.34,2.03)* 2.47(2.01,3.03)*</td>
</tr>
<tr>
<td>45+</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>1.42(1.04,1.93)* 1.05(0.84,1.33)</td>
<td>1.49(1.18,1.87)* 1.41(1.18,1.69)*</td>
<td>1.07(0.66,1.74) 1.33(0.94,1.87)</td>
</tr>
<tr>
<td>Hispanics</td>
<td>1.19(0.81,1.74) 0.69(0.50,0.96)*</td>
<td>1.65(1.26,2.15)* 1.62(1.33,1.98)*</td>
<td>0.67(0.42,1.07) 1.54(1.16,2.04)*</td>
</tr>
<tr>
<td>Other</td>
<td>0.31(0.17,0.56)* 0.31(0.19,0.51)*</td>
<td>1.62(1.20,2.18)* 1.51(1.21,1.89)*</td>
<td>0.90(0.56,1.45) 0.70(0.42,1.19)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Unmarried</td>
<td>1.66(1.28,2.14)* 1.96(1.65,2.34)*</td>
<td>0.68(0.61,0.77)* 0.71(0.63,0.79)*</td>
<td>0.86(0.69,1.09) 2.11(1.77,2.51)*</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ High school</td>
<td>1.58(1.17,2.13)* 3.39(2.52,4.56)*</td>
<td>1.59(1.35,1.87)* 0.68(0.56,0.82)*</td>
<td>1.95(1.43,2.66)* 1.30(1.03,1.65)*</td>
</tr>
<tr>
<td>High school</td>
<td>1.09(0.85,1.38) 2.85(2.34,3.48)*</td>
<td>0.95(0.84,1.07) 0.62(0.55,0.71)*</td>
<td>1.78(1.46,2.17)* 1.17(0.96,1.43)</td>
</tr>
<tr>
<td>Smoking State</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily-heavy</td>
<td>-</td>
<td></td>
<td>0.20(0.17,0.23) 0.48(0.41,0.55)*</td>
</tr>
<tr>
<td>Daily-light</td>
<td>-</td>
<td></td>
<td>0.35(0.30,0.41) 0.57(0.50,0.66)*</td>
</tr>
<tr>
<td>Non-daily</td>
<td>-</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

\(^a\): p < 0.05. n is un-weighted. The results are all weighted. \(aOR\): adjusted odds ratio. Adjusted multivariable logistic regression model includes gender, age, race/ethnicity, marital status, education, and smoking state (only for cessation).
Chapter 6

Regional Differences in Trends in Liver Transplant Donors and Recipients and the Risk of Waitlist Drop Out

6.1 Introduction

Liver transplantation has been the standard treatment of end stage liver disease for over three decades. During this time, there have been profound changes in all aspects of the field, ranging from advancements in surgical techniques and immunosuppression regimens to changes in organ allocation policies. At the same time, there have been significant changes in the population of patients with liver disease. In particular, patients referred for transplant have gotten older, with an increasing prevalence of NASH (Su et al. 2016, Charlton 2008). Such trends can have a negative impact on transplant, as patients
with NASH are more likely to have cardiovascular disease and other comorbid conditions that could impact pre- and post-transplant outcomes (Targher et al. 2008, 2010, Rinella 2015). Similarly, the aging of the hepatitis C birth cohort may place additional burdens on the transplant community, as more marginal candidates develop hepatic decompensation (Armstrong et al. 2006, Davis et al. 2010).

Further complicating these trends and relationships is the regional variation in transplant practices in the US. There is marked variation in waitlist death rates, transplant rates, and transplant MELD across regions (Yeh et al. 2011). Listing rates also vary by region, and differences in listing rates may be influenced by patient demographics and transplant center practice patterns (Mathur et al. 2014, Adler et al. 2015). Transplant centers also differ in their rates of acceptance of organ offers, which may influence waitlist outcomes (Goldberg et al. 2016).

Policy planning for the future of liver transplant requires a thorough understanding of historical trends in the waitlist, including patient characteristics, outcomes, and regional variation. We sought to describe these historical trends during the MELD era, and to examine the relationship between patient characteristics and outcomes. We used US national data from UNOS to explore these trends and relationships nationally, as well as in two disparate regions to demonstrate regional variation. We specifically examined regions 5 and 11, which have historically differed in transplant rates, waitlist death rates, and MELD scores at transplant (Yeh et al. 2011).
6.2 Method

Overview and Study Sample
For this retrospective study, we used UNOS standard transplant analysis and research files, which contain extensive patient-level data for all waiting list registrations and transplants performed in the U.S. since October 1, 1987. Specifically, we included adults ≥ 18 years of age listed for LT between 2003 and 2014 to study the clinical and demographic attributes of the waitlist population during the MELD era. We excluded those who received living donor and partial liver transplants and those with acute liver failure (UNOS status 1) without chronic liver disease.

In addition to studying the nationwide data, we performed specific analyses for UNOS regions 5 and 11 to examine regional heterogeneity. Region 5 is comprised of Arizona, California, Nevada, New Mexico and Utah. It is one of the largest transplant regions in the US, with high demand and high MELD scores at transplant (Yeh et al. 2011). Region 11 includes North Carolina, Kentucky, South Carolina, Tennessee and Virginia. In contrast to region 5, region 11 is smaller, with lower MELD scores at transplant, and higher transplant rates (Yeh et al. 2011).

Outcomes
After patients are added to the waitlist, they are removed for multiple reasons. For the purposes of this analysis, removals were categorized as removal for either (i) liver transplantation or (ii) other reasons aside from clinical improvement. We termed this latter category dropout.
**Variables**

We considered age (categorized as 18-39, 40-49, 50-59, and $\geq 60$), sex, race (specified as white, black, Hispanic, and other) and year of listing. MELD at listing was specified in four categories (6-15, 16-21, 22-27, and 28-40). The cutoff of 15 was chosen because it corresponds to the survival benefit of transplant and regional sharing in allocation policy (Merion et al. 2005), and 22 and 28 were chosen because of their relevance as HCC exception points (Northup et al. 2015). Liver diagnosis was specified in 6 categories: hepatitis B (HBV), hepatitis C (HCV), nonalcoholic steatohepatitis (NASH), alcohol, hepatocellular carcinoma (HCC) and other based on the primary diagnosis. Those with a secondary diagnosis of HCC or exception points for HCC were categorized as HCC because of the significant difference in organ allocation for those with HCC (Northup et al. 2015).

**Statistical Analysis**

The two outcomes of interest, transplant and waitlist dropout, each prevent the other outcome from occurring at a later time (competing outcomes). For instance, after receiving a transplant, a patient cannot be removed from the waitlist for a non-transplant reason. Similarly, after waitlist dropout, a patient cannot receive a transplant (without being relisted). Therefore, standard survival analysis with Cox regression, which assumes that outcomes can occur after censoring, cannot be used. Instead, we used competing risk analysis, which accurately describes competing outcomes.

The competing risk analysis uses a cumulative incidence function (CIF) to estimate the waiting time for each event (transplant, dropout) which is defined as:

\[ CIF_k(t) = P(T \leq t, \text{“Event”} = k) = P(\text{“Event”} k \text{ occurred before time } t) \]
Using this function, we can derive the probability of transplant and probability of Dropout by letting $t$ goes to $\infty$ as follows:

$$p_{tx} = P(\text{"Transplant"}) = P(T \leq \infty, \text{"Event"} = \text{"Transplant"}),$$

$$p_{dropout} = P(\text{"Dropout"}) = P(T \leq \infty, \text{"Event"} = \text{"Dropout"}).$$

In other words, $P(\text{"Transplant"})$ is the maximum value of $CIF_{\text{transplant}}(t)$, which is reached when $t$ goes to $\infty$ (i.e., the longest possible waiting time). The same concept applies for $P(\text{"Dropout"}).$

We used the above method to determine the probability of dropout, the probability of transplant, and the corresponding waiting times. PROC PHREG in SAS was used to determine the explanatory variables for the waiting time. As indicated in Figure 6.1, diagnosis and MELD score group are the two explanatory variables for waiting time. SAS macro "%cif" was used to estimate the CIF for each diagnosis by MELD score group.

Logistic regression models were built to examine the association of demographic and clinical attributes with the two events of interest: transplant vs. waitlist dropout. Each model included the categorical independent variables of gender, race, age group, diagnosis, and MELD score, and the one continuous variable “year”. Models were generated using a random 80% of data for model derivation, and the remaining 20% of data were used for validation. Results from the logistic regression models for the two regions and the national level are presented as adjusted odds ratios (OR) with corresponding 95% CIs. An association is considered to be statistically significant if the corresponding $p$-value is less than 0.05.
6.3 Result

*Patient Characteristics and Trends*

There were a total of 108,625 nationwide added to the waitlist, 18,341 individuals in region 5, 9,183 in region 11 from 2003-2014 (Table 6.1). The majority of patients are male, and over 70% of them are above age 50. At the national level, over 70% of patients are white, with significant racial variation between regions 5 and 11. Region 5 contains significantly more patients with Hispanic and other race/ethnicity, while region 11 has 30% more whites. More than 70% of patients have MELD below 22, and more than 50% have MELD 15 or below. Among the six disease types, HCV makes up the largest proportion (30%).

