

ABSTRACT

Title of dissertation: DATA ANALYTICS AND MATHEMATICAL
MODELS TO FACILITATE DISEASE
PREVENTION IN THE U.S.

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The U.S. is leading in healthcare expenditures worldwide, but health outcomes in the U.S. are not reflective of the level of spending. Prevention plays a crucial role in improving the health of individuals in the U.S., since it helps people live longer and healthier lives. Preventive services include actions that prevent diseases from ever occurring, detect diseases at an early stage, and manage diseases that have already been diagnosed. In this dissertation, we use data analytics and mathematical modeling techniques to better understand factors that influence disease prevention and help provide efficient solutions.

In the first part of this dissertation, we study two problems of disease prevention at the public health level. First, we investigate the impact of state-level vaccination exemption policy and of the highly publicized Disneyland measles outbreak on MMR vaccination rates of young children. At the same time, we highlight the impact that the choice of socioe-

conomic factors can have on measurement results. We estimate the impact of these policies using multiple linear regression. Furthermore, we study the sensitivity of the results by examining a number of different approaches for the selection of socioeconomic control variables. Second, we utilize big data to estimate the additive cost of chronic diseases and study their cost patterns. We model the cost based on a cost hierarchy; that is, the cost of each condition is modeled as a function of the number of other more expensive chronic conditions the individual has. Using large scale claims data, we identify members that suffer from one or more chronic conditions and estimate their healthcare expenditures. Through our analysis, we categorize the chronic conditions into different expenditure groups based on the characteristics of their cost profiles.

In the second part of this dissertation, we study two problems of disease prevention at the healthcare provider level, focusing in the area of cardiology. First, we study the adoption of conversational agent technology by patients with heart failure. Conversational agents can help patients with heart failure to manage their condition and provide frequent feedback to their healthcare providers. We analyze data from two studies, with each study focusing on a different type of conversational agent. We compare the two types of conversational agent technologies in terms of patient engagement, and investigate which patient characteristics are important in determining the patient engagement. Second, we tackle the problem of outpatient scheduling in the cardiology department of a large medical center. The outpatients have to go through a number of diagnostic tests and treatments before they can complete the final procedure. We develop an integer programming model to schedule

appointments that are convenient for the outpatients by minimizing the number of visits that the patients have to make to the hospital and the time they spend waiting in the hospital. Furthermore, we investigate whether scheduling outpatients in groups can lead to better schedules for the patients.

DATA ANALYTICS AND MATHEMATICAL MODELS TO
FACILITATE DISEASE PREVENTION IN THE U.S.

by

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Κάλλιον το προλαμβάνειν ἢ το θεραπεύειν.

- Prevention is better than cure -

Hippocrates of Kos, 460-370 BC

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List of Abbreviations

BPH	Benign prostatic hypertrophy
CABG	Coronary artery bypass grafting
Cath	Cardiac catheterization
CDC	Centers for disease control and prevention
CT	Computed tomography
DC	District of Columbia
EP	Electrophysiology
FF	Final formulation
GDP	Gross domestic product
GU	Genitourinary
HF	Heart failure
HIV	Human immunodeficiency virus
ICD-9	International classification of diseases, Ninth revision
IF	Initial formulation
IP	Integer program
IRB	Institutional Review Board
MIP	Mixed integer program
MMR	Measles mumps rubella
MS	multiple sclerosis
MSK	musculoskeletal
NIS	National immunization survey
OECD	Organisation for economic co-operation and development
OID	Opportunity Index database
OR	Operating room
PFO	Patent foramen ovale
PFT	Pulmonary function tests
PREP	Procedure readiness evaluation and preparation
STI	Sexually transmitted infections
TAVR	Transcatheter aortic valve replacement
TB	tuberculosis
TEE	Transesophageal echocardiogram
TMVR	Transcatheter mitral valve repair
TTE	Transthoracic echocardiogram
UMCP	University of Maryland College Park
UMMC	University of Maryland Medical Center
VAD	Ventricular assist device
VIF	Variance inflation factor

Chapter 1: Introduction

1.1 U.S. healthcare

The national health expenditures in the U.S. in 2018 were \$3.6 trillion, which corresponds to 17.7% of the gross domestic product (GDP). During the 2000 to 2018 time period, the average annual increase in national health spending was 5.7%, with a total increase of 167% from 2000 to 2018. In particular, the per capita annual expenditures increased from \$4,855 ¹ in 2000 to \$11,172 in 2018 [34]. Based on the current rate of increase, projections estimate that by 2027, the annual health expenditures will reach \$6.0 trillion, and correspond to 19.4% of the GDP [35]. Thus, based on U.S. population projections [31], the per capita annual expenditures in 2027 will be \$17,207. Increases in health expenditures in the U.S. are mostly attributed to the increasing prices of healthcare services and goods [8], but also, to a smaller extent, to the aging population and the population growth [42]. On the other hand, disease prevalence is not as strongly associated with the increase in expenditures in the U.S., and for some conditions it has been found to even have a negative association with total health expenditures [42].

Across all OECD (Organization for Economic Co-operation and Development) coun-

¹All amounts in 2018 dollars

tries, the U.S. has the highest per capita health expenditures and the highest percentage of GDP associated with health expenditures. However, the U.S. is not associated with improved health outcomes. In particular, the U.S. is the only OECD country that spends more than the OECD average but has lower than average life expectancy and higher than average avoidable mortality rates (i.e., deaths that could have been avoided through public health or medical interventions [119]). Furthermore, the U.S. is associated with lower than average healthcare coverage and fewer doctors than the OECD average [120]. Comparing the U.S. with 10 high-income countries (i.e., Australia, Canada, Denmark, France, Germany, Japan, the Netherlands, Sweden, Switzerland, and the United Kingdom), yields similar results, with the U.S. having the highest percentage of GDP spent on healthcare but the lowest life expectancy and the highest infant mortality across the 11 countries [125].

From the above, we see that improvements can be made to the U.S. healthcare system, both in terms of healthcare expenditures, and health outcomes. In order to reduce healthcare expenditures, proposed actions that could be taken include reducing the prices for prescription drugs, administration fees, and hospital services [40, 41]. On the other hand, in order to improve health outcomes it is crucial to focus more on preventive care, which can help prevent or treat a condition at an early stage. Treating a condition early means that it is more likely that future, more complex, and expensive treatments will be avoided [40]. There is no clear evidence that prevention initiatives lead to lower healthcare expenditures, with one reason being that prevention leads to increased longevity, which increases the likelihood of developing other conditions [115]. Nevertheless, prevention is crucial in

improving the health of individuals in the U.S., since it helps people live longer and lead healthier lives [52]. For that reason, it is critical to identify areas that require prevention interventions and investigate ways to make it easy for people to use existing preventive services.

1.2 Facilitating disease prevention

There are three levels of preventive services [115]. In primary prevention, the goal is to prevent a disease before it occurs. Examples of primary prevention include vaccinating children against an infectious disease, educating the population about sexually transmitted diseases, promoting healthy foods and regular exercise, and banning smoking in restaurants. In secondary prevention, the goal is to detect a disease at an early stage, which will make it easier to stop its further development. Examples of secondary prevention include mammogram screenings, bone density tests, and and regular blood pressure testing. Finally, in tertiary prevention, the goal is to manage a disease that has been diagnosed in order to stop or slow its progression and minimize its symptoms. Examples include screening for complications, rehabilitation, and surgery.

Prevention can be promoted both at the state level, through public health policy and interventions, and at the healthcare provider level, by helping patients manage their conditions, promoting screenings, and even creating a positive healthcare experience for the patients, such that the patients will not avoid seeking necessary treatment in the future [61]. In this dissertation, we study four prevention-related problems, starting with two

problems at the public health level, and continuing with two problems at the healthcare provider level. These are introduced below.

First, we study a problem in vaccination uptake, which is an example of primary prevention. Vaccines not only help save lives but also contribute to economic growth, and efficient healthcare systems. Increasing the percentage of the population that is healthy, means that more people are able to work or get an education, which leads to immediate and future productivity gains. Furthermore, vaccination decreases the number of disease outbreaks in a society, which helps to maintain more stable levels of resource requirements in the healthcare system [138]. In the U.S., it was estimated that the economic burden of unvaccinated adults suffering from vaccine-preventable diseases was \$7.1 billion during one year (2015) [124]. Thus, it is important to identify factors that influence vaccination uptake in the U.S.

In this dissertation, we focus on measles vaccination uptake across the U.S. The cost of a measles outbreak can be broken down into three categories [157]. First, the immunologic costs have to do with the measles infection as well as post-infection implications which can last up to a few years. Second, the financial cost of dealing with measles can be up to \$142,000 for each individual infection if we also take into account the cost of tracking down people that were exposed to the infection, putting people in quarantine, and informing the public about measles prevention. Third, the stress imposed on the public health system during an outbreak can affect the capability of the system to cope with other potential infections. It is estimated that a 5% decrease in the current measles coverage in the

U.S. would triple the number of annual measles cases of children 2 to 11 years old. That would correspond to an additional cost of \$2.1 million in the public sector [92]. In our study, we investigate how vaccination exemption policies and media coverage of previous outbreaks impact the measles vaccination rates. Furthermore, we demonstrate that different approaches in the way that socioeconomic controls (i.e., education, health, community, and economic characteristics) are chosen can lead to considerably different conclusions, which can have serious implications for policy studies.

Second, we study the costs related to the management of chronic conditions. In the U.S., one in two adults is diagnosed with at least one chronic condition [171], with the direct costs associated with the treatment of chronic conditions equal to \$1.1 trillion in 2016 [173]. If the economic burden of lost productivity is also taken into account, the total costs of chronic conditions increases to \$3.7 trillion, which was the equivalent of nearly 20% of the GDP during that year [173]. A number of chronic conditions are considered to be preventable since they can be avoided or treated by following more healthy lifestyles and going through the necessary screenings [11]. Examples include many types of heart conditions, cancers, pulmonary conditions, diabetes, and hypertension, which together cost over \$433 billion in 2013 [143]. From the above, we see that it is crucial to investigate ways to prevent chronic conditions. In order to decide where to direct the prevention efforts, it is critical to better understand the costs associated with each condition and the effect that combinations of chronic conditions have on the healthcare expenditures.

In our work, we study the healthcare costs of multiple chronic conditions. About one

in four adults in the U.S. have multiple (at least two) chronic conditions [171]. Thus, it is important to understand how the healthcare expenditures for each type of chronic condition change when other conditions are also present. This information can be used to better estimate the effect of preventive programs and policies on the healthcare expenditures of a population and, thus, help to decide on the direction of the interventions. In our study, we expand our analysis to 69 chronic condition categories, which is a larger set of conditions compared to previous studies. We propose a novel approach to model the cost based on a cost hierarchy, where the cost of each condition is modeled as a function of the number of other more expensive chronic conditions the individual has. Furthermore, based on the results of our model, we categorize the chronic conditions into different expenditure groups based on their cost behavior characteristics.

The other two studies in this dissertation focus on promoting prevention at the healthcare provider level. Both studies deal with problems in tertiary prevention, since they investigate ways of helping patients to manage and treat their conditions as necessary. Furthermore, both studies are dealing with the management of heart conditions, which are the chronic conditions associated with one of the highest annual healthcare expenditures in the U.S. In particular, the cost of heart conditions in 2013 was equal to \$147 billion and was second only to the cost of mental disorders (\$201 billion) [143].

In our third study, we focus on the management of heart failure. Heart failure is a condition with high prevalence and high hospitalization and readmission rates [179]. The direct annual healthcare costs of heart failure are estimated at over \$30 billion in the U.S.

and are expected to increase over time [75]. Thus, it is important to investigate ways to help patients manage their condition. A crucial factor for the successful management of heart failure is self-care, which includes taking medication, limiting salt intake, and also looking for symptoms that might cause concern [141]. One approach to help with the management of the condition at home is through telehealth. With telehealth, the healthcare provider can get daily feedback from the patient and understand whether the patient is following the provided instructions correctly, whether there are any concerning symptoms present, and whether intervention is necessary.

In this dissertation, we investigate the use of conversational agent technology by patients with heart failure. The advantage of using this type of technology for telehealth is that the patient can hear the questions and answer them through speech. This allows patients with limited experience with technology to participate in telehealth, since it is more intuitive to use speech to answer questions instead of, for example, entering answers through a screen. In our work, we compare two types of conversational agent technologies, one is based on the Amazon Alexa technology and only uses voice, while the other uses an Avatar to ask questions through a tablet, combining voice and image. Furthermore, we examine which patient characteristics are linked to higher levels of technology usage.

In our fourth and final study, we focus on making access to healthcare services as effortless as possible for patients, in order to ensure that they will not avoid seeking treatment when necessary. For example, if long waiting times are observed in an emergency center of a hospital, then some patients may decide to leave before being seen by a physician [145].

This can be dangerous for the health of the patients and can cause an additional burden to the hospital in the future, since treating patients will become more difficult and expensive if the health of the patients deteriorates. Similarly, people who have experienced long waiting times in the past in a hospital or a physician's office may avoid going to the doctor in the future or may be more likely to not show up for an appointment [158]. Therefore, it is crucial to make the experience of visiting a healthcare provider as efficient as possible in terms of patient waiting times. This can be achieved through scheduling.

In particular, in this dissertation, we investigate the problem of multi-appointment scheduling for outpatients. We focus on outpatients who plan to have an elective procedure in cardiology. These patients have to first complete a number of diagnostic tests and/or treatments before they are ready for the final procedure. This means that they have to travel to the hospital on multiple occasions and have to spend time waiting from one appointment to the next. Since some of these patients may depend on someone else to drive them to and from the hospital, it is important to generate schedules that are convenient for them and match their availability. This is currently done manually by the scheduling staff, which can be complicated and time consuming. We propose a mathematical programming formulation in order to help obtain better solutions to this problem. The patients in this case would not have to travel to the hospital more often than necessary or have to wait in the hospital for long periods of time.

1.3 Summary of contributions

The rest of the dissertation is organized as follows.

Chapter 2 investigates factors that are linked with high or low measles vaccination rates at the state level in the U.S. The main contributions of this chapter are that we examine the effect of allowing personal belief exemptions on vaccination rates of younger children, who do not necessarily attend school, and study the impact of the Disneyland outbreak on vaccination rates of subsequent years. Furthermore, we demonstrate the importance of socioeconomic control selection in policy studies.

Chapter 3 examines the contribution of different types of chronic conditions to the total healthcare cost of individuals. We contribute to the existing literature by proposing a novel approach to model the cost of chronic conditions, when more than one conditions might be present in the patient. This allows us to expand the number of chronic conditions and their combinations taken into account, and thus examine the cost patterns of multiple chronic conditions.

Chapter 4 discusses the use of conversational agents by patients with heart failure. In particular, the contribution of this chapter is twofold. First, we compare two types of conversational agent technologies with respect to patient engagement. Second, we identify patient characteristics (including demographic, clinical, and technology-related characteristics) that impact engagement with conversational agent technology.

Chapter 5 studies the problem of multi-appointment scheduling for outpatients in cardi-

ology. The contributions of this chapter include proposing an IP formulation for scheduling outpatients in a cardiology setting, and providing formulation improvements that can be applied to other scheduling problems following a similar formulation approach. Finally, we study whether and how patients should be grouped when scheduling under different scenarios of resource availability and external demand.

Finally, Chapter 6 concludes the dissertation and presents potential directions for future research.

Chapter 2: MMR vaccination rates of 19-35 months old children: The importance of socioeconomic factor selection

2.1 Introduction

In this chapter, we study factors influencing the measles vaccination uptake in the U.S., which is a problem at the primary prevention level. Measles is an infectious disease, which has caused millions of deaths in the past. A vaccine for measles was first introduced in the U.S. in 1963 and led to a drastic decrease in the number of measles cases reported per year [106]. Currently, in most instances, the measles vaccine is distributed in combination with vaccines against two other diseases. The resulting vaccine is called MMR (measles, mumps, and rubella) and is the one most commonly used to protect against measles. It is recommended that children get their first MMR dose before the age of 15 months, and the second dose between the ages of 4 and 6 years [29].

Some medical conditions that cause a weak immune system may prohibit the vaccination of a child. For example, children going through chemotherapy cannot get the MMR vaccine. These children still get protected from the infection through *herd immunity*. This means that if enough people in a community get vaccinated, even if some people are not

able to get vaccinated, they will still get protected from the infection [177], as the infection is unable to spread from one person to the next. In the case of measles, for herd immunity to work, at least 96% of the population has to be vaccinated [17]. If the vaccination coverage drops below that, measles outbreaks can occur in the population. Children must be vaccinated in order to attend school; however, exemptions due to medical reasons are allowed in all U.S. states and some states allow religious and personal belief (philosophical) exemptions as well [114].

Some parents choose to not vaccinate their children, even if their child does not meet the requirements for a medical exemption. Those parents usually believe that vaccines are unsafe for their children, that they do not work, or that the diseases they protect from are very rare and not too dangerous [20]. A now infamous and discredited [32, 159] study published in 1998 [170] linked the MMR vaccination to autism. Later, the original article was retracted. However, many parents still believe that MMR vaccinations increase the risk for autism spectrum disorders, which has led to a decrease in the vaccination rates. Studies have shown that states with easier exemption procedures have higher non-medical exemption rates [16, 122], and states allowing personal belief exemptions have higher exemptions and lower vaccination rates [122, 151]. Similarly, states that have easier procedures for obtaining a medical exemption have significantly higher exemption rates [156].