The proportion of patients aged ≥ 60 doubled from 21% to 42% during the study period, with a concomitant decrease in those aged 40-59 (Figure 6.1). The histograms of patients aged 60 above are shown in Figure 6.2. The percentage of patients aged over 70 increased from 1.35% to 2.1% from 2003-2014 nationally. Although race/ethnicity varied between regions, the racial distribution remained relatively constant nationally and within regions over time; from 2003-2014 the absolute change in any racial/ethnic category did not exceed 4%. The proportion with MELD ≤ 15 decreased nationally and in both regions, though it remained greater in region 5 compared to region 11 in each year. With this decrease in the MELD ≤ 15 group, there was significant regional variation in the increase in the higher MELD groups. Region 5 saw an increase exclusively for those with MELD ≥ 28, whereas in region 11, increases were seen only for MELD 16-27, with no change in the MELD ≥ 28 group. The prevalence of HCV in listed patients has been decreasing nationally and in both regions, with a more pronounced decrease in region...
5. Concomitantly, NASH has increased across regions and nationally, although in every year, the prevalence of NASH remained higher in region 11 compared to region 5. The prevalence of HCC has also increased in each group, though it has been higher in region 5 compared to region 11 (33% vs. 22% in 2014). For those with HCC as their primary diagnosis, about 40% of their secondary diagnosis are Hep C, and 40% are in the “Other” category at the national level. For those with HCC as secondary diagnosis, about 70% of their primary diagnosis is Hep C at the national level.

Waitlist Entrants, Exits, and Waitlist Size

The number of new patients added to the waitlist each year increased nationally from 7,641 to 9,561, with little change since 2010 (Figure 6.3). Region 11 also saw an increase, while the number of new registrants remained flat in region 5. There were also regional differences in the annual number of transplants and waitlist dropout, with waitlist dropout, outpacing transplants in region 5 since 2007 and a continued increase in transplants in region 11 with comparatively fewer waitlist dropout. Like region 5, the national volume of transplants has remained relatively flat since 2006, with a continued increase in the number of dropouts.

With the continued increase in new waitlist registrants outnumbering transplants and dropouts, the average waitlist size has grown each year (Figure 6.3). Growth in the waitlist size for region 5 has mirrored the national increase, while region 11 has seen slower growth, particularly since 2005.

For patients who ultimately do not receive a transplant, time on the waitlist is similar between regions and nationally, and has been decreasing since 2003 (Figure 6.4). There
is significant regional variation in waitlist time for those who get transplanted. For these patients, there has not been a trend toward shorter or longer wait times in either region or nationally.

Cumulative Incidence of Transplant vs. Dropout

In competing risk analysis, the cumulative incidences of transplant and waitlist dropout vary significantly between regions (Figure 6.5). For those in MELD group 3 (MELD score 22-27), the 1-, 3-, and 5-year incidences of transplant in region 5 are 0.461, 0.499, and 0.505, compared to 0.791, 0.805, and 0.808 in region 11. The corresponding 1-, 3-, and 5-year incidences of incidences of waitlist dropout are 0.352, 0.437, and 0.463 in region 5; and 0.172, 0.187, and 0.191 in region 11. Nationwide, the incidences of both transplant and waitlist dropout are higher in patients with greater listing MELD scores in the first few years, but this stepwise relationship is lost with further time accumulated on the waitlist (Figure 6.5).

Factors Associated with Transplant vs. waitlist dropout

The results of the multivariable logistic regression analysis of factors associated with transplant vs. waitlist dropout are shown in Table 6.2. Women and Hispanic patients are less likely to receive a transplant. Patients with HCC have three times greater odds of receiving a transplant compared to patients with HCV without HCC. There are significant differences between the regions in the odds of transplant for different MELD scores. In region 11, the odds of transplant are greater for those with MELD 16-27; in region 5, the odds of transplant is are greatest for MELD > 27. The odds of transplant declines with age in each group. In region 11, the odds of transplant increases with time, while the year of listing is not related to the odds of transplant nationally or in region 5.
6.4 Discussion

In this chapter, we focused on the regional differences in the trends of liver transplant recipients and the risk of waitlist dropout versus receiving transplant. For recipient characteristics, we observed increased MELD, older age group, more HCC patients at the time of registration for both regions (Su et al. 2016, Charlton 2008). The number of new patient registrants continues increasing over the years for both regions, outnumbering the number of transplants with region 5 having a lower proportion of patients who receive transplants than region 11. For the risk of waitlist dropout, in both regions, women and Hispanic patients are less likely to receive a transplant. HCC patients are much more likely to receive a transplant compared to HCV patients. Significant differences are observed between the two regions in the odds of transplant for different MELD scores. In region 11, the odds of transplant are greater for MELD 16-27 group, while in region 5, the odds are the greatest for MELD > 27 group.

Quantification of these regional differences will be important in informing public health policy. Important decisions looming for the transplant community include redrawing UNOS regions to lessen the effect of geographic location on access to organs. While redrawing the UNOS regions will not change the net number of livers available for transplant, waitlist times may change, thus characterizing the regional difference is critical. To create an equitable strategy for organ allocation, understanding the disparities among the regions is fundamental.
Table 6.1: Descriptive Statistics for Region 5, Region 11, and the US.

<table>
<thead>
<tr>
<th></th>
<th>National Level (%) (N=108,625)</th>
<th>Region 5 (%) (N=18,341)</th>
<th>Region 11 (%) (N=9,183)</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>66</td>
<td>65</td>
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<td>Age groups</td>
<td>18-39</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>40-49</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>50-59</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>60+</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>71</td>
<td>53</td>
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<td></td>
<td>Black</td>
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<td>4</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>15</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>MELD</td>
<td>6-15</td>
<td>53</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>16-21</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>22-27</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>28+</td>
<td>13</td>
<td>15</td>
</tr>
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<td>Diagnosis</td>
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<td>3</td>
</tr>
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<td>HCV</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>NASH</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>HCC</td>
<td>20</td>
<td>24</td>
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<tr>
<td></td>
<td>Other</td>
<td>20</td>
<td>15</td>
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<td>72.7</td>
<td>72.2</td>
</tr>
<tr>
<td></td>
<td>Type I</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Type II</td>
<td>18.8</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>Type Other</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Type Unknown</td>
<td>4.6</td>
<td>4.4</td>
</tr>
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<td></td>
<td>Unknown</td>
<td>1.4</td>
<td>2.1</td>
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<tr>
<td>Obesity</td>
<td>(yes)</td>
<td>18.9</td>
<td>13.6</td>
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<tr>
<td>Blood Type</td>
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<td>37.7</td>
<td>35.1</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>12.3</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>3.8</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>46.2</td>
<td>48.3</td>
</tr>
</tbody>
</table>
Table 6.2: Multivariable Logistic Regression Analysis of Factors Associated with Transplant vs. Dropout

<table>
<thead>
<tr>
<th>Attributes</th>
<th>National</th>
<th>Region 5</th>
<th>Region 11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR(a) (95% CI)</td>
<td>p-value</td>
<td>OR(a) (95% CI)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>&lt;0.0001</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>0.80 (0.77, 0.82)</td>
<td>0.76 (0.69, 0.82) *</td>
<td>0.82 (0.72, 0.93)*</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Black</td>
<td>1.0 (0.95, 1.06)</td>
<td>1.00 (0.83, 1.21)</td>
<td>1.14 (0.95, 1.38)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.71 (0.68, 0.74)*</td>
<td>0.90 (0.83, 0.98)*</td>
<td>0.86 (0.63, 1.18)</td>
</tr>
<tr>
<td>Other</td>
<td>0.79 (0.74, 0.85)*</td>
<td>1.03 (0.90, 1.16)</td>
<td>1.66 (1.07, 2.56)*</td>
</tr>
<tr>
<td>Disease type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>1.11 (0.99, 1.25)</td>
<td>1.10 (0.86, 1.39)</td>
<td>0.98 (0.64, 1.49)</td>
</tr>
<tr>
<td>HCV</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>NASH</td>
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<td>1.16 (1.01, 1.25)*</td>
<td>0.98 (0.83, 1.16)</td>
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<td>0.87 (0.77, 0.99)*</td>
<td>1.03 (0.85, 1.25)</td>
</tr>
<tr>
<td>Other</td>
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<td>1.33 (1.18, 1.50)*</td>
<td>1.33 (1.13, 1.57)*</td>
</tr>
<tr>
<td>HCC</td>
<td>3.07 (2.93, 3.22)*</td>
<td>2.85 (2.56, 3.18)*</td>
<td>4.47 (3.62, 5.54)*</td>
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<td>MELD score</td>
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<tr>
<td>6-15</td>
<td>1</td>
<td></td>
<td>1</td>
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<tr>
<td>16-21</td>
<td>1.76 (1.70, 1.83)*</td>
<td>1.45 (1.31, 1.60)*</td>
<td>2.05 (1.79, 2.35)*</td>
</tr>
<tr>
<td>22-27</td>
<td>2.52 (2.35, 2.60)*</td>
<td>2.22 (1.95, 2.52)*</td>
<td>2.92 (2.40, 3.55)*</td>
</tr>
<tr>
<td>28+</td>
<td>2.47 (2.35, 2.60)*</td>
<td>3.65 (3.26, 4.09)*</td>
<td>1.67 (1.38, 2.00)*</td>
</tr>
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<td>Age</td>
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</tr>
<tr>
<td>18-39</td>
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</tr>
<tr>
<td>40-49</td>
<td>0.85 (0.79, 0.92)*</td>
<td>0.81 (0.68, 0.97)*</td>
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<td>50-59</td>
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<td>0.80 (0.68, 0.95)*</td>
<td>0.87 (0.68, 1.11)</td>
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<tr>
<td>60+</td>
<td>0.65 (0.61, 0.70)*</td>
<td>0.65 (0.55, 0.77)*</td>
<td>0.70 (0.54, 0.90)*</td>
</tr>
<tr>
<td>Year</td>
<td>0.98 (0.98, 0.99)b</td>
<td>0.988</td>
<td>1.00 (0.98, 1.01)*</td>
</tr>
</tbody>
</table>

\(a\) Odds Ratio for transplant vs. dropout.
\(b\) The value for “Year” variable is a slope, not odds ratio.
Figure 6.1: Temporal Trends in Waitlisted Patients
Figure 6.2: Histogram of patients aged over 60 years old
Figure 6.3: Trends in Waitlist Entrants and Exits
Figure 6.4: Time on the Waitlist
Figure 6.5: Cumulative Incidence Functions for Transplant and Dropout, by Region and MELD at Listing
Chapter 7

The Changing Etiology of End Stage Liver Disease and the Implications for the Liver Transplant Waitlist

7.1 Introduction

With the advent of highly effective medications for hepatitis C (HCV) and the ongoing epidemic of non-alcoholic fatty liver disease (NAFLD), the main etiology of end stage liver disease (ESLD) and liver transplantation (LT) will change over the next two decades (Kabiri et al. 2014, Charlton 2008). Implementation of birth-cohort screening for HCV and new medications with sustained virologic response rates > 90% may render HCV a rare disease in the future (Kabiri et al. 2014). Continued increases in diabetes and obesity will increase the incidence of NAFLD, and as this population ages, many will develop cirrhosis and ESLD. The changing etiology of ESLD may impact the utility of listing patients for LT as older patients with multiple comorbidities may be more likely to die
or be removed from the wait list than receive a transplant (Su et al. 2016, Chapter 6).

Already, the transplant community has seen stagnation if not slight decline in the numbers of deceased donor liver transplants performed nationally since 2006. Much of this decline is due to donor graft quality and donation after cardiac death (DCD) procurement strategies (Orman et al. 2013). Transplant centers are less likely to use livers from donors with significant steatosis, advancing age, obesity, and DCD, even when they can transplant the donor’s other organs (Orman et al. 2013). The recent decline in LT may be a harbinger of further reductions in LT in the coming years (Orman et al. 2015). Such a decline in transplant availability would place a greater burden on centers managing ESLD patients on the waitlist.

Prior work has shown changes in waitlist attributes over the past decade and variability in regional waitlist characteristics (Chapter 6). In order to anticipate potential changes to waitlist attributes, we aimed to determine future demographic characteristics of the LT waiting list and determine the rate of waitlist removal and receipt of liver transplantation through discrete event simulation (DES). We performed our analyses using both national United Network of Organ Sharing (UNOS) data and data from two disparate regions to demonstrate the heterogeneity among UNOS regions.

7.2 Method

Overview

We used the Standard Transplant Analysis and Research (STAR) dataset files from the Organ Procurement and Transplant Network (OPTN), a.k.a. the ‘UNOS database’ to
create a DES model to predict patient characteristics and waitlist times on the liver transplant waitlist. The DES model was informed by data from 2003-2012 (Chapter 6). Data from 2013-2014 were withheld for validation of the model. We previously used this database to study the clinical and demographic attributes of the patient population on the waiting list (i.e., forecasting demographic trends (gender, age, race) and other clinical attribute trends (model for end stage liver disease-MELD score, disease type, etc.), accounting for possible correlations.) (Chapter 6). Then, a DES model was constructed to dynamically track waiting list development into the future while considering the changes in demographic and clinical attributes over time as well as liver availability. Each patient’s length of stay on the waitlist in controlled by his/her assigned “waiting time”, which is estimated by competing risk analysis.

**Inclusion/Exclusion criteria**

Inclusion and exclusion criteria for the simulation model are similar to the previously reported retrospective analysis (Chapter 6). Briefly, living donors and partial liver transplant were excluded. Pediatric patients under age 18 years of age were excluded. Acute liver failure (Status 1) patients were excluded. Data prior to the MELD era (February 2002) were excluded.

**Setting**

We studied the waitlist at the national level and specifically looked at region 5 and region 11. Region 5 includes Arizona, California, Nevada, New Mexico and Utah. It is one of the geographically largest and most populous transplant regions in US and transplants at very high MELD scores; we believe these data are representative of the high MELD regions. Region 11 includes North Carolina, Kentucky, South Carolina, Tennessee and
Virginia. Contrary to region 5, region 11 is a representative of smaller regions that are able to transplant at relatively lower MELD scores.

Variables

Initial MELD score:
Initial MELD score is the first MELD score recorded when a patient joins the list. The score ranges from 6 to 40, and was categorized in quartiles based on clinical factors (6-15, 16-21, 22-27, 28-40). A patient with a MELD score between 6 and 15 is very unlikely to get a liver transplant; 22 and 28 were common levels for hepatocellular carcinoma exception points until October 2015 (patients now get 28 points after a 6 month waiting period).

Disease type:
In the UNOS database, there are two variables for diagnosis: “primary diagnosis” and “secondary diagnosis”. The two variables have 79 different descriptions for the disease. We grouped them into 6 categories: hepatitis B (HBV), hepatitis C (HCV), nonalcoholic steatohepatitis (NASH), Alcoholic Cirrhosis, hepatocellular carcinoma (HCC) and other. The HCV group is inclusive of HCV plus alcohol. In the analysis, HCC became the primary diagnosis if it was listed as first or second due to the MELD exception point advantage it confers.

Construction of the Simulation Model

Figure 7.2 shows the conceptual overview of the simulation model. Patients arrive to the list and their characteristics are assigned to them, according to the flow chart in Figure 7.2. After that, the system will determine if the patient is predicted to dropout or re-
ceive transplant as their end outcome based on the probabilities, $p_{dropout}$ and $p_{tx}$, from the competing risk analysis. A corresponding waiting time $T_{dropout}$ or $T_{tx}$ is assigned to the patients. However, if a patient has waited in the queue until his or her preassigned transplant time $T_{tx}$ when the patient actually gets on the top of the list (i.e., he/she is the next to receive transplant offer), but there is no liver available in the system at that time. This could occur because the analysis is built on past data in which livers were available. But as we forecast potential future scenarios, the waiting time pre-assigned to the patient may make the patient to the top of the list without livers available. When this happens, this patient waits until a pre-assigned dropout time $t_{dropout} (> T_{tx})$. Before $t_{dropout}$, he/she has the priority to get the newly-available liver. If no new liver becomes available, he/she drops out at $t_{dropout}$. For example, a patient joins the list on day 1. He is determined to get a transplant in the end, and is assigned a waiting time of 100 days. Then, the patient waits 100 days until he gets to the top of the list, but there is no liver available at the 100th day. Then, he waits until the pre-assigned dropout time: say the 120th days. So he waits an extra 20 days. He has the priority to get the new available livers within the 20 days. If no new liver is available to him, he/she drops out after 20 additional days. The model was implemented using the software Arena version 15 (Rockwell Automation). The simulation model runs from 2003-2025 and is performed by running 5 replications, this number of replications allowed us to achieve a 95% confidence interval half-width of 1% or less around the mean. Figure 7.1

Waitlist additions arrival and liver graft availability

For the waitlist additions and liver graft availability from 2003-2014, we used the historical values because the number of arrivals did not present a clear pattern and we did not feel arrivals were adequately modeled using a regression model. We proposed several
possible trends for patient arrival and liver availability after 2014 which are based on a range of possible scenarios. In the simulation model, patients arrive according to a constant daily rate which is calculated by dividing the historical number of patient arrivals in that year by 365. Similar to patient arrival, the total available livers in each year are distributed daily in the simulation system, i.e., livers arrive to the system according to a constant daily rate which may vary in different years.

Model Validation

The simulation model was constructed using data from 2003-2012. Data from 2013-14
were withheld for validation. Actual and simulated national and regional values from 2014 are shown in Table 7.1.