A reduction in vaccination rates has led to a decrease in the percentage of the population that is immune to measles, which has led to a number of outbreaks [19]. Figure 2.1 includes the number of reported measles cases in the U.S. from 2006 to 2017 [27] and the monthly

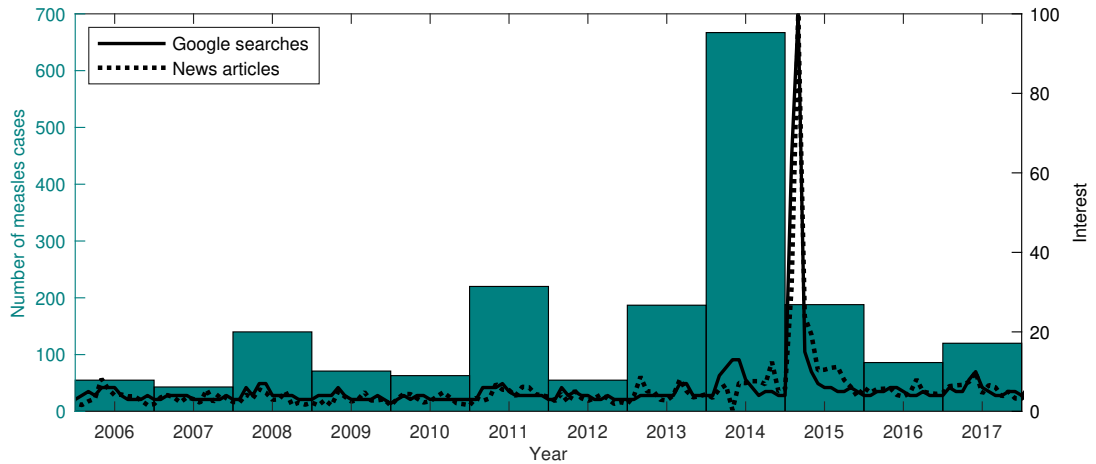


Figure 2.1: Measles cases in the U.S. and popularity in the news and Google searches per month. The bars show the number of annual measles cases. The number of news articles were obtained from the Lexis Uni [89] database after searching for the word *measles*, and filtering for articles in the U.S.. The Google searches were obtained through Google trends (trends.google.com). Both are normalized to a maximum value of 100.

media coverage of measles as well as the Google searches of the word *measles* from 2006 to 2017. The most publicized measles outbreak originated in Disneyland, California, and started in late December 2014 and continued into early February 2015 [180]. In total, 125 measles cases were reported in connection with this outbreak, affecting people from several states. Even though there were worse outbreaks around the time of the Disneyland outbreak, resulting in a larger number of measles cases, the Disneyland outbreak was the event that worried or, at the very least, interested the most people. In other words, in early 2015 a large portion of the U.S. population found out about the effects of measles and how low vaccination rates can lead to outbreaks.

Prior research has linked media coverage of the MMR vaccine to vaccination rates. In Wales, there were significantly lower vaccination rates in a region where a newspaper was

publishing articles against MMR vaccination [99]. A study conducted in Denmark covering the period 1997 to 2014 found a positive correlation between MMR vaccination rates and pro-vaccination or neutral media coverage in the period 1997 to 2004 [63]. A study utilizing data from the National Immunization Survey (NIS) from 1995 to 2004 found a limited association between media coverage and MMR vaccination in the U.S. [154]. There has been limited research into the impact of the Disneyland outbreak. A survey in Colorado found that women with children had a more positive attitude towards MMR vaccines after the Disneyland outbreak [22]. However, very few women planning to not vaccinate their children changed their intention.

Controlling for socioeconomic factors is critical when studying policy effects on health outcomes, as socioeconomic factors influence health care choices, health care utilization, and lifestyle choices [103, 116, 132] just to name a few. Socioeconomic factors that have been shown to influence childhood vaccination rates include education, material deprivation, and population density [177].

In the age of big and easily accessible data, there is access to a wide range of socioeconomic controls, with numerous correlated indicators available. As an example, the state of the economy (which has been linked to healthcare utilization and health outcomes in numerous studies) can be represented by the unemployment rate [161], average or median wages [88], income inequality [129], affordable housing [131], and others. Simply including all available socioeconomic factors in a model is not a good solution as it can lead to multicollinearity, increasing variability in the model's estimates, and, potentially, to incor-

rect conclusions. The selection of socioeconomic factors is, therefore, a complex modeling question, which has not been fully addressed in the literature. In this chapter, we will demonstrate its importance. At the same time, there is significant under-reporting on the socioeconomic factors included in the vaccination policy literature and on the method of selection. For example, in papers studying the impact of vaccination policies on childhood vaccination rates in the U.S., it is common for the complete output of the model, including information about which socioeconomic factors are used, their corresponding coefficients and statistical significance to be missing [19, 151, 156]. In addition, the reporting of the explanatory power of the corresponding models is often missing, limiting the understanding as to what extent the included factors drive the outcome.

The goal of this study is threefold. First, we seek to understand whether exemption regulations for school age children translate to infants and young toddlers. Prior studies of the vaccination and exemption rates in the U.S. focus on children going to kindergarten [16, 19, 122, 151, 156]; the impact of these policies on vaccination rates of younger children has not been studied. Second, we aim to understand the effect of the Disneyland outbreak on vaccination rates at the national level. To the best of our knowledge, there is no study of MMR vaccination focusing on the period after the Disneyland outbreak [151]. Finally, we demonstrate the importance of carefully selecting socioeconomic factors for health policy studies. We show that the outcome of the study is highly sensitive to the selection; small changes can lead to different results and conclusions, highlighting the importance of careful reporting of socioeconomic controls.

2.2 Methods

2.2.1 Data

We used state level data (all 50 states and the District of Columbia (DC)) from 2011 to 2017. The data were obtained from a number of sources, as detailed below.

The dependent variable is the annual percentage of children 19 to 35 months old that have gotten at least one dose of the MMR vaccine, obtained from the Centers for Disease Control and Prevention's (CDC's) ChildVaxView database [26]. These percentages were estimated based on the annual NIS - Child survey [28]. This annual survey uses telephone interviews as well as immunization histories. The state level estimation rate is estimated based on the answers obtained from those surveyed.

Independent variables were created to reflect the vaccination exemptions in each state using information from the National Conference of State Legislatures [114]. Exemptions allowed in each state are either only medical, medical and religious, or medical, religious, and personal belief exemptions. There were changes in the exemption policy of two of the states in 2015, which were accounted for. California stopped allowing religious and personal belief exemptions, while Vermont removed personal belief exemptions. In 2017, three states only allowed medical exemptions, 29 states and DC allowed medical and religious exemptions, and 18 states allowed medical, religious, and personal belief exemptions. The independent variable used in our analysis is a binary variable showing whether a state allowed personal belief exemptions in a specific year or not.

We account for nationwide changes in underlying vaccination rates by including annual control variables. The annual control variable for 2015 is of special interest to understand the impact that the Disneyland outbreak may have had on overall vaccination rates. We hypothesize that the increased awareness of measles outbreaks would lead to higher vaccination rates in 2015.

The socioeconomic independent variables in our analysis come from the Opportunity Index database (OID) [123]. The data include a number of variables covering education, economics, community, and healthcare (see Table 2.1 for the variables and their descriptions). Where the OID data did not include full information for our study period, additional data were collected. Specifically, information on the number of medical doctors (per 100,000 population) in each state in 2016 and 2017 was gathered from the Association of American Medical Colleges [1], and the percentage of the population without health insurance in each state from 2011 to 2015 was collected from the American Community Survey [3]. The OID also includes indices for overall education, economics, community, and healthcare in each state, which are averages of the rescaled underlying factors (see [123] for additional information). In our analysis, we consider the individual factors as well as the indices for the economy, education, and community dimensions.

Additionally, we incorporated demographic information for each state, obtained from the Henry J. Kaiser Family Foundation [77]. In particular, our dataset includes separate variables for the population percentage of white, black, Hispanic, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and multiracial. In total, the data

Table 2.1: Variables obtained from the Opportunity Index database.

Variable	Description
Jobs	Unemployment rate
Wages	Median household income
Poverty	Pct. of population below the federal poverty level
Income Inequality	Ratio of household income at the 80th percentile to that at the 20th percentile
Access To Banking Services	Banking institutions per 10,000 population
Affordable Housing	Pct. of households spending less than 30% of their income on housing
Preschool Enrollment	Pct. of 3- and 4-year-olds attending preschool
High School Graduation	Pct. of on-time high school graduations
Postsecondary Education	Pct. of adults with Associate's degree or higher
Health Insurance Coverage	Pct. of population without health insurance
Access to Medical Care	Medical doctors per 100,000 population
Volunteering	Pct. of adults who volunteered during the previous year
Youth Disconnection	Pct. of youth not in school and not working
Violent Crime	Incidents of violent crime per 100,000 population
Access to Healthy Food	Grocery stores and produce vendors per 10,000 population

contains 32 independent variables and 357 observations, corresponding to information for all 50 states and DC over the seven-year study period.

2.2.2 Methodology

We use multiple linear regression to model the impact of state exception policies and other factors on annual vaccination rates, using different approaches for the selection of socioeconomic factors. In addition to socioeconomic factors, all models include the exemption policy of each state, annual indicator variables (using 2011 as a reference category), and the percentages of white, black, Hispanic, and Asian populations. The goodness-of-fit of the various models is reported using R^2 . All analysis was conducted in R, version 3.5.3, using the *olsrr* package for variable selection models.

A number of approaches exist to address multicollinearity [43, 55], ranging from manually selecting a few key factors to running principal component regression. We apply expert selection as our base model. Using an *econometric* approach, key socioeconomic factors were manually selected based on past research findings. The advantage of this approach is that the factors are pre-selected, enabling the study of a specific set of socioeconomic factors. This is the most common approach used in the health policy literature, including the papers studying the effect of state policy on vaccination rates [19, 151, 156]. The socioeconomic controls chosen were poverty rates, on-time high school graduations, lack of insurance coverage, and access to medical care.

As sensitivity analysis, we implemented multiple different approaches to understand

the sensitivity of the results to the socioeconomic factor selection, each discussed below. We examined all regression models for multicollinearity using the variance inflation factor (VIF). As a rule of thumb, a VIF value larger than 10 indicates an issue with multicollinearity [6].

2.2.2.1 Manual index creation

As a first alternative, we implemented an *econometric approach using the OID indices*. Instead of adding individual socioeconomic factors as independent variables, one can summarize factors into indices and combine the socioeconomic factors into a few socioeconomic indices. We utilized the OID indices for education, economy, and the community. This is a knowledge-driven approach, since the indices are estimated based on the underlying factors that are known to be linked to the state of the education, economy, and community of a state.

2.2.2.2 Variable selection methods

Next, we applied variable selection methods. Variable selection methods include or exclude variables from the model based on statistical measures of the variable's influence on the outcome (for example the p-values of the regression coefficients). As a result, variables are automatically selected based on the data and not based on prior domain knowledge. These models typically have fewer variables while retaining predictive power, facilitating interpretability.

Variable selection methods have been widely applied in the health policy literature, with studies focusing on the impact of healthcare campaigns [70], on online healthcare adoption [152], and on hospital readmission [110]. In our analysis we implemented *forward selection*, *backward elimination*, *stepwise selection*, and the *best subset* methods (based on the adjusted R^2 value). For each model, all the individual socioeconomic factors are initially included in the analysis (the OID indices were excluded).

2.2.2.3 Principal Component approach

Fundamentally, principal component analysis uses transformations to convert a set of correlated variables into a set of values of linearly uncorrelated variables called principal components. We included *the principal components* in the regression in the place of socioeconomic controls. Principal component analysis has been used in the literature to summarize information on socioeconomic characteristics in order to, for example, explain mortality rates in rural areas [53] and evaluate the effect of population-based payment models on health care quality and spending [155]. The principal components were generated based on the 15 socioeconomic factors included in the study (see Table 2.1). The number of components was selected based on the cumulative proportion of the variance accounted for using the scree test [2]. The advantage of using principal components is that it is ensured that there will not be any multicollinearity issues, since the resulting variables (or components) are uncorrelated. However, the disadvantage is lack of interpretability.

2.2.2.4 All possible combinations

In addition to the above models, in order to highlight the potential variability in policy and annual estimates based on which socioeconomic factors are included, we built a linear regression model for each possible combination of socioeconomic factors. As there are 15 factors, this corresponds to 32,767 unique regression models. We examined the value of each regression coefficient and its level of significance in every model. We focus on the impact of the exemption policy as well as the annual indicator variables.

2.3 Results

2.3.1 Correlation analysis

In order to highlight the correlations within socioeconomic factors, we ran a correlation analysis. Figure 2.2 shows the correlations between every pair of continuous independent variables. We note that some of the variables are strongly correlated. For example, the poverty rate is strongly negatively correlated with the median household income in a state. Similarly, the percentage of the population that is white is negatively correlated with the variables for other populations. These correlations highlight the importance of considering multicollinearity. Summary statistics of the continuous variables can be found in Table A.1 in Appendix A.

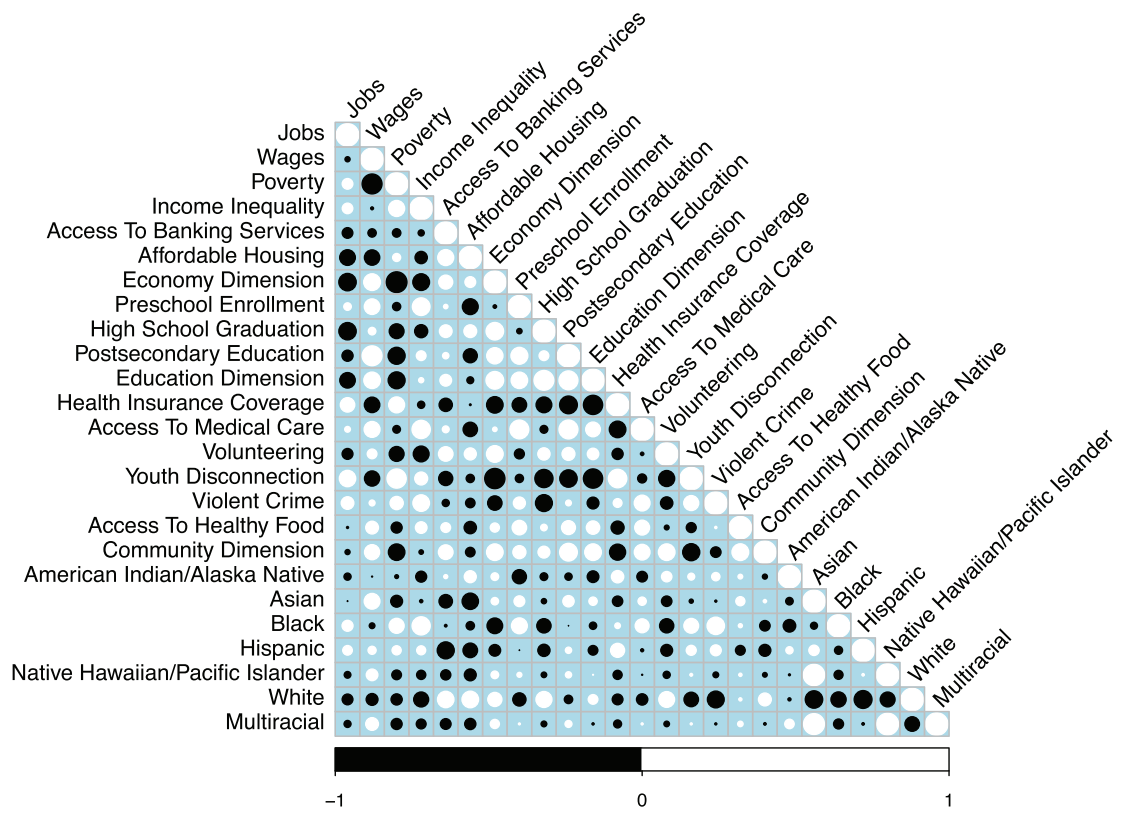


Figure 2.2: Correlations of all continuous independent variables in the dataset. White circles indicate positive correlation and black circles indicate negative correlation, the size of the circles indicates the magnitude of the correlation.

Table 2.2: Econometric model for predicting MMR vaccination rates ($R^2 = 22.2\%$).

Variable	Coefficient	p-value	VIF
(Intercept)	90.545	<0.001	
Policy			
Allow medical, religious, and personal belief exemptions	-0.972	0.001	1.14
Socioeconomic			
Poverty	-0.091	0.124	2.11
Access To Medical Care	0.000	0.906	2.90
Health Insurance Coverage	-0.178	0.005	4.89
High School Graduation	0.071	0.016	2.50
Demographic			
Pct. of Asian population	-0.025	0.744	9.60
Pct. of black population	0.055	0.136	9.20
Pct. of Hispanic population	0.031	0.408	8.47
Pct. of white population	-0.014	0.745	26.8
Year			
2012	-0.411	0.406	1.75
2013	0.075	0.882	1.84
2014	-0.059	0.911	1.98
2015	0.115	0.830	2.04
2016	-1.026	0.063	2.17
2017	-1.180	0.039	2.32

2.3.2 Regression results

2.3.2.1 The Base Model

The linear regression model for the *econometric* approach has an R^2 of 22.2%. The complete output can be found in Table 2.2.

The regression results highlight that states that allow personal belief exemptions have lower MMR vaccination rates compared to states that do not, but are otherwise similar. The corresponding coefficient in the model is -0.972, (p-value <0.01).

There was a small increase in the observed vaccination rates in 2015 compared to both 2014 and 2016. However, none of the annual regression coefficients between 2012 and 2016 are statistically significantly different from the base year of 2011. Only the annual control for 2017 is statistically significant and shows on average vaccination rates in 2017 were a full percentage point lower after accounting for all other variables in the model (-1.180, p-value <0.05). Further, the difference between the estimated coefficients from 2012 to 2015 are minor, within half a percent. In contrast, in both 2016 and 2017, the rates decreased below the 2011 levels. In other words, *we do not observe a significant increase in vaccination rates following the 2015 Disneyland outbreak.*

In the econometric model, the socioeconomic factors that were statistically significant were the percentage of population without medical insurance and the percentage of on-time high school graduations. States with a higher percentage of the population being uninsured tend to have lower vaccination rates (-0.178, p-value <0.01) and states with higher percentages of on-time high school graduations have higher vaccination rates (0.071, p-value <0.05). The coefficients corresponding to the percentage of the population below the poverty level and the access to medical doctors were not significant in the model.

In the econometric model, the VIF for the percentage of the white population equals 26.8, indicating possible issues with multicollinearity, caused by the strong negative correlation between the percentage of the white population and the percentages of the other demographic groups. Removing this variable from this model resolved the multicollinearity issue, and had minimal impact on the remaining coefficients (the resulting model is

included for comparison in Table 2.3).

Table 2.3: Econometric model (excluding pct. of white population) for predicting MMR vaccination rates ($R^2 = 22.1\%$).