**Scenario analyses**

We considered three simulation scenarios acknowledging that there may be unanticipated events that impact the available numbers of grafts for liver transplantation, the volume of new arrivals on the transplant waitlist and the health and demographic characteristics of patients on the waitlist. Several scenarios were defined and analyzed. Each scenario is composed of three parts: A: liver graft availability after 2014; B: Waitlist additions after 2014; C: Patients’ demographic and clinical trends after 2014. For each part, sub scenarios are designed. For the first part “A: liver yearly availability”, we considered three possibilities: 1. liver supply from 2015-2020 stays the same as 2014; 2. supply will increase 2% each year from 2014-2020; 3. a 2% decrease in the available liver in the future, utilizing the result from Toro-Diaz et al. (Toro-Diaz et al. 2014). For the second part: “B: Patient yearly arrival”, we also designed three different situations, each corresponding to increasing by 3% yearly after 2014, increasing by 5%, and yearly patient arrival remaining stagnant after 2014. For the last part: “C: Patient’s attributes”, we proposed two possible situations: one suppressed the effect of time after 2014 for those variables (age, MELD score group, disease type) for which time was a significant predictor. In other words, predictions of age group, MELD score group and diagnosis depend on time in the simulation model. In this case, the “year” variable was held constant at the 2014 value after year 2014. Similarly, the other one assumes that those variables keep changing with time until year 2020. By combining different possibilities from each of the three pieces, three scenarios are constructed (Table 7.2): baseline, optimistic, and pessimistic scenarios.
7.3 Results

National waitlist

In our baseline scenario the size of the national liver transplant waitlist will change from 13950 in 2015 to 17355 in 2025, a 24% increase. Nationally, the rate of drop out will increase from 41.3% to 45.8%. Patients on the waitlist will be older with an increase in the proportion of older than 60 from 35.9% to 47.1%. HCC will be the leading indication for liver transplantation, increasing from 16.5% to 28.5% and NASH will overtake HCV as the leading etiology of liver disease for new arrivals on the waitlist, increasing from 15.9% to 18.6%. A patient listed in 2015 with a MELD score between 22 and 27 will wait on average 82 days for a liver transplant. This time will increase to 123 days in 2020 and to 182 days in 2025. Under optimistic conditions (an increase in liver availability with unchanged waitlist additions and patient characteristics), the waitlist drop out will decrease from 39.3% to 28.7% by 2025. Accordingly, expected wait time for a patient entering the waitlist with a MELD score between 22 and 27 would fall from 88 days to 62 days. Under pessimistic conditions (a decrease in liver graft availability, an increase in patients added to the waitlist and further changes in patient attributes), the drop out rate would increase from 44.9% to 69.9% by 2025. Wait times for a patient entering the waitlist with a MELD score between 22 and 27 would increase from 96 days to 368 days by 2025. Selected characteristics of the national waitlist for the baseline, optimistic and pessimistic scenarios are shown in Table 7.3 and Figure 7.3.

Regions 5 and 11

Regional waitlists will have considerable variability. In the neutral scenario, the region 5 waitlist size will change from 2681 in 2015 to 3107 in 2025, a 15.9% increase. The rate
of drop out will change from 52.9% to 63.7%. Patients listed at a MELD score between 22 and 27 will have an increase in wait time from 110 days to 191 days by 2025. In comparison, region 11 will change from 706 in 2015 to 863 in 2025, a 22.2% increase. The rate of drop out will change from 30.3% to 43.9%. Wait times in region 11 will increase from 48 days to 82 days by 2025. The region 5 waitlist will have a greater proportion of HCV and HCC while NASH will be more common in region 11. Patients in region 5 will be older at the time of listing with a higher proportion over age 60 compared to region 11. Selected characteristics of the region 5 and 11 waitlists for the neutral, optimistic and pessimistic scenarios are shown in Table 7.4 and Figure 7.3.

![Figure 7.2: Overview of the simulation concept](image-url)

The table and figure are not provided here, but they are referenced in the text. The figure illustrates the simulation process with decision points and probabilities for dropout and liver availability.

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7.4 Discussion

This is the first detailed simulation that seeks to predict future liver transplant waitlist characteristics. Such modeling endeavors are critically important as we anticipate potential changes in UNOS region realignment and organ allocation as well as adjust to the reality of changing epidemiology of cirrhosis and end stage liver disease. We anticipate that there will be continued upward pressure on MELD scores for liver transplant listing resulting in longer waitlist times and greater risk of waitlist dropout. These events may have a multifaceted impact on the transplant community.

The complications of ESLD are expensive, and as patients wait longer for transplant, these episodes will become more common. In 2008 dollars, complicated variceal bleeding hospitalization costs were $23,207 per person (Viviane and Alan 2008). From 2005 to 2009, inpatient charges for hepatic encephalopathy rose from 4.7 billion to 7.2 billion (Stepanova et al. 2012). During the same time period, HCC related inpatient charges rose from 1.0 billion to 2.0 billion (Mishra et al. 2013). These complications may occur repeatedly while patients wait for a transplant offer. In a single center study of 402 patients
discharged after a complication of cirrhosis, 69% had at least one non-elective readmission. Additional costs for readmissions ranged from $20,581 to $29,898 (Volk et al. 2012).

Increased MELD at the time of transplant and increased donor comorbidities have been shown to increase transplant related costs and the combination of these two factors is synergistic (Salvalaggio et al. 2011). Donors in the highest risk quartile of the Donor Risk Index add $12,000 to the cost of transplant and another $22,000 to post transplant costs, relative to low risk donors, pushing overall one year costs to over $200,000 in 2008 U.S. dollars. DCD donors increased costs by $21,000 over standard donation after brain death (DBD) donors (Salvalaggio et al. 2011). These costs are directly attributable to longer post transplant hospital stays associated with increasing donor comorbidities (Axelrod et al. 2007).

Quantification of these future trends will be important in informing public health policy. Important decisions looming for the transplant community include redrawing UNOS regions to lessen the effect of geographic location on access to organs. Accurate forecasting of future waitlist times and the economic impact of rezoning UNOS regions and donor service areas will be vital. While rezoning the UNOS regions will not change the net number of livers available for transplant, waitlist times may change, thus anticipating future waitlist times will be integral. Such rezoning is controversial and focused primarily on equitable allocation of organs in the near (<5 years) term. There has been less emphasis on long term (10 years) forecasting. To create an equitable strategy for organ allocation long term, multiple complex interactions must be considered with accurate forecasts of the changing transplant candidate and organ donor demographics.
Worsening organ shortages have already reignited a push for uniformly higher donation rates across the U.S. As patients get sicker on the waitlist, risk tolerance for marginal liver grafts may change. Communicating these risks to patients, payers, and the public will be vital to avoid unintended side effects of policy changes such as those made by CMS in 2007 (Dolgin et al. 2016).

Any forecasting model is subject to certain limitations. The accuracy and the validity of the simulation are dependent upon the data used to inform the model. In this simulation, we utilize over a decade of robust patient data from the UNOS database. Interdependencies among health and demographic variables are calculated from tens of thousands of patients. A discrete event simulation can also run retrospectively as well. We used this strategy to validate our model by comparing withheld data from 2014 and demonstrating that our model predicted most variables to within 1-2% of the actual values. Additionally, we utilized alternate scenario analyses to account for likely changes in the waitlist. Unknowns such as transplant volume, new waitlist additions and patient health characteristics were altered to give a plausible range of optimistic and pessimistic outcomes.

In sum, we are concerned that patients on the liver transplant waitlist will become older, wait longer, receive a transplant at a higher MELD score, and have a greater risk for waitlist drop out. Different regions will experience these changes to different degrees. These potential changes are a call to action for equitable organ allocation, reassessment of risk/benefit ratios for transplant and innovations to improve liver graft availability.
Table 7.1: DES model validation: actual and predicted waitlist characteristics in year 2014

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>National</th>
<th>Region 5</th>
<th>Region 11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual Value</td>
<td>Simulated Value</td>
<td>Actual Value</td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-39</td>
<td>8.79</td>
<td>7.3 (0.8)</td>
<td>8.5</td>
</tr>
<tr>
<td>40-49</td>
<td>16.7</td>
<td>13.9 (1.6)</td>
<td>16.8</td>
</tr>
<tr>
<td>50-59</td>
<td>41.8</td>
<td>44.8 (2.2)</td>
<td>41.5</td>
</tr>
<tr>
<td>60+</td>
<td>32.8</td>
<td>34.1 (1.2)</td>
<td>33.2</td>
</tr>
<tr>
<td>Diagnosis Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hep B</td>
<td>2.1</td>
<td>1.4 (0.4)</td>
<td>3.1</td>
</tr>
<tr>
<td>Hep C</td>
<td>27.6</td>
<td>30.5 (1.0)</td>
<td>39.9</td>
</tr>
<tr>
<td>NASH</td>
<td>16.0</td>
<td>17.6 (1.3)</td>
<td>11.5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>19.7</td>
<td>17.7 (0.5)</td>
<td>17.2</td>
</tr>
<tr>
<td>Other</td>
<td>15.1</td>
<td>15.0 (1.3)</td>
<td>20.8</td>
</tr>
<tr>
<td>HCC</td>
<td>19.5</td>
<td>17.9 (0.9)</td>
<td>17.5</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62.9</td>
<td>64.7 (1.4)</td>
<td>62.2</td>
</tr>
<tr>
<td>Female</td>
<td>37.1</td>
<td>35.1 (1.4)</td>
<td>37.8</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>70.0</td>
<td>72.8 (1.5)</td>
<td>50.9</td>
</tr>
<tr>
<td>Black</td>
<td>7.3</td>
<td>8.3 (0.8)</td>
<td>3.3</td>
</tr>
<tr>
<td>Hispanic</td>
<td>16.8</td>
<td>14.4 (0.9)</td>
<td>33.8</td>
</tr>
<tr>
<td>Other</td>
<td>5.87</td>
<td>4.6 (0.2)</td>
<td>12.1</td>
</tr>
<tr>
<td>Initial MELD group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-15</td>
<td>73.4</td>
<td>74.6 (1.4)</td>
<td>74.6</td>
</tr>
<tr>
<td>16-21</td>
<td>21</td>
<td>19.7 (0.9)</td>
<td>19.4</td>
</tr>
<tr>
<td>22-27</td>
<td>4.4</td>
<td>4.3 (0.4)</td>
<td>4.8</td>
</tr>
<tr>
<td>28+</td>
<td>1.2</td>
<td>1.4 (0.5)</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Table 7.2: Scenario Descriptions