Variable	Coefficient	p-value	VIF
(Intercept)	89.298	<0.001	
Policy			
Allow medical, religious, and personal belief exemptions	-0.979	0.001	1.14
Socioeconomic			
Poverty	-0.092	0.122	2.11
Access To Medical Care	0.000	0.863	2.83
Health Insurance Coverage	-0.172	0.004	4.35
High School Graduation	0.069	0.016	2.38
Demographic			
Pct. of Asian population	-0.002	0.948	1.34
Pct. of black population	0.066	<0.001	2.12
Pct. of Hispanic population	0.042	0.015	1.78
Year			
2012	-0.410	0.406	1.75
2013	0.081	0.872	1.83
2014	-0.043	0.935	1.96
2015	0.137	0.796	2.01
2016	-0.990	0.067	2.08
2017	-1.134	0.040	2.18

2.3.2.2 Other modeling approaches

We summarize the results from the different modeling approaches in Figure 2.3. From the top panel of the figure, we note that the models built based on the variable selection methods have slightly higher R^2 compared to the other models. In particular, the R^2 of the data-driven approaches ranges from 27.4% (stepwise selection) to 31.1% (backward elimination and best subset). In the *econometric approach using the OID indices*, the R^2 was 21%. In the *principal component* regression, the regression included the five first

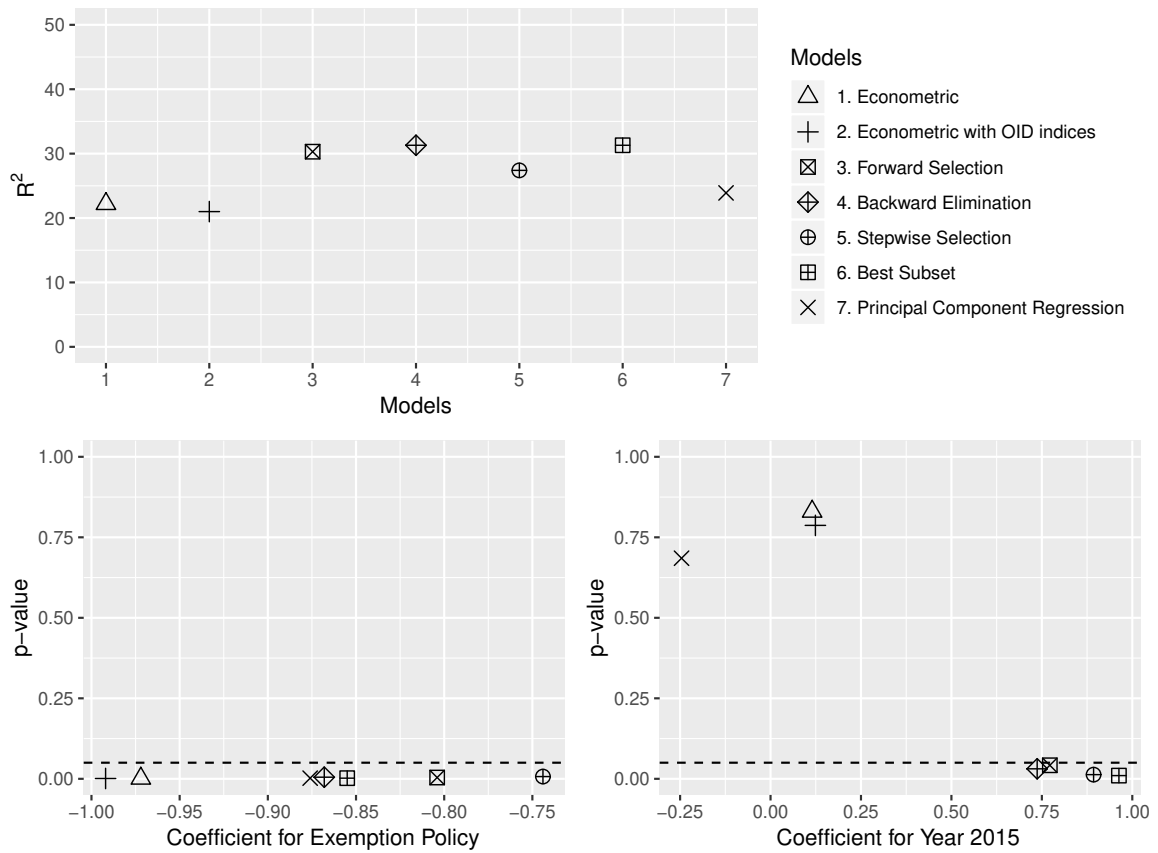


Figure 2.3: Summary of the different approaches (the dashed horizontal lines in the lower panels indicate statistical significance at the 5% level).

principal components, which account for about 84% of the variation in the socioeconomic data. The resulting R^2 from the principal component regression was 23.9%. The results highlight the improved fit of the data-driven models compared to the manual approach, as well as the fact that a large part of the variation in the vaccination rates is not explained by the data. The complete output of the regression models can be found in Tables 2.4 through 2.9.

The lower left panel of Figure 2.3 summarizes the value and the significance of the regression coefficient for the indicator variable for personal belief exemptions. The variable

was selected in all data-driven approaches. For all models, we note that regression coefficient is negative and statistically significant. The magnitude of the impact ranges from -0.744 (stepwise selection) to -0.992 (*econometric approach using the OID indices*) or a relative difference of 28%.

The annual control variable for 2015, the year after the outbreak in Disneyland, was also selected by all the data-driven approaches. However, as highlighted in the lower right panel of Figure 2.3, the magnitude and statistical significance is not consistent across the various models. In particular, the coefficient ranges from negative (-0.246, p-value = 0.685 in the principal component regression) to positive values (0.963, p-value <0.05 in the best subset approach). It is worth pointing out that all the models based on variable selection methods have similar coefficients for the 2015 control, which is positive and statistically significant. *This highlights that depending on the modeling approach chosen, the conclusion about the effect of the Disneyland outbreak can vary considerably.*

Regarding the socioeconomic controls, in the *econometric approach using the OID indices*, the only statistically significant OID index is the education index. The coefficient equals to 0.106 (p-value <0.001), indicating that the higher level of education in a state is linked to higher MMR vaccination rates.

The variable selection models have similarities in terms of the variables included and their coefficient values. Variables that were selected by all four methods were the number of banking institutions per 10,000, where the coefficient ranges from 0.545 to 0.664 (p-value <0.01), the percentage of affordable housing, with the coefficient ranging from -0.220

Table 2.4: Regression model for predicting MMR vaccination rates based on the forward selection method ($R^2 = 30.3\%$).

Variable	Coefficient	p-value	VIF
(Intercept)	110.669	<0.001	
Policy			
Allow medical, religious, and personal belief exemptions	-0.804	0.005	1.24
Socioeconomic			
Affordable Housing	-0.186	<0.001	3.38
Access To Banking Services	0.630	0.001	2.37
Access To Medical Care	0.004	0.193	6.29
Health Insurance Coverage	-0.078	0.170	4.43
Preschool Enrollment	-0.014	0.614	3.49
High School Graduation	0.027	0.328	2.54
Postsecondary Education	-0.133	0.022	7.50
Youth Disconnection	-0.398	<0.001	5.30
Violent Crime	-0.003	0.033	3.90
Volunteering	-0.042	0.252	2.54
Demographic			
Pct. of American Indian/Alaska Native population	0.161	0.014	2.06
Pct. of black population	0.102	<0.001	4.05
Pct. of Hispanic population	0.039	0.056	2.71
Year			
2012	-0.466	0.221	1.15
2015	0.772	0.040	1.12

Table 2.5: Regression model for predicting MMR vaccination rates based on the backward elimination method ($R^2 = 31.3\%$).

Variable	Coefficient	p-value	VIF
(Intercept)	130.351	<0.001	
Policy			
Allow medical, religious, and personal belief exemptions	-0.868	0.002	1.15
Socioeconomic			
Median household income	0.000	0.094	16.1
Poverty	-0.293	0.059	16.2
Affordable Housing	-0.185	<0.001	3.30
Access To Banking Services	0.545	0.005	2.42
Access To Medical Care	0.006	0.059	7.88
Health Insurance Coverage	-0.101	0.088	4.92
High School Graduation	0.036	0.193	2.48
Postsecondary Education	-0.151	0.007	7.03
Youth Disconnection	-0.314	0.003	6.66
Violent Crime	-0.004	0.010	4.17
Demographic			
Pct. of Asian population	-0.225	<0.001	4.78
Pct. of Hispanic population	-0.054	0.012	3.05
Pct. of white population	-0.142	<0.001	11.6
Year			
2012	-0.514	0.172	1.14
2015	0.737	0.050	1.14

Table 2.6: Regression model for predicting MMR vaccination rates based on the stepwise selection method ($R^2 = 27.4\%$).

Variable	Coefficient	p-value	VIF
(Intercept)	104.326	<0.001	
Policy			
Allow medical, religious, and personal belief exemptions	-0.744	0.007	1.13
Socioeconomic			
Affordable Housing	-0.123	<0.001	1.45
Access To Banking Services	0.561	0.001	1.81
Youth Disconnection	-0.376	<0.001	1.69
Volunteering	-0.086	0.005	1.70
Demographic			
Pct. of black population	0.049	0.001	1.48
Year			
2015	0.893	0.013	1.01

Table 2.7: Regression model for predicting MMR vaccination rates based on the best subset method ($R^2 = 31.3\%$).

Variable	Coefficient	p-value	VIF
(Intercept)	123.319	<0.001	
Policy			
Allow medical, religious, and personal belief exemptions	-0.855	0.002	1.20
Socioeconomic			
Affordable Housing	-0.220	<0.001	3.43
Access To Banking Services	0.664	<0.001	2.28
Health Insurance Coverage	-0.146	0.008	4.18
High School Graduation	0.032	0.256	2.59
Postsecondary Education	-0.107	0.025	5.21
Youth Disconnection	-0.378	<0.001	5.01
Volunteering	-0.053	0.135	2.41
Violent Crime	-0.003	0.024	2.99
Demographic			
Pct. of Asian population	-0.320	<0.001	13.6
Pct. of Hispanic population	-0.044	0.051	3.36
Pct. of multiracial population	0.212	0.090	7.35
Pct. of white population	-0.111	<0.001	8.38
Year			
2014	0.455	0.217	1.10
2015	0.963	0.010	1.11

Table 2.8: Econometric model with OID indices for predicting MMR vaccination rates ($R^2 = 21\%$).

Variable	Coefficient	p-value	VIF
(Intercept)	83.244	<0.001	
Policy			
Allow medical, religious, and personal belief exemptions	-0.992	0.001	1.10
Socioeconomic			
Economy Dimension	0.002	0.960	2.84
Education Dimension	0.106	<0.001	2.75
Community Dimension	0.052	0.102	3.06
Demographic			
Pct. of Asian population	0.026	0.309	1.12
Pct. of black population	0.045	0.005	1.72
Pct. of Hispanic population	0.011	0.463	1.33
Year			
2012	-0.520	0.292	1.72
2013	-0.131	0.791	1.74
2014	-0.209	0.683	1.86
2015	0.124	0.809	1.88
2016	-0.395	0.506	2.50
2017	-0.306	0.615	2.63

Table 2.9: Principal Component regression for predicting MMR vaccination rates ($R^2 = 23.9\%$).

Variable	Coefficient	p-value	VIF
(Intercept)	91.350	<0.001	
Policy			
Allow medical, religious, and personal belief exemptions	-0.876	0.002	1.12
PCA of Socioeconomic factors			
1st component	-0.559	<0.001	1.59
2nd component	-0.123	0.273	3.01
3rd component	0.174	0.193	1.85
4th component	0.446	0.006	1.71
5th component	0.150	0.450	2.10
Demographic			
Pct. of Asian population	0.005	0.873	1.67
Pct. of black population	0.069	0.001	3.03
Pct. of Hispanic population	0.037	0.056	2.22
Year			
2012	-0.637	0.201	1.82
2013	-0.238	0.646	1.96
2014	-0.473	0.405	2.36
2015	-0.246	0.685	2.69
2016	-1.298	0.045	3.04
2017	-1.381	0.046	3.49

to -0.185 (p-value <0.01), and the percentage of youth not in school or working, where the coefficient ranges from -0.398 to -0.314 (p-value <0.01). Furthermore, the variables corresponding to the percentage of adults with higher education (coefficient ranges from -0.151 to -0.107), and the incidents of violent crime per 100,000 population (coefficient ranges from -0.004 to -0.003) were included in three out of the four models and are in all cases statistically significant at the 5% level. Other variables that were included in three of the four models were the percentage of adults who volunteer, where the coefficient ranges from -0.086 to -0.042, only statistically significant in the stepwise selection model (-0.086, p-value <0.01), the percentage of population without health insurance, where the coefficient ranges from -0.146 to -0.078, only statistically significant in the best subset model (-0.146, p-value <0.01), and the percentage of on-time high school graduations, where the coefficient ranges from 0.027 to 0.036, but is not statistically significant in any of the models.

From the above, we see that education is linked in general to higher MMR vaccination rates. Nevertheless, populations with a higher percentage of postsecondary education are linked to lower vaccination rates. While this might be surprising, it is similar to the results of [177]. Factors that are associated with economic prosperity are also linked to higher vaccination rates. However, affordable housing is an exception since it is associated with lower MMR rates in the models discussed above.

Multicollinearity is observed in some models resulting from *variable selection methods*. In the backward elimination model, the variable corresponding to the percentage of white

population in a state has a VIF equal to 11.6. This is similar to the multicollinearity observed in the *econometric* model, since this variable is strongly negatively correlated with the other two demographic variables included in the model. Some multicollinearity is also observed in the demographic variables in the best subset model. Again in the backward elimination model, the variables corresponding to the median household income and the percentage of the population below the federal poverty level have increased VIF values. Those two variables were identified to be strongly negatively correlated in the correlation analysis. Since the above models were chosen based on variable selection methods, we did not remove any of the variables. Nevertheless, this shows that the commonly used variable selection methods do not fully safeguard against multicollinearity.

2.3.2.3 All possible combinations

Figure 2.4 summarizes the regression coefficients for all possible combinations of socioeconomic factors; each model controlled for a different set of socioeconomic factors. In all possible regressions, the coefficient for allowing personal belief exemptions was negative and statistically significant at the 5% level. Thus, we can safely conclude that the states that allow personal belief exemptions have statistically significantly lower MMR vaccination rates. However, the range of the coefficient varies significantly between -0.62 and -1.21. The regression coefficient for 2015 in some cases was negative but not statistically significant. In other cases, the coefficient was positive, sometimes statistically significant and sometimes not. Out of the 32,767 experiments run, only 1,269 had a pos-

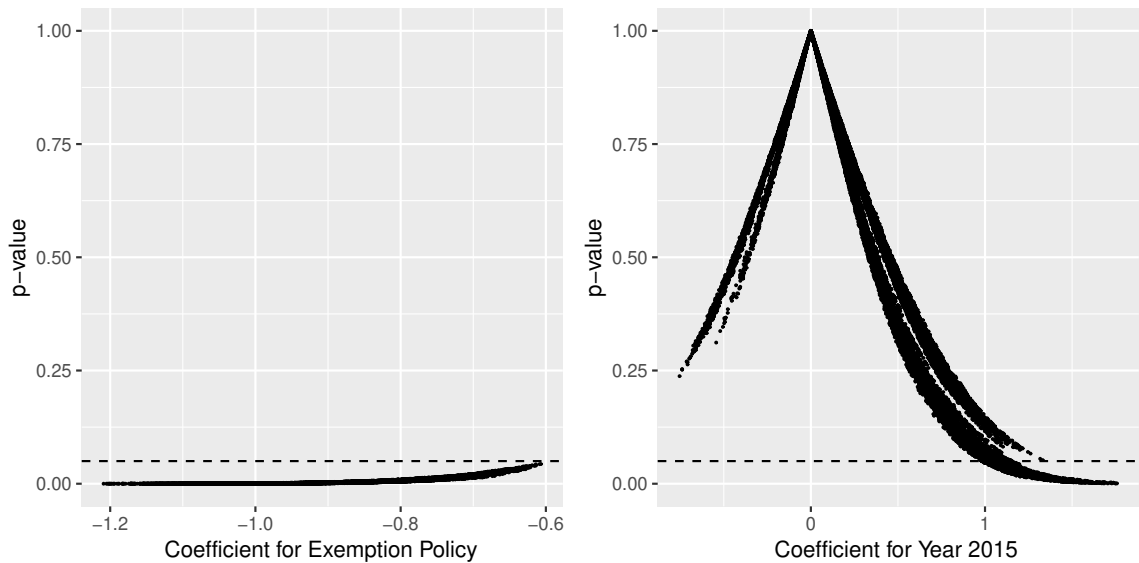


Figure 2.4: Coefficients and significance observed for various combinations of socioeconomic controls (the dashed lines indicate statistical significance at the 5% level).

itive and statistically significant coefficient for year 2015, which corresponds to less than 4% of all possible combinations. Taking a closer look at this subset of models, two variables commonly appear; the percentage of affordable housing and the number of banking institutions. Out of the 1,269 models, 1,027 models included both variables, 87 included affordable housing but not banking, and 109 included banking and not affordable housing. In total, the above corresponded to over 96% of the models with a positive and statistically significant coefficient for 2015.

2.4 Discussion

This study focused on the vaccination rates of children between 19 and 35 months old. Independent of the modeling approach taken, the coefficient of allowing personal exemp-

tions was negative and statistically significant. From our baseline model, we estimate the impact of allowing personal exception to be -0.97 percentage points. The impact was estimated to be between -0.74 and -0.99 percentage points when using other modeling approaches commonly applied in the literature. Allowing for selection of any socioeconomic controls the estimated impact is between -0.62 and -1.21 percentage points. Our study demonstrated the sensitivity of the choice of socioeconomic factors on policy impact estimates, highlighting the importance of carefully selecting socioeconomic factors in regression modeling aimed at estimating policy effects.

Our study population does not necessarily attend preschool [113] and is, therefore, not directly influenced by school vaccination requirements. However, we observe that young children living in states where personal belief exemptions are not allowed get vaccinated at higher rates. This shows the significance of the vaccination exemption policies on MMR immunization rates in young children. This is important because it is crucial for young children to get vaccinated, since children younger than 5 years old have a higher risk of serious measles complications [175].

Our empirical study of Google searches and media coverage suggests great interest in measles following the Disneyland outbreak. This was an outbreak that affected people from numerous states and was extensively discussed in the media. However, we cannot draw any clear conclusions from our regression analyses about the effect of the Disneyland outbreak on the vaccination rates. Our baseline model does not find the indicator variable for 2015 to be statistically significant. Some of the other modeling approaches resulted in

a positive and statistically significant effect on vaccination rates in the year of the outbreak. The sensitivity analysis further highlights the differences in the results, which depend on the selected socioeconomic controls.

Most of the models that resulted in a positive and statistically significant annual indicator variable for 2015 included at least one of two specific socioeconomic controls, affordable housing and the access to banking institutions. Notably, those two controls were also selected by all the variable selection methods, which all resulted in regression models with a positive and statistically significant annual indicator variable for 2015. Both controls are linked to the overall prosperity of a state, and they are correlated ($\rho = 0.50$). Interestingly, while access to banking institutions is positively correlated with vaccination rates, affordable housing is negatively correlated with vaccination rates.