<table>
<thead>
<tr>
<th>Scenario</th>
<th>A. Liver Availability</th>
<th>B. Patient Arrival</th>
<th>C. Patient Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Scenario</td>
<td>Stagnant after 2014</td>
<td>Increase 3% after 2014</td>
<td>Stagnant after 2020</td>
</tr>
<tr>
<td>Optimistic Scenario</td>
<td>Increase 2% after 2014</td>
<td>Stagnant after 2014</td>
<td>Stagnant after 2014</td>
</tr>
<tr>
<td>Pessimistic Scenario</td>
<td>Decrease 2% after 2014</td>
<td>Increase 5% after 2014</td>
<td>Stagnant after 2020</td>
</tr>
</tbody>
</table>
Table 7.3: Selected waitlist attributes 2015-2025, national data

<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>Age≥60</th>
<th>HCV</th>
<th>NASH</th>
<th>HCC</th>
<th>Expected Wait time for MG3 (days)</th>
<th>Waitlist drop out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>2015</td>
<td>64.7</td>
<td>35.9</td>
<td>29.6</td>
<td>18.2</td>
<td>16.5</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>64.5</td>
<td>44.9</td>
<td>22.9</td>
<td>21.1</td>
<td>25.5</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>2025</td>
<td>64.5</td>
<td>47.1</td>
<td>21.0</td>
<td>21.9</td>
<td>28.5</td>
<td>182</td>
</tr>
<tr>
<td>Opti</td>
<td>2015</td>
<td>64.7</td>
<td>35.3</td>
<td>30.2</td>
<td>18.0</td>
<td>15.4</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>64.3</td>
<td>36.5</td>
<td>30.2</td>
<td>19.5</td>
<td>13.0</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>2025</td>
<td>63.3</td>
<td>36.8</td>
<td>29.5</td>
<td>20.4</td>
<td>12.0</td>
<td>62</td>
</tr>
<tr>
<td>Pessi</td>
<td>2015</td>
<td>64.7</td>
<td>36.0</td>
<td>29.5</td>
<td>18.1</td>
<td>16.7</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>64.7</td>
<td>45.3</td>
<td>22.2</td>
<td>20.5</td>
<td>27.7</td>
<td>205</td>
</tr>
<tr>
<td></td>
<td>2025</td>
<td>64.9</td>
<td>47.7</td>
<td>19.6</td>
<td>20.7</td>
<td>32.4</td>
<td>368</td>
</tr>
</tbody>
</table>

Note: All numbers are in percentages except the wait time. Base., Opti., Pessi. stand for Baseline, Optimistic, and Pessimistic Scenario, respectively.

Table 7.4: Selected waitlist attributes 2015-2025, regions 5 and 11

<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>Age≥60</th>
<th>HCV</th>
<th>NASH</th>
<th>HCC</th>
<th>Expected Wait time for MELD 22-27, days</th>
<th>Waitlist drop out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>2015</td>
<td>63.6</td>
<td>65.9</td>
<td>38.5</td>
<td>36.0</td>
<td>29.5</td>
<td>14.1</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>63.9</td>
<td>65.6</td>
<td>50.3</td>
<td>45.1</td>
<td>31.8</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>2025</td>
<td>64.2</td>
<td>68.5</td>
<td>54.0</td>
<td>49.7</td>
<td>31.8</td>
<td>13.7</td>
</tr>
<tr>
<td>Opti</td>
<td>2015</td>
<td>63.2</td>
<td>66.2</td>
<td>36.3</td>
<td>32.9</td>
<td>33.5</td>
<td>29.2</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>62.7</td>
<td>64.6</td>
<td>38.1</td>
<td>35.2</td>
<td>33.5</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td>2025</td>
<td>62.1</td>
<td>66.2</td>
<td>38.3</td>
<td>35.1</td>
<td>31.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Pessi</td>
<td>2015</td>
<td>63.8</td>
<td>65.8</td>
<td>38.6</td>
<td>33.7</td>
<td>31.4</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>63.9</td>
<td>65.6</td>
<td>51.0</td>
<td>45.2</td>
<td>20.5</td>
<td>21.8</td>
</tr>
<tr>
<td></td>
<td>2025</td>
<td>64.0</td>
<td>67.3</td>
<td>54.0</td>
<td>47.9</td>
<td>18.7</td>
<td>18.8</td>
</tr>
</tbody>
</table>

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Chapter 8

Incorporating Natural History Model in the Liver Transplant Waitlist Simulation Model

8.1 Introduction

Liver transplantation is a standard and sometimes the only therapy for end-stage liver disease (Starzl and Fung 2010). This procedure offers patients a 5 year survival rate of 74% (Thuluvath et al. 2010). Despite the increasing number of transplants in US in the recent years, demand has always exceeded supply. From the United Network for Organ Sharing website, as of December 2015, the number of waiting list candidates for liver transplant in the US is 14,928, and the number of liver transplant performed in 2014 were only 6,729. Usually, the waiting process is lengthy, often taking years to get a transplant (Barone et al. 2008).
In the US, patients who require a liver transplant are put on the waiting list. An initial Model for End-Stage Liver Disease (MELD) score, which is based on standard blood work (serum bilirubin, creatinine, INR), is assigned to each patient. The score indicates the mortality rate in the next three months, and therefore the priority on the waiting list. It was approved by the OPTN/UNOS Board of Directors in November 2001 and went into effect in February 2002. Briefly, when a liver becomes available, it is offered first to the candidates with the highest MELD score among those who matched on common elements, such as blood type. The MELD score changes over time, and it is assessed about every three months. Therefore, patients’ MELD scores do not stay the same due to the changes of their own health.

There are many publications in the liver transplant area with different focus. Some focused on the donor population. For example, Toro-Díaz et al. [2014] predicted liver transplant capacity and found that the number of available livers will decrease in the future. Some focused on improving the allocation policies (Mustafa et al. 2014), post transplant survival (Haddad et al. 2015, Klein et al. 2013), accepting or declining an organ offer for transplantation while optimizing a particular patient’s welfare (Alagoz et al. 2004, 2007a,b), a queueing model for liver transplant waiting list (Zenios [1999], Zenios et al. [2000], Dreicic et al. [2014]). There are also papers focused on the whole process (from patients arrival to the completion of transplant) (Mustafa et al. [2014]).

For the evolution of patients’ health status (MELD score) on the waitlist, there are few papers. This may due to the fact that the progression of the disease is often chaotic. For example, a patient may undergo a slow and steady decline for a long period and then experience an acute exacerbation. One common approach for researchers to model
the dynamic of MELD score is the cubic spline function (Alagoz et al. 2005, Shechter et al. 2005). This method updates the MELD score of a particular simulated patient by searching the subset of actual patients with similar lab values, and randomly choosing 1 patient from the sample, and returns an indication if the patient is dead by the next period, or, if the patient is alive, it returns the spline-estimated MELD score of that patient at the next time period. In another paper, Mustafa et al. [2014] modeled two transitions (improve and deteriorate) of the evolution of the patients.

In this chapter, we contribute to the literature of modeling the evolution of patient health status. Six states are defined to represent the patients health status on the list. Then, a Markov model is developed model the transitions among the six states. The Markov model is then embedded into the simulation model developed in Chapter 7 to predict future liver transplant trends.

8.2 Method

8.2.1 Data and overall method

We used the data for region 5 from the same datafile (Standard Transplant Analysis and Research (STAR) dataset files from the Organ Procurement and Transplant Network (OPTN)) as described in detail in Chapter 6 and Chapter 7 to create a DES model to predict patient characteristics and waitlist attributes of the liver transplant waitlist. Different from the DES model in Chapter 7, we update the patients’ MELD score periodically, and give the highest MELD score patients higher preference for incoming livers, instead of using waiting time to control patients’ stay on the list as in Chapter 7.
**Variables**

We considered three demographic variables: age group (categorized as 18-39, 40-49, 50-59, and 60+), gender, and race (specified as White, Black, Hispanic, and other). Three clinical attributes: blood type (A, B, AB, O), initial MELD score group (6-15, 16-21, 22-27, 28-40), and diagnosis type (hepatitis B (Hep B), hepatitis C (Hep C), nonalcoholic steatohepatitis (NASH), alcohol, hepatocellular carcinoma (HCC) and “other”).