In this work, we report the R^2 for each model, which highlights that socioeconomic, demographic, and exemption policies only explain up to 31% of the variation in state level vaccination rates. Therefore, together with the inherent variability in the survey results that this study is based on, variability in other state specific factors or personal factors appears to drive more than half of state level variability in vaccination rates. Such factors could, for example, include information or vaccination campaigns and the level of anti-vaccination activity.

2.5 Conclusions

One goal of this chapter was to study the effect of the vaccination exemption policy on the vaccination rates of young children. A second goal was to study the effect of the highly publicized Disneyland outbreak on vaccination rates in subsequent years. The results showed that personal belief exemptions were linked to lower vaccination rates, which agrees with the results of previous studies focusing on children attending kindergarten. However, the magnitude of the policy impact changed based on the modeling approach used. We could not conclude whether the Disneyland outbreak had any effect on future vaccination rates, since different models provided contradictory results.

The above highlights the importance of choosing appropriate socioeconomic controls in regression analysis. When studying retrospective data, there is no one superior approach to controlling for complex phenomena such as “the economy,” and as our study shows, the different methods commonly applied in the literature can reach different conclusions. We, therefore, argue that minimally, it is crucial to present complete regression models, including information about the choice of socioeconomic factors, for both replicability and model evaluation. Further, this study suggests the importance of studying the sensitivity of the results with respect to socioeconomic factors, as the choice can significantly influence the estimate of the policy impact.

Chapter 3: The cost of multiple chronic conditions: A study of chronic cost burden using a condition hierarchy

3.1 Introduction

In this chapter, we introduce a new modeling approach to study the cost of chronic conditions. Understanding the costs of chronic conditions can help in designing better prevention interventions.

Roughly half of the U.S. adult population is estimated to have at least one chronic condition, with one in four adults having multiple (two or more) chronic conditions [171]. The healthcare utilization patterns of those with chronic conditions are characterized by more frequent outpatient, and emergency department visits [133, 139], and the resulting and often high cost burden of chronic disease is well documented [10, 30, 51, 153]. In addition to higher costs, chronic conditions have been linked to worse health outcomes and to the prevalence of other chronic conditions [4, 59, 62, 146].

It is, therefore, unsurprising that a large literature focuses on the impact of disease burden on healthcare costs and the correlation between chronic diseases. Typically these studies focus on one condition at a time. For example, diabetic patients have been found

to be at higher risk of depression, and the combination of diabetes and depression is linked to increased total healthcare costs [45]. Similarly, diabetics who have a thyroid disease have higher healthcare expenditures compared to those who do not have a thyroid disease [137]. Cancer survivors are more likely to get (multiple) chronic conditions, and have higher medical costs for those chronic conditions (e.g., heart disease, stroke) compared to people without a history of cancer [59]. Depression is another condition studied in the literature; depression is linked to higher non-mental health costs in patients with chronic conditions, while at the same time chronic conditions are more prevalent in people with depression [174]. Other studies that focus on disease burden and costs include studies of chronic obstructive pulmonary disease [15], rheumatoid arthritis [62], and autism spectrum disorders [168]. A summary of the existing literature focusing on costs linked to multiple chronic conditions can be found in [146].

There are a handful of papers that study the cost of combinations of chronic conditions. The cost of four chronic conditions, arthritis, diabetes mellitus, heart disease, and hypertension, is studied in [104]. The study concludes that adults with all four chronic conditions have the highest cost. In the cases where only two or three conditions are present, combinations including arthritis, diabetes mellitus, and/or heart disease lead to the highest overall costs. Combinations of two and three chronic conditions are studied in [95], and ordered based on prevalence and cost. In particular, the authors focus on 69 chronic conditions and generate all possible combinations of conditions (of size 2 or 3), gender, and age group. This allows them to investigate the burden of combination of conditions in the

population studied, compare the results with the national numbers, and identify subsets of the population that might cause concern. In this population, the most common dyad is hypertension and hyperlipidemia, and the most common triad is diabetes, hypertension, and hyperlipidemia. The cost of 10 common chronic conditions and all combinations of two of the conditions is studied in [38]. For most combinations of two chronic conditions a super-additive effect is observed, which indicates that the sum of the cost of having each condition separately is lower than the cost of having both conditions. However, some combinations have the opposite effect. For example, the combination of cancer and stroke leads to lower costs than the sum of the costs of the individual conditions.

Improved understanding of the chronic disease cost burden will aid in the design of policy and programs. For example, in value-based payment schemes, cost-based models are often used as the justification for clinical outreach and interventions. A deeper understanding of the chronic cost burden can help develop insights for these targeted programs [95, 135]. While it is well known that chronic diseases generally increase utilization and cost, limited knowledge exists about the interactions and the cost implication of multiple chronic diseases.

The presence of comorbid conditions may affect both the severity of other conditions and the course of treatment. More specifically, the aggressiveness of the treatment of each chronic disease (and, therefore, potentially the associated costs) may be affected by the number of other more serious diseases that are present. In this chapter, we aim at building a comprehensive picture of the costs of multiple chronic conditions. We introduce a novel

approach to model the cost of chronic conditions as a function of each condition's place in a cost hierarchy, and study a larger set of chronic conditions than previously in the literature. Our modeling approach enables the study of how each condition contributes to the overall cost based on the number of other (more costly) conditions that the person has.

3.2 Methodology

3.2.1 Data

This study is based on claims data, provided by two large insurance companies in the Rochester area of New York State. The dataset is a repository of fully de-identified HIPAA compliant data containing several years of historical claims records. The repository is administered by the Finger Lakes Health Systems Agency, and comprises data from commercial accounts, Medicare Advantage and Medicaid Managed Care accounts, and account data for which the two insurers serve as third-party administrators. The repository contains more than 300 million claims records related to outpatient, inpatient, and pharmacy services. The data extends from 2007 through 2013.

Important to this study is the fact that the total cost of each service is averaged across all providers to protect proprietary pricing information, and can be separated into: (1) group costs, which are the total costs attributed to hospital resources utilized during a patient's inpatient stays (such as room charges); and (2) claim costs, which are the total costs attributed to physician services provided by medical staff either in an inpatient setting (such as the services delivered by an anesthesiologist not employed by the hospital) or outpa-

tient settings. In this study, we combine the group and claim costs as well as the costs of pharmaceutical claims, as the total healthcare cost of members. Note that the cost is not limited to the expenses related to the chronic conditions under study, but is the total annual healthcare cost for the member.

3.2.2 Chronic condition identification and inclusion criteria

A number of approaches and definitions have been used to determine which conditions are considered to be chronic [12, 146]. With our goal of building a comprehensive picture of chronic cost burden, we adapted the algorithm provided in [94], which summarizes diagnosis codes for 69 chronic conditions. This algorithm has been used to identify chronic conditions in a number of recent studies [64, 166, 169]. For certain clinical conditions, we augmented the algorithm with additional codes as detailed in Appendix B. This was done in order to improve the sensitivity of the algorithm and ensure that no diagnoses are overlooked. Table 3.1 includes the chronic conditions included in the study and the corresponding abbreviations used in figures and tables throughout the chapter. It also includes the number of members identified with each condition. This study focuses on explaining the overall healthcare costs in 2012. Therefore, a member was considered to have a chronic condition if (s)he had at least one claim with a corresponding diagnoses code in 2012, and a second claim with a diagnoses code (for the same condition) at least three months apart (in 2012 or earlier). This ensured the exclusion of short term treatment of chronic conditions, or potentially erroneous diagnoses coding of claims associated with diagnostic

testing. Sensitivity analysis of the inclusion criteria is provided in Appendix D. Note that all diagnoses codes were considered (not only primary) as secondary (or other) diagnosis codes are considered as a confirmation of the existence of the chronic condition. Finally, only members that are at least 18 years old in 2012 are included in the study.

Table 3.1: Chronic condition studied and the number members identified.

Chronic Conditions	Abbreviations	Member Count
Allergy, ENT and other upper respiratory disorders	allergy	50,740
Anemia and other non-cancer heme disorders	anemia	9,709
Aneurysm	aneurysm	3,993
Anxiety disorders	anxiety	45,914
Asthma, COPD, other chronic lung disease	asthma	46,364
Coronary atherosclerosis	athero	38,324
Back problems	back	27,075
Behavior disorders	behavio	9,555
Benign neoplasm	benign	537
Bipolar disorder	bipol	7,494
Benign prostatic hypertrophy (BPH)	bph	19,586
Breast non-cancer	breast	1,284
Cerebrovascular Disease	cerebro	14,164
Congestive heart failure	chf	11,435
Chronic Infectious and Parasitic Diseases	chroninf	1,120
Other central and peripheral nervous system disorders	cnspps	29,651
Congenital Heart Disease	concard	2,213
Non-cardiac congenital disorder	congen	6,668
Cystic fibrosis	cystic	51
Organic brain problem (dementia)	dem	7,840
Dental and mouth disorders	dental	14
Depression and depressive disorders	depress	65,975
Diabetes mellitus	dm	68,641
Conduction disorder or cardiac dysrhythmia	dysrhy	35,208
Epilepsy	epilepsy	2,891
Esophageal disorder and GI ulcers	esoph	50,353
Degenerative eye problem (glauco/eye)	eye	87,833
Female infertility and GU anatomic disorders (e.g. prolapse, endometriosis)	femalegu	21,211
Diverticulosis, diverticulitis, enterocolitis, intestinal malabsorption	gi	20,838

continued ...

... Table 3.1 continued

Chronic Conditions	Abbreviations	Member Count
Gout or other crystal arthropathy	gout	8,248
Chronic Hepatitis	hep	1,749
Human immunodeficiency virus	hiv	913
Hypertension	htn	188,613
Hyperlipidemia	hyprlip	179,822
Immunity disorder	immun	3,019
Kidney and Vesicoureteral Disorders (excl. renal failure)	kidney	11,870
Chronic Liver Disease (excl. chronic hepatitis)	liver	5,155
Lupus	lupus	3,416
Male GU excluding BPH	malegu	6,666
Malignant neoplasm	malig	30,323
Malnutrition (not obesity/overweight)-includes disorders of metabolism	malnutr	48,801
Menopause and perimenopause	menop	9,456
Acute myocardial infarction	mi	1,313
Migraines	migrain	12,040
Misc mental health	miscmh	1,064
Multiple sclerosis	ms	2,208
Obesity	obesity	30,229
Osteoarthritis	osteo	58,626
Other endocrine	othendo	72,465
Other MSK including osteoporosis	othmsk	31,774
Chronic pancreatitis	panc	295
Paralysis	para	941
Parkinson's disease	parkin	1,891
Peripheral atherosclerosis	periph	8,728
Personality disorder	persnal	2,546
Pulmonary heart disease	pulmhrt	1,322
Chronic renal failure	renal	11,757
Rheumatoid arthritis	rheum	7,376
Schizophrenia and Psychotic Disorders	schiz	3,039
Sickle cell anemia	sickle	126
Chronic skin ulcer	skin	14,596
Sleep disorders	sleep	21,233
Sexually Transmitted Infections	sti	497
Cardiomyopathy and Structural Heart Disease	strcght	10,556
Substance-use Disorders	subst	36,407
Tuberculosis	tb	1

continued ...

... Table 3.1 continued

Chronic Conditions	Abbreviations	Member Count
Thrombosis and Embolism	thrombemb	400
Heart valve disorder	valve	15,440
Non-thrombotic, non-atherosclerotic vascular disease	vasc	5,167

3.2.3 Model formulation

As previously discussed, the cost of chronic conditions is affected by the presence of other chronic conditions. Previous work has focused on studying the cost of comorbid conditions in isolation, or studying all combinations of a small set of conditions. When studying a large set of chronic conditions, the number of possible combinations grows exponentially (considering all combinations of two, three, or four combinations of any of the 69 chronic conditions results in over 900,000 combinations). Therefore, we utilize cost as a surrogate for severity and model the cost of any chronic condition as a function of whether the condition is the one that is the most expensive the member has, the second most expensive, and so forward. As an example, the model captures the cost of obesity when it is the most costly condition the person has, the second most costly condition, and so forth. This formulation enables us to study whether the cost of each condition increases or decreases with disease burden.

To support this analysis, we order the conditions in decreasing order of cost. The cost for each condition is the average annual cost across all members with each chronic condition and no other chronic conditions. In order to estimate the effect that each chronic

condition has on healthcare cost as a function of its cost order (or rank) for each member, we formulate the problem using linear regression. The dependent variable (y) is the member's annual healthcare cost in 2012, and the model is specified as follows:

$$y = \alpha + \sum_{j=1}^N \sum_{l=1}^{L_j} \beta_{jl} x_{jl} + \varepsilon, \quad (3.1)$$

where N is the number of chronic conditions taken into account (i.e., $N = 69$), and

$$x_{ijl} = \begin{cases} 1, & \text{if condition } j \text{ is ranked as the } l^{\text{th}} \text{ costliest condition for member } i, \text{ where } l < L_j \\ 0, & \text{otherwise} \end{cases}$$

$$x_{ijL_j} = \begin{cases} 1, & \text{if condition } j \text{ is ranked as the } l^{\text{th}} \text{ costliest condition for member } i, \text{ where } l \geq L_j \\ 0, & \text{otherwise.} \end{cases}$$

Thus, the independent variables show whether a member has each type of chronic condition, and also how this condition is ranked (based on how expensive it is to treat) compared to all other chronic conditions that the member has. We refer to a condition of a specific rank as the *order* that it appears for a member. For example, a condition ranked as the third most expensive condition in an individual, appears in order 3 for this individual.

The parameters L_j are a threshold for each condition j , which limits the cost level of the model. Setting $L_j = 1$ for all j would result in a model that would simple regress the total healthcare cost on each condition (i.e., the x_{ijl} would be binary indicators of the presence of the chronic conditions under study). Increasing L_j allows for more detailed

analysis. However, there are practical limitations to how large L_j can be, even with a large data set. For example, if $L_j = 10$ for all j , we would attempt to estimate the cost of each chronic condition when it is the most expensive condition for a member, all the way to the tenth most costly condition. As most members suffer from a limited number of chronic conditions, for high values of l there are very few (if any) observations for most conditions. In addition, it is important to note that for rare conditions, there may not be a large enough population to estimate its impact when it is the l^{th} most costly condition that a person suffers from. For example, there are only 8 people in our data that have dental and mouth disorders as their fifth most expensive condition, and when the corresponding variable is included in the regression it leads to a coefficient that is not statistically significant.

Note that the costliest conditions also have a limit to the value that L_j can take. For example, in our data, cystic fibrosis is ranked as the most expensive condition. For cystic fibrosis, $L_j = 1$, since either a member has cystic fibrosis as the number one ranked condition or not. Similarly, for conditions ranked second, third, and fourth the maximum value that L_j can take is at most 2, 3, and 4, respectively.

As a result, L_j is set for each condition through an iterative process, to ensure the statistical significance of the regression coefficients. We first set $L_j = L_{\text{max}}$ for all conditions, with two exceptions. First, for the conditions that are ordered as the $L_{\text{max}} - 1$ most expensive conditions, we set their L_j equal to their place in the cost hierarchy. Second, for rare conditions, we observe their maximum position in the hierarchy. For example, in our data, chronic infectious and parasitic diseases appear as the most expensive condition

for some individuals, up to the fourth most expensive condition in others. Thus, for this type of condition $L_j \leq 4$, regardless of the value of L_{max} . After setting the initial L_j for all conditions j , we run a number of regression models to remove variables that are not statistically significant. From the initial run, we study the regression coefficients of all conditions with $L_j = L_{max}$, and in particular on $\beta_{jL_{max}}$ (their coefficient corresponding to the condition when it is the L_{max} most expensive condition for the patient or higher). If $\beta_{jL_{max}}$ is not statistically significant, we update $L_j = L_j - 1$ and update the data accordingly (i.e., $x_{ij(L_{max}-1)} = x_{ij(L_{max}-1)} + x_{ij(L_{max})}$). We then rerun the analysis, and in the next iteration focus on the statistical significance of the $\beta_{j(L_{max}-1)}$ for those conditions that have $L_j = L_{max} - 1$. We continue this process, until β_{jL_j} is statistically significant for all conditions. For example, based on the model resulting from our data, chronic infectious and parasitic diseases include coefficients β_{j4} , and β_{j3} , which are not statistically significant. Thus, after applying the algorithm, this type of condition consists of two coefficients (i.e., β_{j1} , and β_{j2}), since the information from variable x_{j4} was merged to x_{j3} , and in the subsequent iteration the resulting variable was merged to x_{j2} . This procedure is detailed in Algorithm 1.

3.2.3.1 Condition hierarchy example

In this section, we use an example to illustrate the different values that the variables of our model may take. Table 3.2 shows the values that variables take in our condition hierarchy model, before we apply Algorithm 1. In this case, we have set $L_{max} = 5$. For the

Data: Initial set of variables $x^1 = \{x_{ijl}^1 \forall i, j, l\}$.

Result: Reduced set of variables $x^L = \{x_{ijl}^L \forall i, j, l\}$.

Initiation: $m = \{L_{max}, L_{max} - 1, \dots, 2\}$
 L_j equals L_{max} (with exceptions discussed in the main text);
 Build a linear regression model based on x^1 , and obtain initial set of coefficients
 $\beta^1 = \{\beta_{jl}^1 \forall j, l\}$;

Updates: **for** $n = \{2, 3, \dots, L_{max}\}$ **do**

- $x^n = x^{n-1}$;
- $\bar{m} = m_{n-1}$;
- for** *each chronic condition j* **do**
 - if** ($L_j = \bar{m}$)
 - AND** ($\beta_{j\bar{m}}^{n-1}$ is not statistically significant at the 5% level) **then**
 - $x_{ij(\bar{m}-1)}^n = x_{ij(\bar{m}-1)}^n + x_{ij\bar{m}}^n \forall i$;
 - remove $x_{j\bar{m}}^n = \{x_{ij\bar{m}}^n \forall i\}$ from x^n ;
 - set $L_j = \bar{m} - 1$;
 - end**
- end**

Build a linear regression model based on the updated x^n , and obtain set of coefficients β^n ;

end

Algorithm 1: Reducing the variable set based on statistical significance.

Table 3.2: Example showing the values of the variables in our model (before Algorithm 1).

j	Ordered Conditions	L_j	i	Conditions	Variables
1	cystic	1	1	hiv	$x_{1,2,1} = 1,$ and $x_{1,j,l} = 0$ for all other j, l
2	hiv	2			
3	thrombemb	3	2	panc	$x_{2,9,1} = 1,$ and $x_{2,j,l} = 0$ for all other j, l
4	ms	4			
5	hep	5	3	thrombemb, ms, renal	$x_{3,3,1} = 1, x_{3,4,2} = 1, x_{3,8,3} = 1,$ and $x_{3,j,l} = 0$ for all other j, l
6	mi	5			
7	benign	5	4	thrombemb, ms, mi, benign, panc, rheum	$x_{4,3,1} = 1, x_{4,4,2} = 1, x_{4,5,3} = 1,$ $x_{4,7,4} = 1, x_{4,9,5} = 1, x_{4,10,5} = 1,$ and $x_{4,j,l} = 0$ for all other j, l
8	renal	5			
9	panc	5			
10	rheum	5
...			

Table 3.3: Example showing the values of the variables in our model (after applying Algorithm 1).

j	Ordered Conditions	L_j	i	Conditions	Variables
1	cystic	1	1	hiv	$x_{1,2,1} = 1,$ and $x_{1,j,l} = 0$ for all other j, l
2	hiv	1			
3	thrombemb	1	2	panc	$x_{2,9,1} = 1,$ and $x_{2,j,l} = 0$ for all other j, l
4	ms	2			
5	hep	2	3	thrombemb, ms, renal	$x_{3,3,1} = 1, x_{3,4,2} = 1, x_{3,8,2} = 1,$ and $x_{3,j,l} = 0$ for all other j, l
6	mi	5			
7	benign	4	4	thrombemb, ms, mi, benign, panc, rheum	$x_{4,3,1} = 1, x_{4,4,2} = 1, x_{4,5,3} = 1,$ $x_{4,7,4} = 1, x_{4,9,5} = 1, x_{4,10,3} = 1,$ and $x_{4,j,l} = 0$ for all other j, l
8	renal	2			
9	panc	5			
10	rheum	3
...			

purpose of this example, we assume that there exist enough members in our data set, such that each of the presented conditions appears first, up to at least the fifth most expensive condition in a member. Thus, $L_j = 5$, for all conditions. The only exceptions are the four most expensive conditions in our data. Table 3.3 shows the corresponding values after we apply Algorithm 1. We see that for some conditions the value of L_j has decreased, due to some variables not being statistically significant. This has also affected the corresponding

values that the variables take in the last column of the table.

3.2.4 Model fitting

The dependent variable is the annual healthcare cost of the members. Since the distribution of healthcare costs is skewed with non-negative values, we use a gamma regression with log link [38, 96], a common approach with data that has these characteristics. Note that the log link is not the same as a logarithmic transformation of the dependent variable. The log link is a function of the mean of the dependent variable, while a regression with a logarithmic transformation gives the relationship with the mean of the natural logarithm of the dependent variable. Thus, using the log link makes it easier to transform back to the original dollars, since there is no need to correct the retransformation bias [146].

3.2.5 Model interpretation

The regression coefficients β_{jl} in our regression model can be interpreted as the percentage change in the expected annual healthcare cost of the individual member when a specific chronic condition is the l^{th} most expensive condition, when $l \leq L_j$ (and if $l = L_j$ the interpretation is the percentage change when the condition is at least the L_j most expensive condition). Because the underlying costs of someone with no other chronic conditions vs. someone with, say, four other conditions is quite different, then the same percentage increase can correspond to very different cost impacts. As a result, in order to compare cost impact across positions in the cost hierarchy for the same condition, we transform the

coefficients to reflect the change in actual dollars. For this translation, we use the average healthcare cost corresponding to individuals that have a specific condition in a specific order as our estimate. In particular, the dollar contribution of each condition in each order is estimated as $c_{jl} = \frac{e^{\beta_{jl}} - 1}{e^{\beta_{jl}}} \bar{c}_{jl}$, where β_{jl} is the coefficient corresponding to condition j appearing in order l , and \bar{c}_{jl} is the average annual cost of people having condition j in order l .

The above cost contribution is estimated in the following manner. Since we have a logarithmic relationship between the dependent variable and the mean of the independent variables in our model, condition j appearing in order l (i.e., $x_{ijl} = 1$) leads to a total annual cost that is $e^{\beta_{jl}}$ times the total annual cost we would get if condition j did not appear in order l (i.e., $x_{ijl} = 0$). Since we are interested in the contribution of condition j appearing in order l (i.e., the difference in cost between having condition j in order l and not having this condition in order l), we have $c_{jl} = \bar{c}_{jl} - \frac{1}{e^{\beta_{jl}}} \bar{c}_{jl} = \frac{e^{\beta_{jl}} - 1}{e^{\beta_{jl}}} \bar{c}_{jl}$. Thus, $\frac{e^{\beta_{jl}} - 1}{e^{\beta_{jl}}}$ gives us the proportion of the average annual cost that is explained by a member having condition j appearing in order l .

3.2.6 Characterizing cost patterns

We summarize the results of the regression model from three different angles.

First we summarize the average cost contribution (across all possible orders) of each condition ¹ as well as the corresponding variance. Specifically, the average cost contribu-

¹Unweighted average (not weighted by the number of members with condition in each order)

tion for a condition j equals $\frac{1}{L_j} \sum_{l=1}^{L_j} c_{jl}$, and the variance equals $\frac{1}{L_j} \sum_{l=1}^{L_j} (c_{jl} - \frac{1}{L_j} \sum_{l=1}^{L_j} c_{jl})^2$.

As a second step in summarizing the cost characteristics of the different chronic conditions, we fit a simple linear regression model to each condition to capture whether the cost is (on average) increasing or decreasing as a function of the number of other more expensive conditions the member has. Specifically, for each condition j we fit the following regression model:

$$c_j = \gamma_j + \delta_j o_j + \varepsilon_j, \quad (3.2)$$

where $o_j = \{o_{jl} \forall l = 1, \dots, L_j\}$ is the independent variable consisting of the possible orders in which a condition j can appear in our model, and the dependent variable $c_j = \{c_{jl} \forall l = 1, \dots, L_j\}$ is the cost contribution of condition j appearing in each possible order o_j , which is estimated based on the coefficient values of this particular condition, as described in Subsection 3.2.5. The δ_j (the slope for each condition) is an indicator of whether the cost is increasing or decreasing in the order o_j .

Third, we apply k-means clustering in order to group conditions together that have similar cost characteristics. In order to decide on the number of clusters, we computed multiple cluster metrics that reflect the quality of the resulting clusters, such as the silhouette [144], the Hubert index [71], the D index [84], and others. The k was determined by a majority rule of the different metrics, which was done through the *NbClust* package in R. The attributes used in the clustering reflect the curves formed by the resulting regression coefficients for each condition. More specifically, the attributes used in the clustering

algorithm are the change in cost contribution from one coefficient to the next divided by the total range of values for this condition. Thus, for a condition j with cost contribution $c_j = \{c_{jl} \forall l = 1, \dots, L_j\}$, the attributes used in the clustering analysis will be equal to vector $a_j = \left\{ \frac{c_{j(l+1)} - c_{jl}}{\max_l c_{jl} - \min_l c_{jl}} \forall l < L_j \right\}$. These features capture the direction and the magnitude of the change as the condition goes from being the most expensive, to the second most expensive, and so on. Furthermore, with this approach, all attributes take values in $[-1, 1]$.

All the analysis was conducted in R version 3.5.3. utilizing packages *NbClust*, *Rmisc*, *rsq* and *ggplot2*. The research plan for the study was reviewed and approved by the Institutional Review Board (IRB) at the University of Maryland College Park (UMCP).

3.3 Results

3.3.1 Population Statistics

We identified 409,238 members with at least one chronic condition in 2012, with the number of members diagnosed with each type of condition presented in Table 3.1. The average age of members with at least one chronic condition was 55.7 years old, 58% were female, about 28% of our population were enrolled in Medicare, and 8% in Medicaid in 2012. The average number of chronic conditions per member was 3.76 (with a standard deviation of 2.79), and the number of members with each number of conditions decreased exponentially as the number of chronic conditions increased, as depicted in Figure 3.1. Figure 3.2 shows the relationship between the number of conditions a member has, and the age and the total healthcare cost of the member. In particular, the top panel contains box

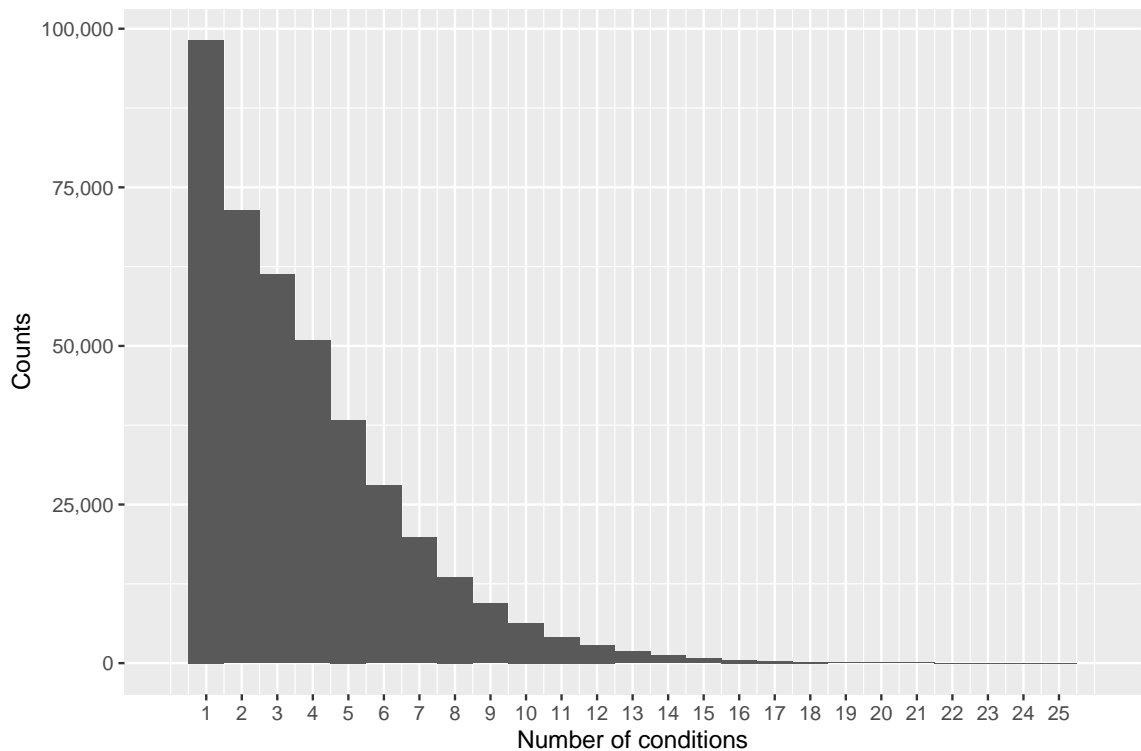


Figure 3.1: Counts of members with each number of chronic conditions.

plots showing the distribution of the number of conditions broken down by age groups. As expected, older members have a higher number of conditions, on average. The bottom panel shows the annual healthcare cost associated with the number of chronic conditions a member has, highlighting that the median annual healthcare cost increases with the number of conditions. Notable, for members with more than 23 conditions, we do not observe a clear increase in the median. This can either be a result of the small number of members (we have 10, 4, and 2 members with 23, 24, and 25 conditions, respectively) as in those cases can easily be affected by only a few observations, or potentially indicating a flattening of the total health care costs when members have a very large number of chronic diseases.

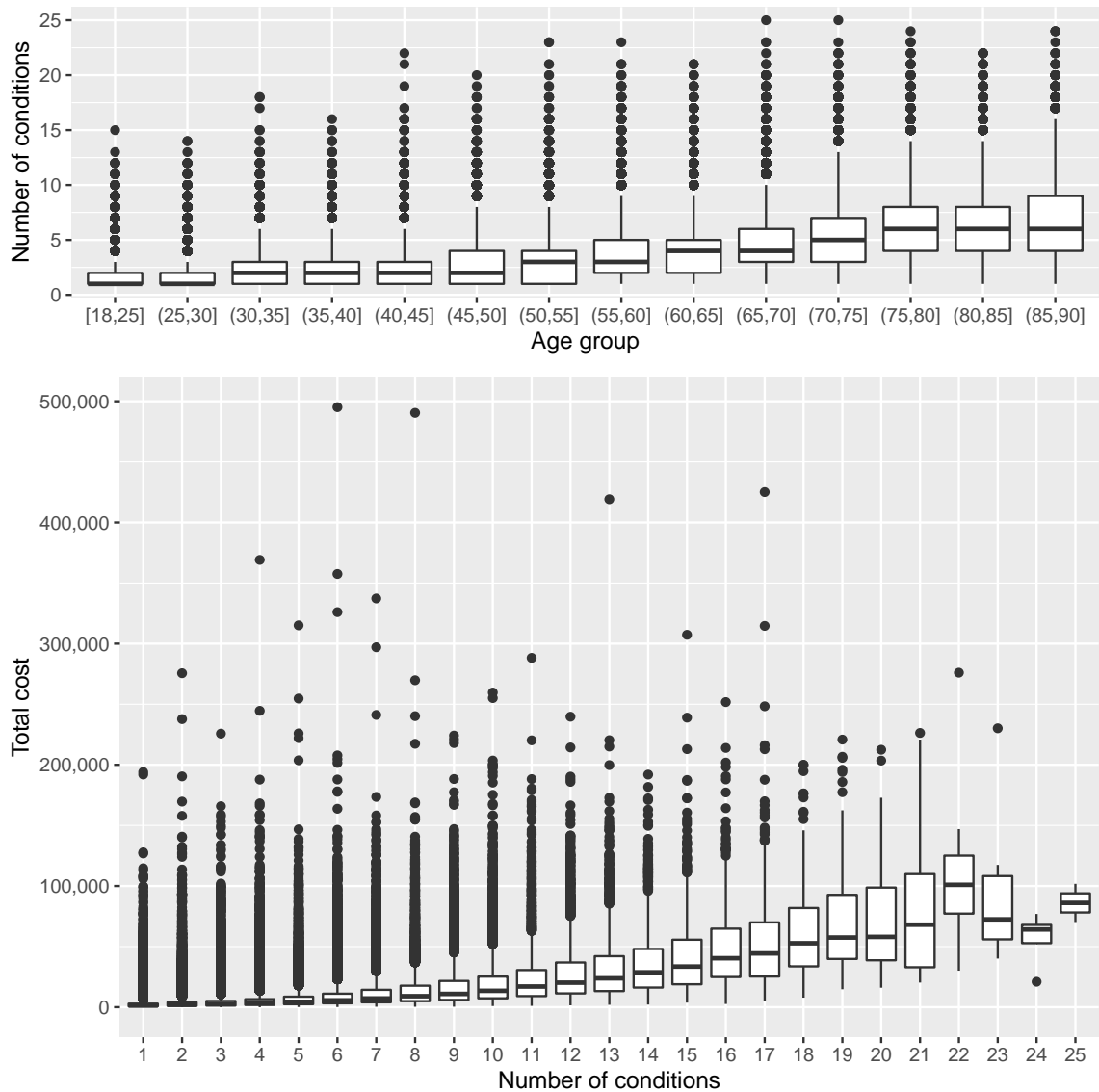


Figure 3.2: Box plots of: number of chronic conditions for each age group (top panel), and annual cost based on number of chronic conditions (bottom panel). Note that in the bottom panel there are very few people with more than 22 conditions (22, 10, 4, and 2 individuals with 22, 23, 24, and 25 conditions respectively).

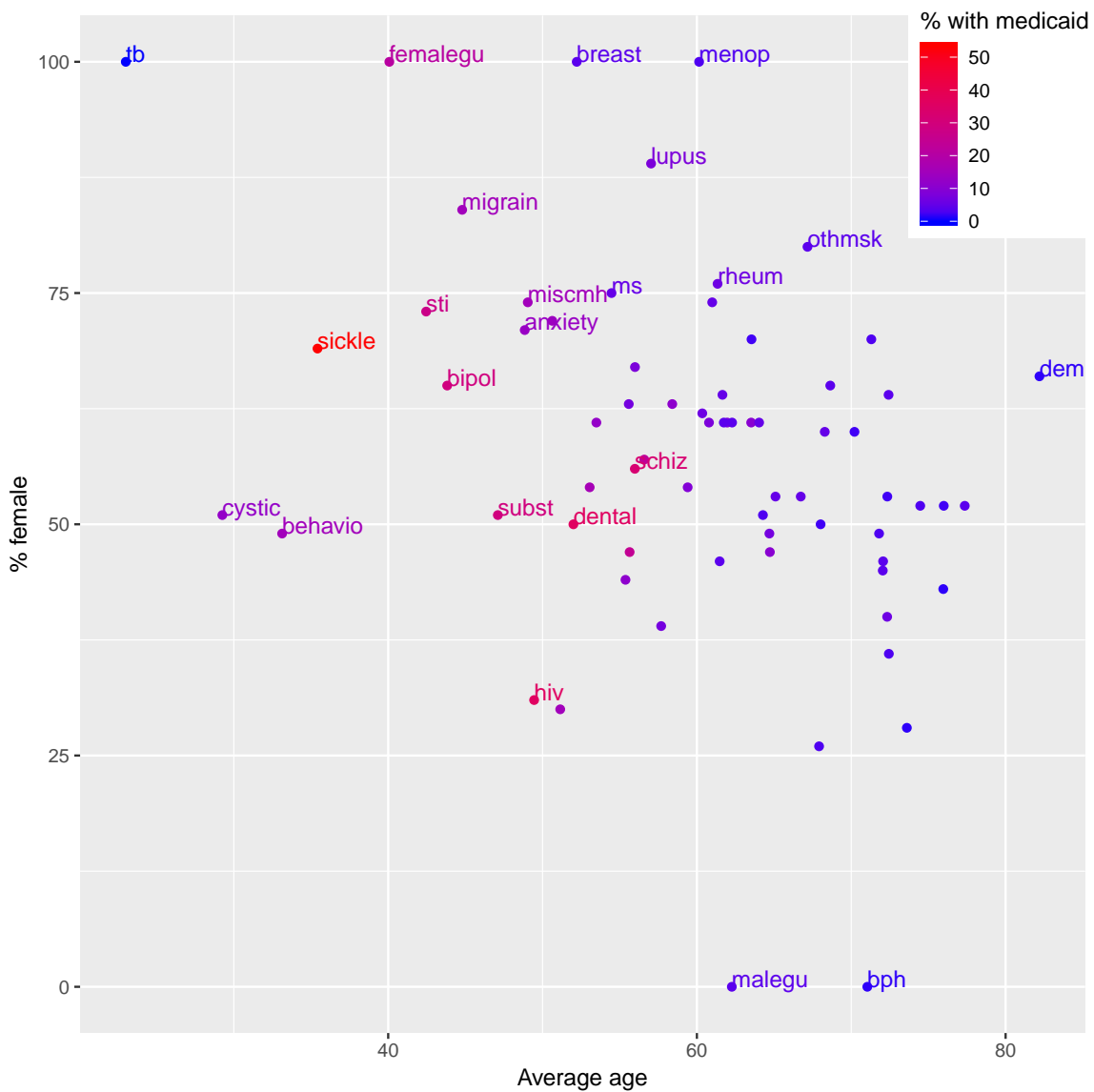


Figure 3.3: Scatter plot of percentage of female population against average age, colored by the percent on Medicaid. The names of conditions that have a higher than 25% of their population covered by Medicaid, an average population age outside the 50 to 80 range, and more than 75% or less 25% of their population being female are labelled.