Figure 8.1 shows the dependencies among the variables. The boxes indicate the model variables, directional arrows indicate dependencies between variables. As we can see from the figure, blood type and all the other variables are independent from each other. “(yr)” indicates the corresponding variable also depend on time (model year).

![Figure 8.1: The relationship of the variables](image-url)
8.2.2 Patient Natural History Module

Patient Waitlist History Dataset

In reality, a patient’s MELD score may go up or down over time depending on the status of his or her liver disease. Most candidates will have their MELD score assessed a number of times while they are on the waiting list. Figure 8.2 shows two examples from the liver waitlist history data from the UNOS datafile. This dataset contains details of all modifications to waiting list record while registrations listed, including changes to medical urgency status, MELD score inputs, etc. For example, the first column “ENCRYPTED WL ID” is the waitlist ID for each registered patient. It links the patient’s record to other datasets such as waiting list registration. The second column “TYPE OF WAITING LIST MODIFICATION” indicates the type of history record: A=ADD, M=MODIFY, D=DELETE. The third column “PATIENTS STATUS CODE” is the patient’s current MELD score (62**). The first two digits “62” indicates the score is MELD, the last two digits is the MELD score. The sixth column “DATE OF WAITING LIST MODIFICATION” keeps the date when this record was being made. We use this dataset to model the evolution of waitlist patient health status.

A Markov Model

Six health statuses are defined to represent the patient’s health status while they are waiting on the list. The six states are: MELD group 1, MELD group 2, MELD group 3, MELD group 4, inactive, and dropout. MELD group 1 - 4 represent the four MELD score groups: 6-15, 16-21, 22-27, and 28+, respectively. “Inactive” state is indicated by “6999” in the dataset, and it means the patient is not available for transplantation at that moment. A patient’s status can be inactive for various reasons. For example, can-
Candidate cannot be contacted, candidate choice, insurance issues, temporarily too sick, or temporarily too well. State “dropout” indicates that the patient leaves the waiting list without getting a transplant. The patient’s initial health status is his/her initial MELD group (explained in Section 8.2 and also in detail in Section 7.2 of Chapter 7).

We estimate each proportion that transitioned between the six states (MELD group 1, MELD group 2, MELD group 3, MELD group 4, inactive, and dropout) using PROC FREQ in SAS. Every state can transition to all the other states, except “dropout”. The “dropout” state is an absorbing state. In other words, the state “dropout” can’t transition to the other five states. The transition diagram is the grey box in Figure 8.3. Similar to other papers, we also found that the evolution of the MELD score depends on the patient diagnosis type (Alagoz et al. 2005). The transition matrices by diagnosis type are
shown in Table 8.5.

From the dataset, we notice that the time for one transition (i.e., time length between two consecutive modifications for one patient) varies. In other words, patient MELD score is not updated after every fixed time interval. The time interval between two consecutive updates is not a constant number. We believe sicker (higher MELD score/group) patients have more frequent updates than less sick (lower MELD score/group) patients.

i.e., a patient with lower current MELD score waits longer until the next MELD assessment/update, while a higher MELD score patient has shorter intervals between two assess dates. The descriptive statistics of this time interval shown in Table 8.1 confirmed our conjecture. The higher the MELD score, the shorter the time interval. For example, from the table, if the patients current MELD score is in MELD group 1 (i.e., MELD score is in 6-15), then the mean time to the next assess time is 72 days. However, the mean time to the next assess time is only 10 days for MELD group 4 (MELD score > 27) patients.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Lower Quartile</th>
<th>Upper Quartile</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD group 1</td>
<td>72</td>
<td>1</td>
<td>1978</td>
<td>19</td>
<td>91</td>
<td>49</td>
</tr>
<tr>
<td>MELD group 2</td>
<td>33</td>
<td>1</td>
<td>1735</td>
<td>7</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>MELD group 3</td>
<td>20</td>
<td>1</td>
<td>478</td>
<td>4</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>MELD group 4</td>
<td>10</td>
<td>1</td>
<td>129</td>
<td>1</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Inactive state</td>
<td>97</td>
<td>1</td>
<td>2362</td>
<td>2</td>
<td>90</td>
<td>15</td>
</tr>
</tbody>
</table>

The natural history module simulates the progression of patients health status from the time a transplant candidate is placed on the waiting list until the occurrence of either
transplantation or dropout according to the Markov model. How this Module is embedded into the simulation model will be explained in next section (section 8.2.3).

8.2.3 The Simulation Model

Construction of the Simulation Model

Figure 8.3 shows the conceptual overview of the simulation model. Patients arrive to the list and their characteristics are assigned to them, according to the flow in Figure 8.1. After assigning the attributes, patients enter the natural history module. i.e., They update their health status (the grey square in Figure 8.1) according to the transition matrices after each corresponding period (mean values from Table 8.1). If the patient transitions into state “dropout”, this patient leaves the system without getting a transplant. Otherwise, when a liver arrives, the system searches for the highest MELD group patient with matching blood type (Table 8.2). “inactive” patients are not in the searching pool because they are currently not available for transplant.

<table>
<thead>
<tr>
<th>Liver Blood Type</th>
<th>Patient Blood Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>A</td>
<td>✓</td>
</tr>
<tr>
<td>B</td>
<td>✓</td>
</tr>
<tr>
<td>AB</td>
<td>✓</td>
</tr>
<tr>
<td>O</td>
<td>✓</td>
</tr>
</tbody>
</table>

Calibration of the Simulation Model

Different from the UNOS/OPTN suggested liver allocation policy, we noticed that it is
not always the patients with the highest MELD score that get the liver, given blood type matches. This could due to the different reasons. For example, (i) The weight or height does not match (a donor liver can be too large for the recipient, and there are no specific guidelines for size); (ii) The highest MELD patient has an infection at that moment but is not marked as inactive; (iii) Direct donation where the donor specifies the recipient he/she wants to donate to; (iv) Multiple organ transplant listing patient may have the “priority” sometimes because usually the physicians prefer to do all the transplant for multiple listing patients all at once. Among all the livers which were assigned to patients with a MELD score not in MELD group 4 (i.e., MELD score lower than 28), a fraction of these livers could have been assigned to a MELD group 4 candidate if blood type is the only matching criterion. The proportion is in Table 8.3. In order to accommodate this phenomenon, we apply the calibration probabilities (Table 8.4) in the simulation model. For example, in 2003, when a liver is about to be assigned to a MELD group 4 patient, the probability that this liver will be taken by this patient is 0.67, will be taken
by another MELD group 1 patient instead is 0.09, by a MELD group 2 patient instead is 0.09, by a MELD group 3 patient instead is 0.15. These calibration probabilities change from 2003-2014, and stay the same for the simulated years (2015-2025) as 2014 in the simulation model.

Table 8.3: A: Historical number of livers assigned to patients with MELD score lower than 28, and B: number of cases out of A where the liver could have been assigned to a MELD score group 4 patients

<table>
<thead>
<tr>
<th>Year</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>97</td>
<td>91</td>
</tr>
<tr>
<td>2004</td>
<td>169</td>
<td>156</td>
</tr>
<tr>
<td>2005</td>
<td>217</td>
<td>205</td>
</tr>
<tr>
<td>2006</td>
<td>341</td>
<td>317</td>
</tr>
<tr>
<td>2007</td>
<td>305</td>
<td>279</td>
</tr>
<tr>
<td>2008</td>
<td>300</td>
<td>286</td>
</tr>
<tr>
<td>2009</td>
<td>203</td>
<td>191</td>
</tr>
<tr>
<td>2010</td>
<td>146</td>
<td>134</td>
</tr>
<tr>
<td>2011</td>
<td>123</td>
<td>117</td>
</tr>
<tr>
<td>2012</td>
<td>114</td>
<td>100</td>
</tr>
<tr>
<td>2013</td>
<td>148</td>
<td>142</td>
</tr>
<tr>
<td>2014</td>
<td>136</td>
<td>125</td>
</tr>
</tbody>
</table>

Waitlist Arrival and Liver Graft Availability

Same as Chapter 7, we used historical values for the waitlist additions and liver graft availability from 2003-2014 because the number of arrivals did not present a clear pattern and we did not feel arrivals were adequately modeled using a regression model. Patient arrival, and the total available livers in each year are distributed daily in the simulation system. i.e., livers arrive to the system according to a constant daily rate which may vary in different years. Different from Chapter 7, all the patients and livers are assigned a blood type (A, B, AB, O) according to an empirical distribution from the dataset.
Table 8.4: Calibration probabilities by year