Figure 3.3 includes a scatter plot of the 69 chronic conditions studied, showing information about the average age of members with the condition, the percentage of the population with the condition that is female, and the percentage that is covered by Medicaid. The figure reflects that our population is 58% female, with the majority of chronic conditions diagnosed in higher percentages in women. Furthermore, we see that some conditions strictly affect women (breast non-cancer, menopause and perimenopause, female infertility and Genitourinary (GU) anatomic disorders) or men (male GU, benign prostatic hypertrophy). Note that tuberculosis (TB) is also a female-only condition in our data, as the one member with TB in 2012 happened to be female. Other conditions that are more common in women (over 75% female), include lupus, migraines, multiple sclerosis (MS), rheumatoid arthritis, and some musculoskeletal (MSK) disorders (including osteoporosis). Specific conditions were also linked to higher percentages of Medicaid coverage. Those included sickle cell anemia, dental and mouth disorders, human immunodeficiency virus (HIV), sexually transmitted infections (STI), schizophrenia and psychotic disorders, bipolar disorder, and substance-use disorders. Finally, we see from the figure that the majority of conditions have an average population age between 50 and 80 years old. The only condition with an average age above 80 is organic brain problem (dementia), while conditions with an average age below 50 include cystic fibrosis, female infertility and GU anatomic disorders, HIV, STI, substance-use disorders, sickle cell anemia, migraines, anxiety disorders, behavior disorders, bipolar disorder, and other mental health disorders.

As discussed in Subsection 3.2.3, we order the conditions in decreasing order of their

Table 3.4: Ordering of conditions and corresponding costs.

Chronic Condition	Order	Average Cost (and Std Dev) members with only this cond.		Average Cost (and Std Dev) all members with this cond.	
cystic	1	18,245	(15,919)	32,056	(24,196)
hiv	2	17,094	(10,167)	24,392	(17,381)
thrombemb	3	16,177	(24,393)	27,853	(34,436)
ms	4	15,599	(15,205)	23,994	(21,190)
hep	5	12,423	(29,036)	21,076	(36,295)
mi	6	12,136	(16,907)	30,792	(33,213)
benign	7	8,473	(16,587)	12,453	(14,776)
renal	8	7,481	(17,098)	23,470	(31,909)
panc	9	7,323	(6,346)	19,722	(21,869)
rheum	10	7,309	(9,896)	13,766	(17,321)
osteo	23	3,626	(5,881)	12,327	(16,707)
dm	33	3,180	(4,426)	11,252	(17,601)
othendo	39	2,822	(5,139)	9,320	(15,281)
asthma	42	2,742	(3,930)	12,526	(18,963)
esoph	43	2,738	(3,491)	10,660	(15,808)
depress	46	2,420	(3,056)	9,570	(15,115)
anxiety	53	2,157	(2,897)	8,921	(14,358)
allergy	55	2,068	(2,914)	7,962	(12,341)
malnutr	56	2,044	(3,660)	9,867	(17,186)
eye	57	2,011	(3,316)	9,602	(14,456)
chf	60	1,958	(2,544)	25,987	(29,871)
menop	61	1,952	(2,132)	7,379	(10,708)
aneurysm	62	1,948	(2,093)	15,961	(21,645)
htn	63	1,925	(3,774)	9,070	(14,753)
periph	64	1,900	(2,646)	20,442	(26,943)
bph	65	1,892	(2,891)	10,001	(15,045)
hyprlip	66	1,669	(2,605)	8,351	(13,736)
gout	67	1,387	(2,116)	13,641	(21,916)
tb	68	1,058	(0)	1,058	(0)
dental	69	706	(479)	14,033	(16,699)

cost in order to generate the variables included in our model. Table 3.4 includes the 10 conditions with the highest, and the 10 conditions with the lowest order, as well as 10 conditions with high occurrence in our population (complete version of table can be found in Table C.1, Appendix C). The table also includes the average annual cost (and standard deviation) of the members in our data that have only been diagnosed with each condition, and none of the other chronic conditions, as well as the average cost (and standard deviation) of all members with each condition.

3.3.2 Modeling Results

3.3.2.1 Overview of resulting coefficients

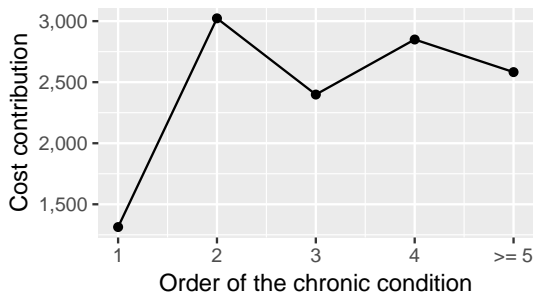
As discussed in Section 3.2.3, a value for the parameter L_{max} needs to be set. To strike a balance between a large enough value of L_{max} in order to observe potential cost patterns in the cost, and at the same time have sufficient sample sizes, we selected $L_{max} = 5$. The full regression model is reported in Table C.2 in the Appendix, and has an R^2 of 42.5%².

A number of conditions have fewer than L_{max} regression coefficients. In particular, four of the conditions have fewer than five coefficients because they were ranked as one of the four most expensive conditions (cystic fibrosis, HIV, thrombosis and embolism, and MS), and 13 have fewer than five coefficients because there were no members in our data that happened to have them in a specific order (benign neoplasm, chronic infectious and parasitic diseases, dental and mouth disorders, GI problems, chronic hepatitis, malignant

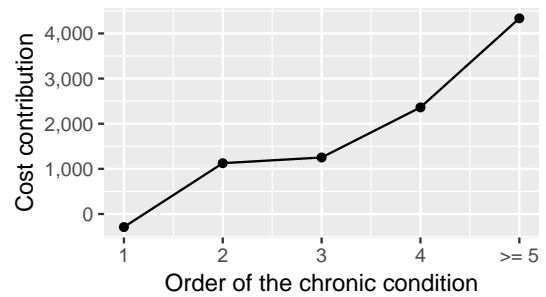
² R^2 for GLM [111], estimated through the *rsq* package in R

neoplasm, acute myocardial infarction, chronic pancreatitis, Parkinson's disease, chronic renal failure, rheumatoid arthritis, sickle cell anemia, tuberculosis). Furthermore, since our data set consists of members who have at least one chronic condition, each member will have exactly one chronic condition ranked as first. Thus, if we include all variables corresponding to a condition being ranked as first in a member, we would have linearly dependent variables. For that reason, we set gout or other crystal arthropathy as the baseline first condition. Additionally, in our data set a single member had acute myocardial infarction as the third condition and chronic renal failure as a fourth condition. In addition, this member was the only member having acute myocardial infarction as a third, and chronic renal failure as a fourth condition. Including both variables in the model would result in linear dependence. For that reason, the variable corresponding to having chronic renal failure as a fourth condition was removed from the regression model. Finally, an additional 60 variables were removed for not being statistically significant by applying Algorithm 1.

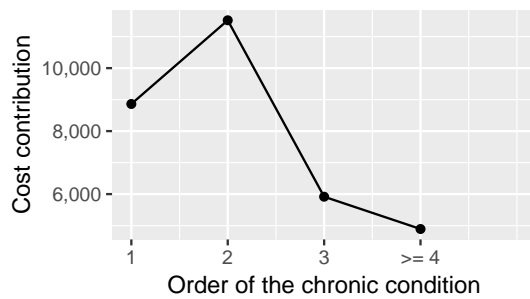
Figure 3.4 includes examples of different cost patterns. Figure 3.4a (coronary atherosclerosis) shows a large increase in the cost contribution when the condition is the second most expensive, compared to when it was the most expensive. However, after that the contribution remains relatively stable, or even a small decrease is observed, when we compare the cost of the condition being the third, fourth, or fifth most expensive to the condition being the second most expensive. In contrast, Figure 3.4b (obesity) shows a relatively stable increase in cost with an increase in the number of more expensive conditions. In other words, the contribution of obesity is increasing in the number of other more expensive



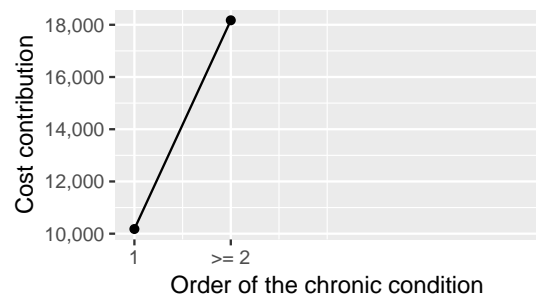
(a) Coronary atherosclerosis



(b) Obesity



(c) Pulmonary heart disease



(d) Chronic renal failure

Figure 3.4: Cost contribution based on the regression coefficients for four chronic conditions

chronic conditions a member has. From Figures 3.4c and 3.4d, we see that some conditions have $L_j < L_{max}$, as discussed above. From Figure 3.4c, we see a clear decrease in the cost contribution, when pulmonary heart disease appears on third order or higher. Finally, chronic renal failure in Figure 3.4d is estimated to have a large increase in cost if the member has at least one additional more expensive chronic condition. From Figure 3.4, it is clear that various conditions have very different cost characteristics as the number other more expensive chronic conditions increases. We summarize the regression coefficients of the different conditions below, first by applying regression analysis, followed by clustering.

3.3.2.2 Average, Variance, and Slope

Figure 3.5 is a scatter plot highlighting the relationship between the average and the variance of the cost contributions of each condition, with each cost contribution given an equal weight in the estimation of the measurement. For the conditions that have L_j equal to one (only have a single regression coefficient) we set the variance to 0. Of the eleven conditions that are identified to have the highest average cost contribution (based on the value of their coefficients), nine were ranked among the eleven most expensive conditions based on the results of Table C.1. The two additional conditions are sickle cell anemia and pulmonary heart disease, which were ranked as the 12th and 34th most expensive conditions, respectively. On the other hand, benign neoplasm, and rheumatoid arthritis were ranked as 7th and 10th based on the results of Table C.1, but were actually the 15th and 12th conditions based on the average cost contribution of their coefficients.

Figure 3.6 summarizes the resulting slopes for all conditions for which L_j is at least 2 (the minimum requirement to be able to estimate a slope). From the figure, we note that the majority of the conditions have a positive slope, meaning that the higher the number of other more expensive chronic conditions, the higher the estimated cost contribution to the annual healthcare. The conditions that have a negative slope are Parkinson's disease, pulmonary heart disease, and rheumatoid arthritis. The conditions with L_j equal to 1, and, therefore, a single cost estimate from equation (3.1) are excluded from the figure. Those conditions are benign neoplasm, cystic fibrosis, dental and mouth disorders, chronic hepatitis, HIV, lupus, acute myocardial infraction, MS, chronic pancreatitis, tuberculosis, and

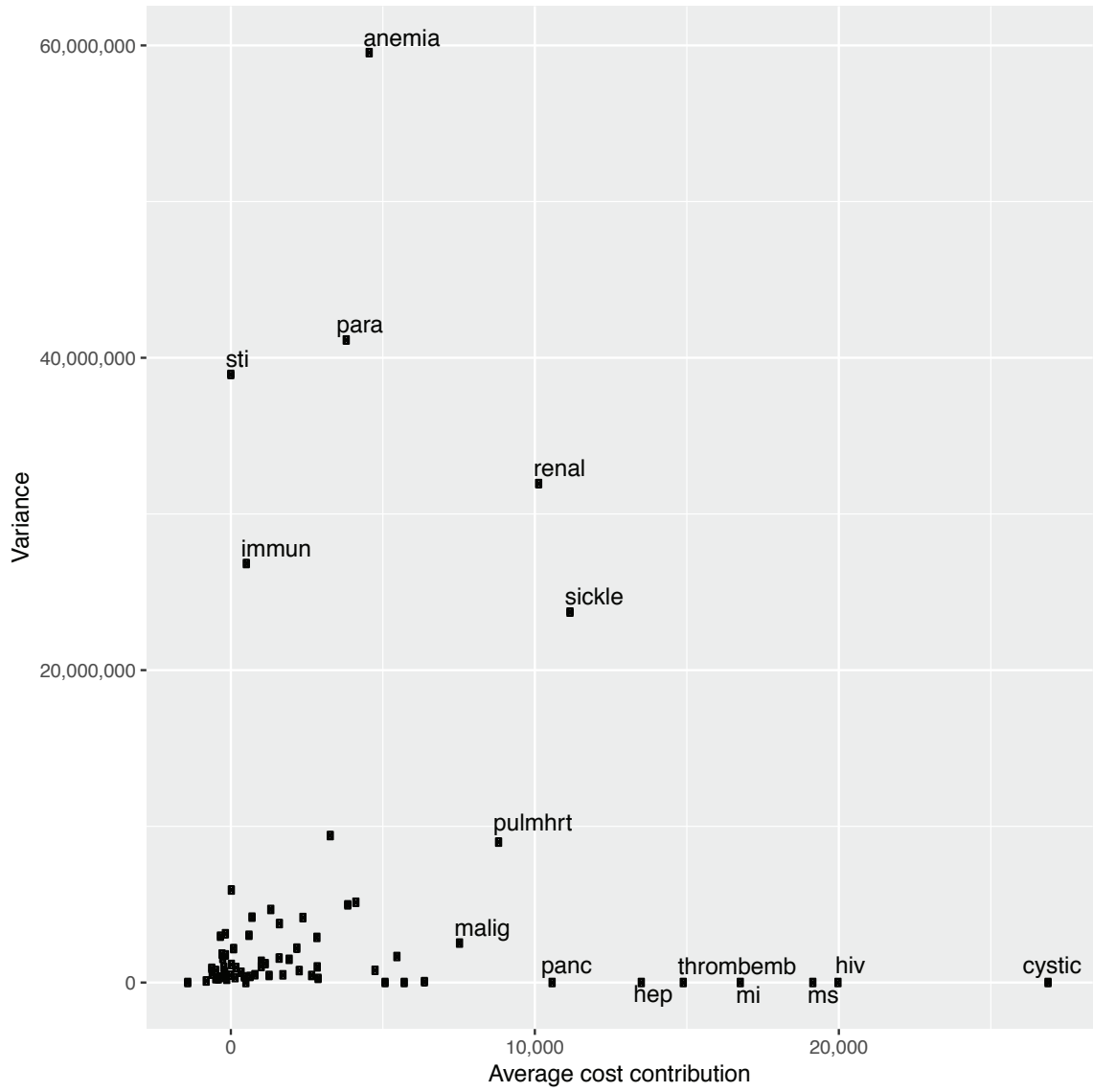


Figure 3.5: Scatter plot of the variance against the average value of the cost contribution of the coefficients.

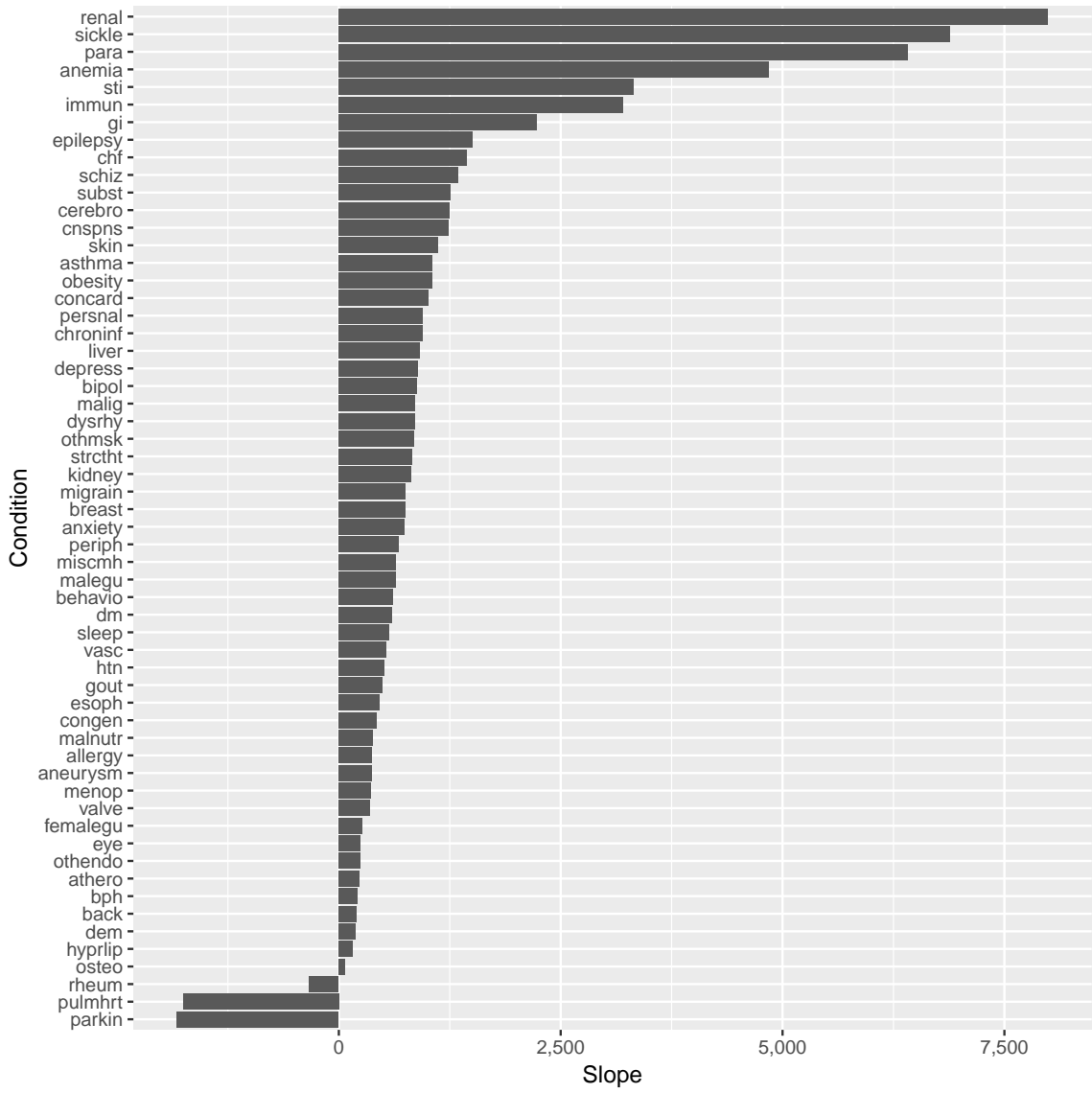


Figure 3.6: Slopes for each chronic condition.

thrombosis and embolism. From the figure, we can summarize the conditions based on the direction and magnitude of their estimated slopes. For example, chronic renal failure, sickle cell anemia, paralysis, anemia and other non-cancer heme disorders, STI, and immunity disorder are conditions with high positive slope. This means that as the number of more expensive condition that the person has increases, the cost contribution of those conditions to the total healthcare cost of the member increases drastically. We note that the conditions identified with the highest variance in Figure 3.5, are the conditions with the largest absolute slopes.