<table>
<thead>
<tr>
<th>Year</th>
<th>MG 1</th>
<th>MG 2</th>
<th>MG 3</th>
<th>MG 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>0.09</td>
<td>0.09</td>
<td>0.15</td>
<td>0.67</td>
</tr>
<tr>
<td>2004</td>
<td>0.05</td>
<td>0.10</td>
<td>0.20</td>
<td>0.65</td>
</tr>
<tr>
<td>2005</td>
<td>0.06</td>
<td>0.11</td>
<td>0.21</td>
<td>0.62</td>
</tr>
<tr>
<td>2006</td>
<td>0.02</td>
<td>0.09</td>
<td>0.39</td>
<td>0.49</td>
</tr>
<tr>
<td>2007</td>
<td>0.01</td>
<td>0.06</td>
<td>0.39</td>
<td>0.54</td>
</tr>
<tr>
<td>2008</td>
<td>0.02</td>
<td>0.07</td>
<td>0.38</td>
<td>0.53</td>
</tr>
<tr>
<td>2009</td>
<td>0.03</td>
<td>0.04</td>
<td>0.25</td>
<td>0.68</td>
</tr>
<tr>
<td>2010</td>
<td>0.01</td>
<td>0.05</td>
<td>0.16</td>
<td>0.78</td>
</tr>
<tr>
<td>2011</td>
<td>0.01</td>
<td>0.04</td>
<td>0.13</td>
<td>0.83</td>
</tr>
<tr>
<td>2012</td>
<td>0.01</td>
<td>0.03</td>
<td>0.11</td>
<td>0.85</td>
</tr>
<tr>
<td>2013</td>
<td>0.01</td>
<td>0.04</td>
<td>0.15</td>
<td>0.80</td>
</tr>
<tr>
<td>2014</td>
<td>0.01</td>
<td>0.04</td>
<td>0.13</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Scenarios

We apply the same scenarios (Realistic, Optimistic, and Pessimistic) as in Chapter 7 in this study. Briefly, we make different assumptions to (1) yearly liver availability after 2014; (2) the number of new registered patients after 2014; and (3) the time effect on patient attributes after 2014. The realistic scenario assumes the current trend in the liver transplant environment continues into the future whereas the optimistic/pessimistic scenario assumes the transplantation situation will improve/get worse in the future.

8.3 Results

8.3.1 Transition Matrices

Table 8.5 shows the transition matrices we derived for the six diagnosis types separately. The values in the matrices represent the one cycle time (Table 8.1) transition probabilities. For example, for a diagnosis type 1 (Hep B) patient, the probability of transitioning
from MELD group (MG) 3 to MG 4 in 20 days is 0.11. We noticed that the probability of transitioning into itself or adjacent MELD group(s) are much higher than the other transitioning into other statuses. Also, different diagnosis types have different transition probabilities. For example, for diagnosis type 6 (HCC) patient, the probability of transitioning from MG 1 to MG 3 is 0.35, much higher than the other diagnosis types. This may be due to the fact that HCC patients often apply for exception points and the successful applicants will receive exception score starting from 22 (MG 3).

8.3.2 Model validation

We used two measures for the model validation. Table 8.6 compares the historical and predicted waitlist characteristics in 2014. Figure 8.4 illustrates the simulated values of the MELD score group distribution at transplant each year from years 2003-2014, compared with the historical values. The simulated values are very close to the historical values.

Figure 8.4: MELD score group distribution in transplant: historical v.s. simulated 2003-2014
8.3.3 Number of Dropout

Figure 8.5 shows the number of dropouts from 2003-2025 under three scenarios, overlaid with historical data. The trend of the simulated values matched the historical values (years 2003-2014). The number of dropouts is the highest for pessimistic scenario, will increase to 1866 in year 2025, while this number decreased to 671 under the optimistic scenario.

![Figure 8.5: Number of dropout: historical v.s. predicted under three scenarios](image)

8.3.4 Transplant by MELD group

Figure 8.6 shows the distribution of MELD score group in transplant in the selected years (2015, 2020, and 2015). From the figure, we noticed the distribution is stable for these years under different scenarios, though the three scenarios have different assumptions to the number of patients arrival, patients attributes, and liver availability. This may result
from the calibration probabilities (Table 8.4) which stay the same from years 2015-2025.

Figure 8.6: The distribution of MELD score group in transplant in year 2015, 2020, and 2025.

8.4 Conclusion

In this chapter, we remodeled the current liver transplant waiting list by adding the patient’s natural history module in the simulation model. The strength of our approach is this model resembles the actual liver allocation system. (1) In the current model, we differentiate liver and patient blood types. (2) Instead of modeling the waiting time for patients, we model the patients’ natural history in terms of MELD score. i.e., dynamically keep track of patients’ MELD score while they are waiting on the list. Then, when a liver arrives to the system, the model picks a patient with the highest MELD score at that time. With this model, we could potentially test the effect of different allocation rules.
Limitations

There are two main limitation of model. (1) We only modeled the dynamics of MELD score group instead of specific MELD score. (2) The transition matrices for the dynamics of patient health status are time-homogeneous, i.e., the transition matrices stay the same throughout the simulated period (year 2003-2025). In reality, this could be time-nonhomogeneous. (3) Instead of using the calibration probabilities to adjust the model, other criteria such as age, BMI, location could be added to the model instead of using blood type as the only criteria in the matching process.
Table 8.5: Health status transition matrices by diagnosis type

**Diagnosis 1**

<table>
<thead>
<tr>
<th></th>
<th>Dropout</th>
<th>Inactive</th>
<th>MG1</th>
<th>MG2</th>
<th>MG3</th>
<th>MG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>0.29</td>
<td>0.41</td>
<td>0.09</td>
<td>0.07</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>MG1</td>
<td>0.04</td>
<td>0.05</td>
<td>0.80</td>
<td>0.08</td>
<td>0.03</td>
<td>0.00</td>
</tr>
<tr>
<td>MG2</td>
<td>0.02</td>
<td>0.05</td>
<td>0.09</td>
<td>0.72</td>
<td>0.11</td>
<td>0.02</td>
</tr>
<tr>
<td>MG3</td>
<td>0.02</td>
<td>0.04</td>
<td>0.02</td>
<td>0.08</td>
<td>0.73</td>
<td>0.11</td>
</tr>
<tr>
<td>MG4</td>
<td>0.06</td>
<td>0.07</td>
<td>0.00</td>
<td>0.00</td>
<td>0.05</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**Diagnosis 2**

<table>
<thead>
<tr>
<th></th>
<th>Dropout</th>
<th>Inactive</th>
<th>MG1</th>
<th>MG2</th>
<th>MG3</th>
<th>MG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>0.30</td>
<td>0.35</td>
<td>0.10</td>
<td>0.09</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>MG1</td>
<td>0.03</td>
<td>0.05</td>
<td>0.78</td>
<td>0.11</td>
<td>0.03</td>
<td>0.00</td>
</tr>
<tr>
<td>MG2</td>
<td>0.02</td>
<td>0.06</td>
<td>0.10</td>
<td>0.67</td>
<td>0.14</td>
<td>0.02</td>
</tr>
<tr>
<td>MG3</td>
<td>0.02</td>
<td>0.06</td>
<td>0.01</td>
<td>0.10</td>
<td>0.69</td>
<td>0.13</td>
</tr>
<tr>
<td>MG4</td>
<td>0.05</td>
<td>0.07</td>
<td>0.00</td>
<td>0.01</td>
<td>0.08</td>
<td>0.78</td>
</tr>
</tbody>
</table>

**Diagnosis 3**

<table>
<thead>
<tr>
<th></th>
<th>Dropout</th>
<th>Inactive</th>
<th>MG1</th>
<th>MG2</th>
<th>MG3</th>
<th>MG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>0.31</td>
<td>0.31</td>
<td>0.10</td>
<td>0.10</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>MG1</td>
<td>0.03</td>
<td>0.05</td>
<td>0.77</td>
<td>0.12</td>
<td>0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>MG2</td>
<td>0.02</td>
<td>0.06</td>
<td>0.09</td>
<td>0.67</td>
<td>0.15</td>
<td>0.01</td>
</tr>
<tr>
<td>MG3</td>
<td>0.02</td>
<td>0.06</td>
<td>0.01</td>
<td>0.10</td>
<td>0.69</td>
<td>0.13</td>
</tr>
<tr>
<td>MG4</td>
<td>0.05</td>
<td>0.07</td>
<td>0.00</td>
<td>0.01</td>
<td>0.09</td>
<td>0.78</td>
</tr>
</tbody>
</table>

**Diagnosis 4**

<table>
<thead>
<tr>
<th></th>
<th>Dropout</th>
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<th>MG1</th>
<th>MG2</th>
<th>MG3</th>
<th>MG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
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<td>0.32</td>
<td>0.08</td>
<td>0.08</td>
<td>0.07</td>
<td>0.08</td>
</tr>
<tr>
<td>MG1</td>
<td>0.04</td>
<td>0.05</td>
<td>0.79</td>
<td>0.09</td>
<td>0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>MG2</td>
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<td>0.06</td>
<td>0.11</td>
<td>0.66</td>
<td>0.13</td>
<td>0.02</td>
</tr>
<tr>
<td>MG3</td>
<td>0.02</td>
<td>0.05</td>
<td>0.01</td>
<td>0.10</td>
<td>0.69</td>
<td>0.14</td>
</tr>
<tr>
<td>MG4</td>
<td>0.04</td>
<td>0.07</td>
<td>0.00</td>
<td>0.01</td>
<td>0.10</td>
<td>0.78</td>
</tr>
</tbody>
</table>