3.3.2.3 Clustering based on the curve form

Finally, we apply clustering to group the chronic conditions together based on their cost characteristics. Note that, as discussed in Subsection 3.3.2.1, not all conditions have five regression coefficients. Thus, we conduct separate clustering analysis based on the number coefficients that each condition corresponds to. We exclude from the analysis conditions only corresponding to one or two coefficients. In total, 18 of the 69 conditions are excluded from the clustering analysis. We use the majority approach discussed in Subsection 3.2.6 on conditions with an equal number of coefficients. In each case, it was recommended to use two centers. After applying the k-means clustering algorithm with $k = 2$ on conditions with an equal number of coefficients, we get the clusters presented in Table 3.5.

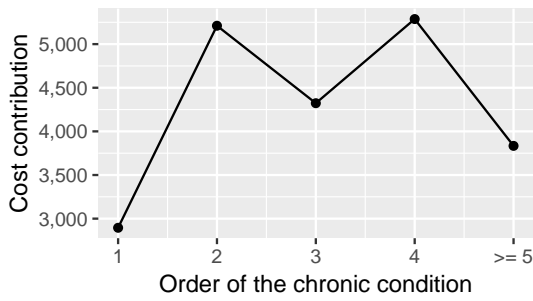
For conditions corresponding to five coefficients, the first cluster includes mostly conditions that either have a small decrease in the contributing cost when the individuals have an

Table 3.5: Resulting clusters using two centers in the k-means clustering algorithm.

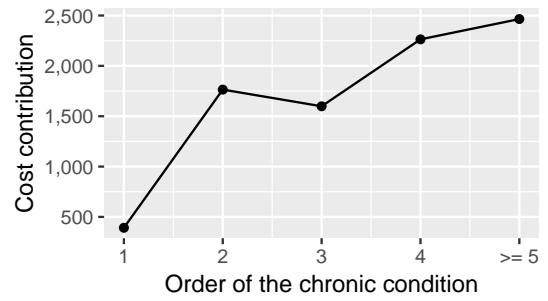
Number of coefficients	Cluster	Numb. in cluster	Names of Conditions
5	1	10	Coronary atherosclerosis Back problems Benign prostatic hypertrophy (BPH) Non-cardiac congenital disorder Diabetes mellitus Conduction disorder or cardiac dysrhythmia Esophageal disorder and GI ulcers Kidney and Vesicoureteral Disorders (excl. renal failure) Other endocrine Non-thrombotic, non-atherosclerotic vascular disease
	2	16	Aneurysm Anxiety disorders Asthma, COPD, other chronic lung disease Congestive heart failure Other central and peripheral nervous system disorders Congenital Heart Disease Depression and depressive disorders Hypertension Immunity disorder Malnutrition (not obesity/overweight)-includes disorders of metabolism Obesity Peripheral atherosclerosis Sleep disorders STI Cardiomyopathy and Structural Heart Disease Substance-use Disorders
4	1	6	Anemia and other non-cancer heme disorders Organic brain problem (dementia) Chronic Liver Disease (excl. chronic hepatitis) Osteoarthritis Pulmonary heart disease Chronic skin ulcer
	2	8	Behavior disorders Bipolar disorder Breast non-cancer Epilepsy Female infertility and GU anatomic disorders Gout or other crystal arthropathy Hyperlipidemia Misc mental health
3	1	7	Allergy, ENT and other upper respiratory disorders Degenerative eye problem (glaucoma/eye) Malignant neoplasm Menopause and perimenopause Migraines Schizophrenia and Psychotic Disorders Heart valve disorder
	2	4	Diverticulosis, diverticulitis, enterocolitis, intestinal malabsorption Other MSK including osteoporosis Paralysis Personality disorder

increased number of more expensive conditions, or the contributing cost remains relatively stable after a relatively large increase from the first to the second order. One representative example for this cluster is included in Figure 3.7a (back problems), where we see that after an initial increase in the cost contribution, the cost decreases. Another example in this cluster is esophageal disorder and GI ulcers (Figure 3.7b), which has a large increase in cost from the first to the second order, and then the cost remains relatively stable (there is a small increase observed). On the other hand, conditions consisting of five coefficients that were included in the second cluster have a more stable increase as the number of other more expensive conditions increases. One example from this cluster is cardiomyopathy and structural heart disease, which is included in Figure 3.7c.

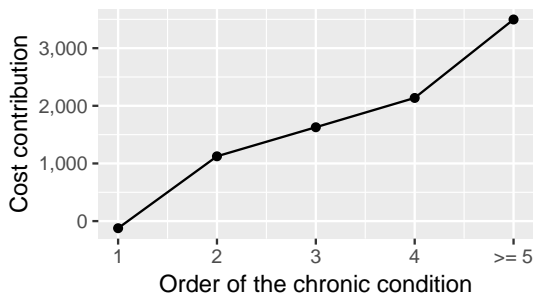
For conditions corresponding to four coefficients, the first cluster again includes conditions that have a decrease in their contributing cost, or a relatively stable cost contribution after an initial increase observed when the condition is the second most expensive. One of the conditions included in this cluster is anemia and other non-cancer heme disorders (Figure 3.7d), which has a constant cost when there is at least one more expensive condition present, and organic brain problem (dementia) (Figure 3.7e), which has a decrease in the cost. On the other hand, the majority of conditions included in the second cluster have an increase in the contributing cost as the number of more expensive conditions that are present increases. For example, this is the case with behavior disorders, included in Figure 3.7f. Nevertheless, two of the conditions included in this cluster (female infertility and GU anatomic disorders, and hyperlipidemia) do not have a clear increase in their contribution,



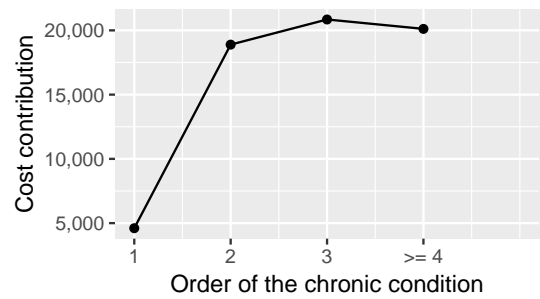
(a) Back problems



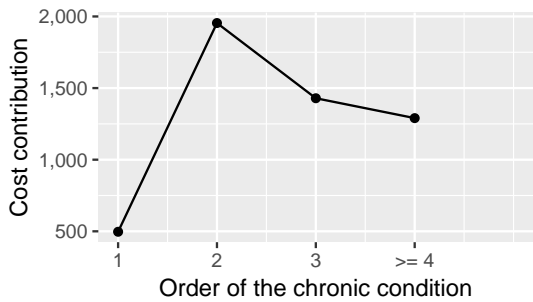
(b) Esophageal disorder and GI ulcers



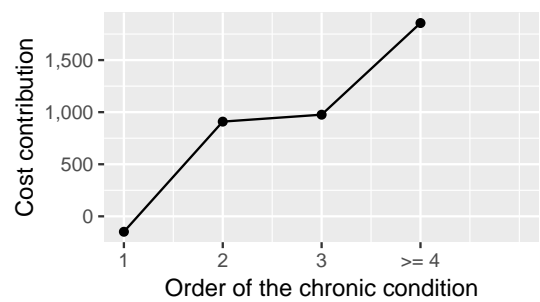
(c) Cardiomyopathy and structural heart disease



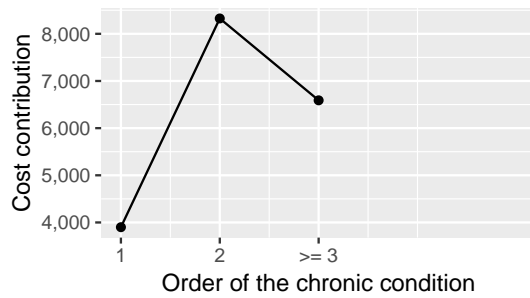
(d) Anemia and other non-cancer heme disorders



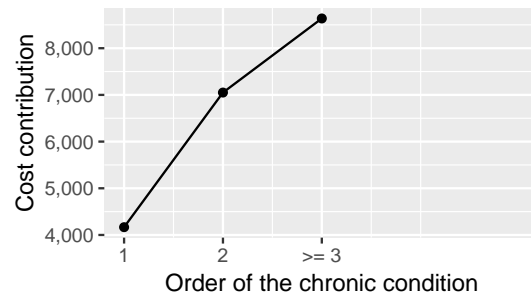
(e) Organic brain problem (dementia)



(f) Behavior disorders



(g) Schizophrenia and Psychotic Disorders



(h) GI problems

Figure 3.7: Chronic conditions representing common patterns observed in each cluster.

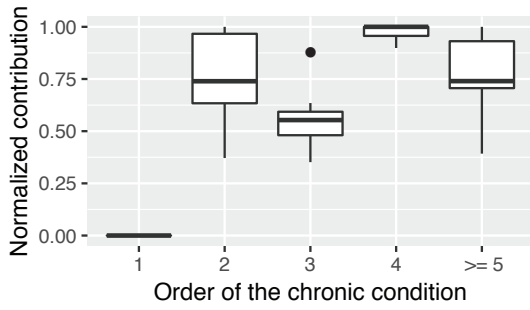
since their costs fluctuate from one order to the next.

Finally, for conditions consisting of three coefficients, the first cluster includes conditions which have an increase in the contributing cost when the condition goes from being the most expensive to being the second most expensive, and a decrease in the cost from having one more expensive condition to having two more expensive conditions present. This can be seen from Figure 3.7g, which includes the costs for schizophrenia and psychotic disorders. On the other hand, the conditions included in the second cluster have a constant increase in cost as the order in which they appear increases. An example of such a condition is GI problems (diverticulosis, diverticulitis, enterocolitis, intestinal malabsorption), which is included in Figure 3.7h.

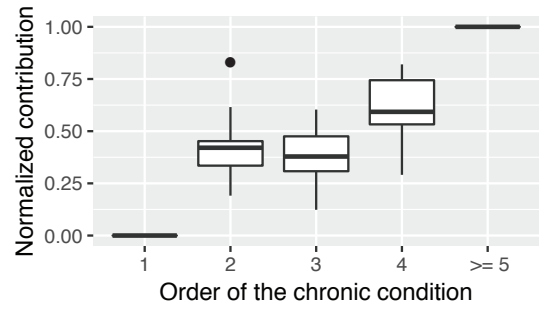
The different cost behavior of each cluster is also summarized in Figure 3.8, where each subgraph includes box plots showing the relative cost contribution across all conditions in the same cluster. In particular, for each condition, all cost contributions are normalized to take values between 0 and 1. The lowest cost contribution of a specific condition takes the value 0, the highest the value 1, and all other costs are normalized to take values in between. This allows us to get a better overview of the cost curves of conditions belonging to the same cluster. For all clusters, we see that there is an increase in the cost contribution from a condition being the most expensive that a person has to the condition being the second most expensive. However, when the number of more expensive conditions increases, different clusters behave in a different manner. In general, all the 2nd-type clusters (Figures 3.8b, 3.8d, and 3.8f) show in most cases an increase in the normalized cost as the number of more

expensive conditions increases. On the other hand, all 1st-type clusters (Figures 3.8a, 3.8c, and 3.8e) in most cases show a decrease with an increase in the number of more expensive conditions that are present, if we exclude the relationship between the condition being the first and the second most expensive for an individual.

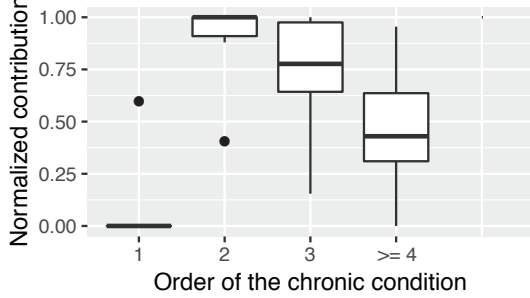
Compared to the slopes presented in Figure 3.6, the clustering analysis provides more information regarding the cost behavior of different conditions. For example, the estimated slopes could not capture as well the decrease in the cost contribution observed in some of the conditions when there are two or more costlier conditions present. Additionally, an important observation is that there seems to be an increase in the cost contribution across all conditions, when the condition goes from being the most expensive to being the second most expensive. This may be a sign of overall worse health. Nevertheless, in some cases, the slope analysis and the clustering analysis highlight the same observations. For example, of the 22 conditions with the highest slope presented in Figure 3.6, only four were included in one of the clusters that indicated a decrease/non-increase in the cost as the number of more expensive conditions increases. Those were anemia and other non-cancer heme disorders, schizophrenia and psychotic disorders, chronic skin ulcer, and chronic liver disease (excluding chronic hepatitis). On the other hand, the one condition with a negative slope that was part of the clustering analysis (pulmonary heart disease), was included in a cluster that had conditions with a decreasing cost. Furthermore, of the 11 conditions with the smallest positive slope, only two (hyperlipidemia, and female infertility and GU anatomic disorders) were included in clusters associated with an increase in the cost contribution as



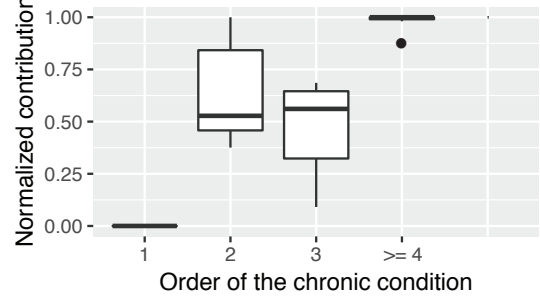
(a) 1st cluster: conditions with 5 coefficients



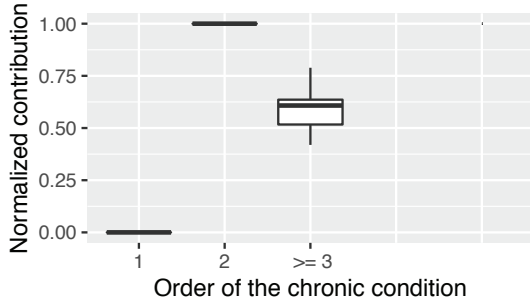
(b) 2nd cluster: conditions with 5 coefficients



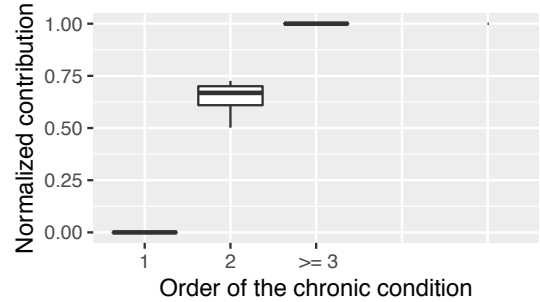
(c) 1st cluster: conditions with 4 coefficients



(d) 2nd cluster: conditions with 4 coefficients



(e) 1st cluster: conditions with 3 coefficients



(f) 2nd cluster: conditions with 3 coefficients

Figure 3.8: Box plots of the normalized cost contributions of the conditions in each cluster.

the number of more expensive conditions increases.

3.4 Discussion

In this chapter, we present a method for estimating the contribution of different chronic conditions to individuals' annual healthcare costs. We estimate the cost for each condition as a function of the number of more expensive chronic conditions that the person has, focusing on 69 different chronic conditions. The methodology we use allows us to model the healthcare cost of individuals with multiple chronic conditions in more detail than the well established literature on the cost of chronic conditions. Based on the results of our estimation model, we group together conditions that have similar cost characteristics.

The clustering analysis highlights that different chronic conditions behave in different ways in terms of their cost contribution. For conditions with a constant increase in cost, it seems that they impose an additional complexity to the treatment of the member leading to an increase to the total healthcare cost. The complexity becomes more distinct as the number of more expensive conditions that the member has increases. On the other hand, for some conditions, as the number of more expensive conditions that the member has increases, the cost that these conditions contribute to the annual healthcare cost starts decreasing. Further study is required to determine the contributing factors, but one hypothesis is that the treatment focus is on other more serious conditions.

The information and the proposed methodology of this chapter can be utilized by researchers and policymakers, to better estimate the effect of interventions on the healthcare

cost of patients with specific chronic conditions, and help make better healthcare cost predictions for people with chronic conditions. Furthermore, it can help identify conditions that are linked to lower costs, and by extension lower healthcare utilization, as the number of other more expensive conditions that the person has increases. This information could be utilized by healthcare providers. A decrease in the cost contribution could be justified by other conditions of the individual or could raise concern since it indicates a need to focus more on a specific sub-population of patients, who are not getting the necessary treatment. This could help improve the quality of healthcare of individuals with chronic conditions.

3.4.1 Limitations

This study focused on the population of a specific geographical region and the corresponding healthcare costs during one calendar year. However, different states have been found to have different prevalence of specific chronic conditions and different hospitalization rates [135]. Thus, our findings cannot necessarily be extrapolated to other states in the U.S. Nevertheless, we expect many of the patterns observed to be similar across states.

Furthermore, our model was built on specific chronic condition specifications. The diagnosis codes used were organized in predetermined groups based on the algorithm provided in [94], with each group consisting of multiple types of conditions in most cases. While diagnoses belonging under the same chronic condition category had similarities to each other, in some cases, we expect to find differences in their treatment costs. For example, asthma and COPD (chronic obstructive pulmonary disease) are included in the same

condition category in the analysis, but the mean annual cost per patient is estimated at \$3,100 for asthma [117], and at about \$6,200 for COPD [126]. Thus, future research could focus on more specific conditions instead of groups of conditions and, thus, expand the identified cost behaviors to more than 69 conditions. However, in order to achieve that, a larger sample size is required, with enough individuals who that have other chronic conditions present at the same time. This would make it possible to draw significant results about the cost behavior of the specific conditions.