**Diagnosis 5**

<table>
<thead>
<tr>
<th></th>
<th>Dropout</th>
<th>Inactive</th>
<th>MG1</th>
<th>MG2</th>
<th>MG3</th>
<th>MG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>0.30</td>
<td>0.33</td>
<td>0.08</td>
<td>0.10</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>MG1</td>
<td>0.03</td>
<td>0.05</td>
<td>0.77</td>
<td>0.11</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>MG2</td>
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<td>0.05</td>
<td>0.09</td>
<td>0.67</td>
<td>0.14</td>
<td>0.02</td>
</tr>
<tr>
<td>MG3</td>
<td>0.02</td>
<td>0.05</td>
<td>0.02</td>
<td>0.08</td>
<td>0.70</td>
<td>0.13</td>
</tr>
<tr>
<td>MG4</td>
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<td>0.07</td>
<td>0.00</td>
<td>0.01</td>
<td>0.08</td>
<td>0.79</td>
</tr>
</tbody>
</table>

**Diagnosis 6**

<table>
<thead>
<tr>
<th></th>
<th>Dropout</th>
<th>Inactive</th>
<th>MG1</th>
<th>MG2</th>
<th>MG3</th>
<th>MG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>0.26</td>
<td>0.36</td>
<td>0.06</td>
<td>0.02</td>
<td>0.20</td>
<td>0.11</td>
</tr>
<tr>
<td>MG1</td>
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<td>0.03</td>
<td>0.49</td>
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<tr>
<td>MG2</td>
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<td>0.05</td>
<td>0.06</td>
<td>0.53</td>
<td>0.30</td>
<td>0.04</td>
</tr>
<tr>
<td>MG3</td>
<td>0.02</td>
<td>0.06</td>
<td>0.04</td>
<td>0.01</td>
<td>0.77</td>
<td>0.09</td>
</tr>
<tr>
<td>MG4</td>
<td>0.04</td>
<td>0.08</td>
<td>0.03</td>
<td>0.00</td>
<td>0.02</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*MG: MELD score group*
Table 8.6: DES model validation: actual and predicted waitlist characteristics-2014

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>2014 Actual Value (%)</th>
<th>2014 Simulated Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-39</td>
<td>5.6</td>
<td>8.5 (0.8)</td>
</tr>
<tr>
<td>40-49</td>
<td>12.7</td>
<td>16.8 (1.7)</td>
</tr>
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<tr>
<td>Hep C</td>
<td>31.7</td>
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<td>NASH</td>
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<tr>
<td>Alcohol</td>
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<td>17.2 (0.3)</td>
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<tr>
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</tr>
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<tr>
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<td>3.3 (0.4)</td>
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</table>
Chapter 9

Conclusions

In this dissertation, we presented two application of statistical analysis and predictive modeling for healthcare management.

In the first application, presented in Chapters 2—5, we built a discrete event simulation (DES) model to predict future smoking prevalence and estimated the effectiveness of different smoking cessation policies. We first constructed a Markov model for smokers’ transitions among five smoking states, defined as: daily heavy, daily light, someday, former and non-smoker, using the TUS-CPS 2002-2003, 2010-2011 longitudinal data. Two transition matrices were developed for two age groups (18-34, 35+), respectively. From the two matrices, meaningful comparisons were made between age groups and smoking states for the two longitudinal cohorts, respectively. Then, based on the Markov model, we built a DES model to forecast smoking prevalence through 2020. Next, in Chapter 3, we presented an application of the simulation model built in Chapter 2. We examined the effects of several proposed scenarios for smoking reduction, and a potential 94-cent federal excise tax increase plan. Finally, in Chapter 5, we compared the changes in cigarette
smoking initiation, cessation, and relapse among U.S. adults by comparing the two longitudi-
nal samples TUS-CPS 2002-2003 and 2010-2011. We quantified the changes between
smoking states for the two longitudinal cohorts, and used a series of multivariable logistic
regression models to examine the association of socio-demographic attributes and initial
smoking states on smoking initiation, cessation, and relapse between waves within each
cohort.

In the second application, presented in Chapters 6—8, we compared regional differences
in liver transplant recipient and developed a DES model to predict future liver trans-
plant waitlist size and composition. First, in Chapter 6, we used the United Network for
Organ Sharing database to perform a retrospective cohort study of patients listed for
liver transplantation in the US between 2003 and 2014. We examined yearly trends in
patient attributes and performed competing risk regression and logistic regression anal-
yses to evaluate factors associated with receiving a transplant versus waitlist removal
for other reasons (dropout). We analyzed nationwide data as well as data from UNOS
regions 5 and 11. Then, in Chapter 7, a discrete event simulation (DES) model was built
to predict future liver transplant trends through 2025. The model was informed by the
characteristics of current patients including demographic (age, race, gender), and clinical
(e.g., disease type) attributes and their dependencies upon each other. With the DES
model, we predicted future wait list size under different possible scenarios by altering
the assumptions about the future liver availability, the number of patient arrivals and
the effect of time on the time-varying attributes. Lastly, in Chapter 8, a modification
to the DES model in Chapter 7 was conducted. Instead of using estimated waiting time
to control patients’ length of stay on the list, natural history model (the dynamics of
MELD score) was developed and embedded into the simulation model so that when a
liver becomes available, the system can assign the liver to the patient with the highest MELD score at the moment in the system. We also predicted future waitlist attributes under the same scenarios as in Chapter 7.

The work in this dissertation suggests a number of avenues for further research. For the first application (the smoking model), For example, we could build another predictive model to forecast future smoking prevalence using both longitudinal cohorts. The use of other tobacco products, such as e-cigarettes, could be added to the analysis since the usage of other tobacco products are emerging rapidly in recent years.

There are many possible future directions for the second application (the liver model). One would be to consider modeling the national level by taking into account of the interaction/sharing among the regions. The interaction among the regions might be important to model especially after the “Share 35” policy became effective in 2014 which allows patients with MELD scores higher than 35 to have priority to receive livers for transplantations across the nation. The other direction for future research related with Chapter 8 would be to model the the evolution of the health status (MELD score) with more details. For example, we could (1) model the evolution of MELD score instead of MELD groups; (2) extend the current natural history model from Region 5 to other representative regions. It may be interesting to study the regional differences from the disease evolution aspect. It is also believed that our models can be extended to other healthcare areas. For example, the liver transplant simulation model/natural history module developed in the second application could be used for other transplantation research, such as kidney transplant. The simulation models could also be used to test potential allocation policies which aims at achieving better equity among patients and regions.
REFERENCES


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NSDUH. National Survey on Drug Use and Health-Cigarette use in life time, 2008-2009, 2014c. URL http://www.samhsa.gov/data/NSDUH/2k10ResultsTables/NSDUHTables2009R/HTM/Sect2peTabs1to42.htm#Tab2.26B.

NSDUH. National Survey on Drug Use and Health-Cigarette use in life time, 2006-2007, 2014d. URL http://www.samhsa.gov/data/NSDUH/2k10ResultsTables/NSDUHTables2007R/HTM/Sect2peTabs1to42.htm#Tab2.26B.

NSDUH. National Survey on Drug Use and Health-Cigarette use in life time, 2004-2005, 2014e. URL http://www.samhsa.gov/data/NSDUH/2k5nsduh/tabs/Sect2peTabs1to57.htm#Tab2.35B.

NSDUH. National Survey on Drug Use and Health-Cigarette use in life time, 2003, 2014f. URL http://www.samhsa.gov/data/nhsda/2k3tabs/Sect2peTabs1to56.htm#tab2.34b.

NSDUH. National Survey on Drug Use and Health-Cigarette use in life time, 2002, 2014g. URL http://www.samhsa.gov/data/nhsda/2k2nsduh/tabs/Sect2peTabs1to111.htm#tab2.34b.


Table 1: Smoking prevalence from simulation results and four other surveys

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<th>Year</th>
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<th>2003</th>
<th>2004</th>
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<td>17.85(0.07)</td>
<td>17.31(0.27)</td>
<td>17.04(0.13)</td>
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<td>17.14(0.09)</td>
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<tr>
<td>Calibrated model</td>
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<td>21.6(0.6)</td>
<td>20.9(0.6)</td>
<td>20.9(0.6)</td>
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<td>17.86(0.1)</td>
<td>17.91(0.37)</td>
<td>17.94(0.16)</td>
<td>17.99(0.13)</td>
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<td>CDC</td>
<td>22.5(0.6)</td>
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<td>20.9(0.6)</td>
<td>20.8(0.7)</td>
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<td>17.86(0.1)</td>
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\(^a\) the value inside the parameter is the half width of the 95% CI.