3.5 Conclusions

In this work, we studied the cost behavior of 69 chronic conditions. Through the proposed modeling approach, we separated the cost contributions of the various chronic conditions depending on the order in which they appear in individuals. This allowed us to study the cost behavior of each condition, based on the number of more expensive conditions that are present. The results indicate that conditions can be divided into two main groups. The first included conditions that do not show a clear increase in the cost contribution as the number of more expensive conditions that are present increases. In particular, in most cases there was an increase in cost when the condition went from being the most expensive to the second most expensive in an individual, and then the cost either remained constant or decreased. The second group included conditions with a relatively stable increase in cost as the number of more expensive conditions increases.

Chapter 4: Conversational agent technology adoption by patients with heart failure

4.1 Introduction

In this chapter, we study the use of two different types of conversational agent technologies by patients with heart failure (HF). This is a problem at the tertiary prevention level, since the goal is to help people better manage their condition. HF is a condition in which the heart of the patient is not able to pump enough blood and oxygen to the organs. HF has high prevalence, affecting over 26 million people worldwide, and it is associated with high mortality, and healthcare utilization [148]. Due to the aging population, the prevalence of HF is expected to increase in the future. In the U.S., there are currently 6.2 million adults with HF, with this number expected to increase to over 8 million by 2030 [167]. Individuals with HF are projected to make up about 2.97% of the U.S. adult population in 2030 [167], with the total (medical and indirect) costs associated with the condition estimated to reach \$70 billion [68]. Currently in the U.S., there are about 800,000 annual hospitalizations for the primary diagnosis of HF, and, after each hospitalization, the 28-day and 1-year mortality is 10.4% and 29.5%, respectively [167]. Thus, it is crucial to support people with HF to

manage their conditions once discharged from the hospital.

The treatment for HF is closely associated with self-care. In addition to taking medications, a patient is advised to reduce salt and fluid intake [25], monitor their weight daily, stay active through appropriate physical activity, and to look for symptoms that could cause concern such as swelling in ankles, weight increase, or shortness of breath [141]. One approach for frequent information exchange is utilizing telehealth. Telehealth allows healthcare providers to get daily feedback from the patients, enabling them to promptly intervene when necessary.

A number of telehealth approaches for HF have been examined. For example, structured telephone-monitoring, allows patients to answer a set of prerecorded questions regarding their symptoms through their telephone keypad [33]. Increased internet access has allowed the development of numerous technologies [7, 48, 81, 87, 97], with some examples presented below. Patients can log in to a designated website to enter information about their daily symptoms, which allows nurses to monitor any changes [97]. Through an Xbox gaming platform, HF patients can navigate through screens, answer multiple-choice questions regarding their symptoms, read further instruction about their self-care, and learn more about their condition [48]. Tablets connected to a weight scale and a blood pressure wrist monitor allow patients to send daily readings to their healthcare provider [87]. Similarly, through an Android phone app, patients can submit daily symptoms, and automatically transmit vital readings, including weight, blood pressure, and glucose levels [7]. A recent review of studies on telehealth adoption by patients with HF can be found in [54].

Across the studies discussed, main factors that are identified to negatively influence telehealth adoption include difficulties with using the required technology, not remembering to use the technology every day, and considering the telehealth procedure to be redundant or boring. It can, therefore, be concluded that a critical component of any telehealth application is its ease of use. Conversational agent technology that uses speech is potentially one such solution, since it can ask questions of the patients through speech and understand the patients' answers through speech recognition.

Conversational agents have been used in numerous healthcare settings, with the literature extensively focusing on mental health applications [83, 134]. However, the conversational agent technology has also been used to help support behavior change and promote a healthy lifestyle [91]. Furthermore, in a few studies, the technology has also been recommended for patients with HF, in order to collect information about their symptoms and help with managing their conditions. In particular, proposed designs for conversational agent technology in patients with HF can be found in [47, 178]. A study on a small cohort of HF patients, investigating their satisfaction and engagement with conversational agent technology, found high user satisfaction and engagement levels [107].

The contribution of our work is twofold. First, we compare two types of conversational agent technologies, to study differences with respect to patient engagement. Both technologies use speech recognition, and were used by HF patients. The first technology utilized the Amazon Alexa technology and only communicated with the patient through speech (audio only). We will refer to this implementation as the Alexa+ throughout this chapter. The sec-

ond technology was an app run on a tablet that used an avatar, thus combining audio and visuals. We will refer to this second implementation as the Avatar throughout this chapter. Second, we investigate which patient characteristics are important factors in determining the patient engagement. To the best of our knowledge, this is the first study examining factors that influence conversational agent technology uptake in patients with HF.

4.2 Methods

4.2.1 Conversational agent technologies

Alexa is a virtual assistant AI technology developed by Amazon. Alexa is voice activated, and has a number of functions, including sending messages, playing music and giving traffic updates. The original capabilities of Alexa were expanded for the purpose of this study, in order to be able to ask patients with HF a series of questions regarding their condition which resulted to an augmented technology (Alexa+). We used Echo Dot devices, which are smart speakers that can be used to access Alexa+. The retail price for an Echo Dot (see Figure 4.1a) is \$50 per unit, making this technology relatively affordable.

The Avatar was developed by ObEN [118]. This technology generates avatars, which have customizable appearance, and can speak in different languages, and can potentially be used in a number of different health care settings. In our study, the avatar was used to ask the patients a series of questions related to their HF treatment and symptoms. The avatar application was saved on tablets which had no other applications. An example of the Avatar technology is presented in Figure 4.1b.

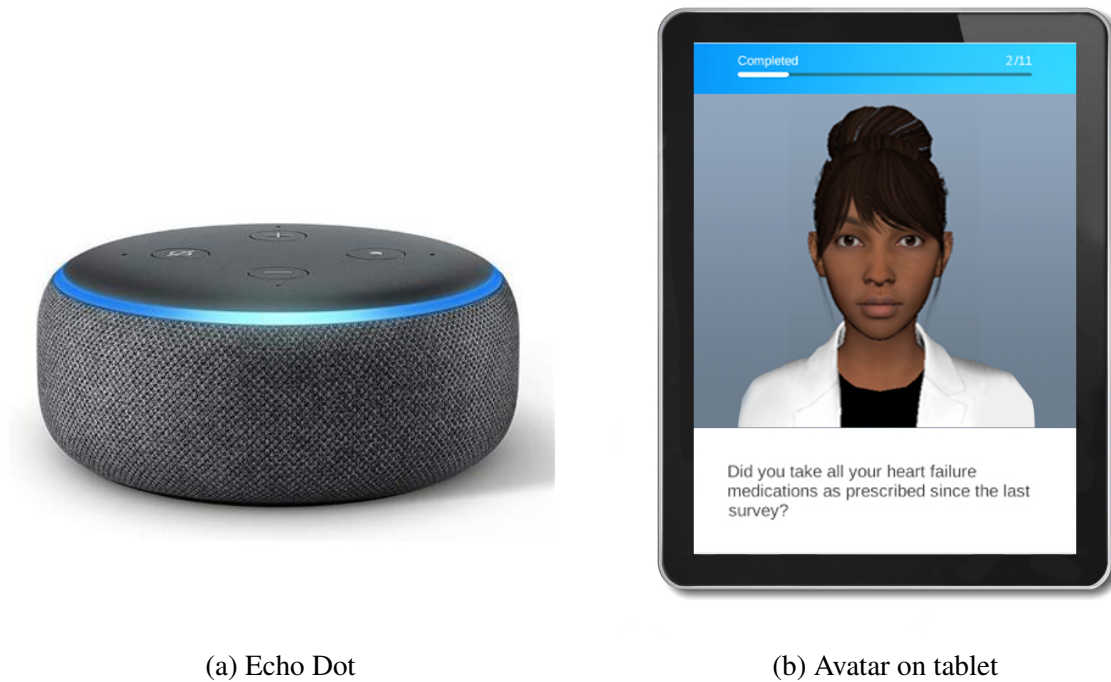


Figure 4.1: Conversational agent technology used.

Note that one difference between the two conversational agent technologies, in addition to the way that information is presented, is that the Alexa+ technology allows patients to set-up daily reminders. Thus, at a specific time during the day patients participating in the Alexa+ study had the option to receive reminders in order to fill out the questionnaire. However, the tablets used in the Avatar study did not have this option.

Both Alexa+ and the Avatar follow the exact same script. In the first stage of the script, the conversational agent asks the HF patients 11 questions, which can be potentially expanded to 13 questions, depending on the answers that the patients give. Patients answer each question separately with yes or no. The answer that the patient gives to each question, affects the type of comment that the conversational agent makes right after the answer, as

well as the next question. The 11-item questionnaire is divided into three components: compliance (questions 1-3), mild HF symptoms (questions 4-6) and moderate/severe HF symptoms (questions 7-11). The compliance questions have to do with whether the patients weighed themselves, took their HF medication, and avoided eating high-salt food. Answering negatively to any of those questions raises a yellow flag. The mild HF symptom questions are intended to find out if the patient has shortness of breath with regular activity, cough, or swollen ankles. If the patients answer positively to any of the mild HF symptoms questions an orange flag is raised for that question. The moderate/severe HF symptoms questions have to do with weight increase, and shortness of breath at rest or while sleeping. If the patient answers yes to any of the moderate/severe HF symptoms questions, a red flag is raised. The raised flags can result in alerts, as we will discuss in Section 4.2.4 (Monitoring), and the red flags affect the tailored advice that the conversational agent gives the patient once the questionnaire is completed. This is done in the second stage of the script, where the agent in addition to the advice summarises the answers provided by the patient. The detailed script including the questions asked, their order, and the comments that the conversational agents make in each case can be found in Tables E.1 and E.2 of Appendix E.

4.2.2 Patient enrollment and training

Thirty patients were enrolled in each of the two studies by using the same eligibility criteria. In particular, in order to participate, the patients should have been admitted or

treated for Chronic HF at MedStar Washington Hospital Center or a MedStar Heart Failure Clinic. Further, the patients had to be 18 or older, and live in a house with wifi access. Finally, the patients could not participate in the studies if they had had a heart transplant or if they had a ventricular assist device (VAD). The participation was optional for the patients. Patients declined the offer to participate for multiple reasons, including: not wanting to take the daily surveys, not wanting another “device” in their lives, or lack of interest.

Participants randomized to the Alexa+ study group were provided an Amazon account, equipped with an Echo Dot configured to access the Alexa+ application, and were provided training on the Alexa Echo Dot including Alexa voice training. Voice training consisted of a session of 25 phrase repetitions that allows Alexa to improve its voice recognition capabilities for the target user. The patients participating in the Avatar study were provided tablets with the Avatar application. They were shown how to use the technology. Furthermore, patients participating in both studies completed their first questionnaire during their training, in order to make sure that the device was working properly and to ensure that the patients understood how to do it.

4.2.3 Demographic and technology survey

Before the patients started using the conversational agent that was assigned to them, they filled out a demographic and technology survey. This allowed us to identify patient characteristics that were associated with low or high conversational agent technology adoption in subsequent analysis. In particular, the demographic section of the survey included

questions about: age, gender, marital status, race, Hispanic heritage, annual household income, education, insurance coverage, number of years with HF, number of medications to manage HF, and visual impairment. The technology section of the survey included questions about: the type of mobile phone they use, whether they use their phone to text messages, whether they access social media, and browse the Internet through their phone, and how confident they feel using computers, or other electronic devices.

4.2.4 Monitoring

Once enrolled, patients were instructed to complete the questionnaire on a daily basis for 90 days. For participants who answered in a manner that indicated HF stability, the response was coded green and no alert was generated. For questions answered in a clinically undesirable manner, the responses were divided into yellow, orange, and red answers to correspond to the compliance questions, mild HF symptom questions, and moderate/severe HF symptom questions, respectively. Alerts were generated for the red questions. The alerts resulted in an immediate text and email to the study nurse, who monitored the alerts each day, including weekends and holidays. The texts contained the participant identification number and contained the following alert: “*We have received a concerning daily response from patient [PatientID] that warrants your attention: [QuestionID] yes*”. In total, 281 alerts were generated for the Alexa+ group, and 404 for the Avatar group. Information about the answers was also summarized as a color display (see example in Figure 4.2).

A baseline was established based on the first time that the participants completed the questionnaire. The study nurse reviewed alerts daily and evaluated participant's stability compared to baseline. Thus, any changes were evaluated based on their initial answers.

As part of the general care practices at the study institution, each HF patient is assigned a nurse navigator, who is responsible for coordinating the clinical care of the participant. A change in status was defined as a change in the moderate/severe HF symptom questions from baseline, multiple red flag responses, or persistent red flag responses. For patients with a change in status, the nurse navigator at the study institution was informed of the alert, as well as the PI and the study physician.

Every three weeks the study coordinator would contact participants who did not complete the questionnaire to check on the participant status and reeducate or encourage completion. In some cases, participants would call and inform the study coordinator that they were traveling out of state/country or on vacation and unable to complete the questionnaire. A weekly phone check-in was completed by the study coordinator to answer any questions and provide additional training to the participants on how to initiate and communicate with the device.

4.2.5 Analysis

We use descriptive statistics to characterize demographic and clinical characteristics of the patients, as well as their experience and confidence in using technology. In particular, we estimate means and standard deviations for the continuous variables, and counts and

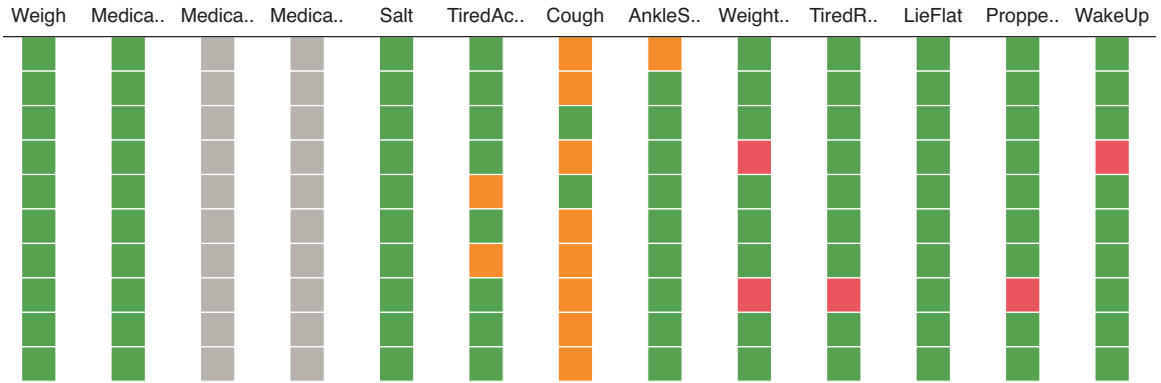


Figure 4.2: Example of color display used in the monitoring of patients.

corresponding percentages for the categorical variables. Furthermore, we report the number of missing values for each variable. We compare the patient populations participating in the Alexa+ study to that of the Avatar study based on the aforementioned characteristics. We use chi-squared tests to compare the counts in the different categories between the two populations for each the 12 categorical variables, and two-sample t-tests to test the difference between the two population means for the 3 continuous variables. We report the corresponding P-values for each variable.

Note that the information discussed above comes from the survey discussed in Subsection 4.2.3. However, in some cases data regarding demographic and clinical characteristics were also retrieved from the electronic health records of the patient in order to decrease the number of missing values.

Patients' engagement is defined as the number of days during the study period that the patient used the corresponding conversational agent to answer the questionnaire. We use visualizations to show the levels of engagement in each study.

We model the relationship between the engagement level and the patient's characteris-

tics using multiple linear regression on the entire population (combining both studies). In particular, the dependent variable is the number of days that the patient utilized the conversational agent technology during the 90-day study period. The independent variables consist of the demographic, clinical, and technology-related characteristics of the patient. Of those, categorical variables consisting of more than two categories were also transformed to binary variables. In particular, we generated a binary variable for patients that have a smartphone, for patients that are very confident to use technology, for patients that have only a little or not at all confidence to use technology, for patients that have college education or higher, for patients that have a high school education or less, for patients with an annual household income higher than \$100,000, for patients with an annual household income less than \$50,000, and for patients that are married. Finally, in order to differentiate between the two studies, we generated a binary variable taking the value 1 for patients that participated in the Avatar study, and 0 for patients of the Alexa+ study. In order to select which variables to include in the regression model we use the best subsets method, based on the adjusted R^2 value. Given the small sample size, variables need to be carefully selected, and therefore we chose to use this method in order to generate a model that explains the variation in the patient's engagement as well as possible based on our available data. However, like any reduced model, the interpretation of the coefficients may be biased if important variables are excluded from the model.

Finally, in order to more closely study the impact of the patient characteristics on the technology usage of each type of conversational agent, we build a separate model for each

study population. We use a subset of the variables selected in the general model described above. This allows us to look for characteristics that might influence the usage of each technology differently.

4.3 Results

4.3.1 Population statistics

Three patients out of the thirty initially enrolled in the Avatar study were subsequently withdrawn from the study, because it was not possible to reach the patients after they provided the initial participation consent. Table 4.1 shows the demographic, clinical, and technology-related characteristics of the patients participating in each study. We see from the table that patients participating in the Alexa+ study were taking a statistically significantly ($P\text{-value} = 0.0075$) different number of medications to manage HF compared to the patients of the Avatar study. In particular, patients in the Alexa+ study were taking more medications, with a mean of 8.7 (standard deviation 4.0), while patients that participated in the Avatar study were taking a mean of 5.8 (standard deviation 3.4) medications. For the remaining variables there were no statistically significant differences between the two patient populations.

Overall, both populations were predominantly male (60% in the Alexa+, 63% in the Avatar), black (60% in the Alexa+, 63% in the Avatar), had an average age of about 55 years (mean age 54 for Alexa+, and 56.5 for Avatar), and had had HF for an average of about 7 years (mean of 7.5 for Alexa+, and 7.3 for Avatar). Furthermore, the majority of

patients in both studies had experience in using smartphones, and had confidence in using similar technology.

Table 4.1: Characteristics of patients participating in the two studies.

Characteristic	Alexa+ (N=30)	Avatar (N=27)	P-value
Age, mean (SD)	54.0 (11.7)	56.5 (12.1)	0.45
Missing	2	1	
Gender, n(%)			1
Male	18 (60.0%)	17 (63.0%)	
Female	10 (33.3%)	10 (37.0%)	
Missing	2 (6.7%)	0 (0.0%)	
Marital status, n(%)			0.80
Single, never married	7 (23.3%)	6 (22.2%)	
Married	11 (36.7%)	15(55.6%)	
Living together, not married	3 (10.0%)	1 (3.7%)	
Separated/Divorced/Widowed	6 (20.0%)	5 (18.5%)	
Missing	3 (10.0%)	0 (0.0%)	
Race, n(%)			0.54
Black	18 (60.0%)	17 (63.0%)	
Asian	0 (0.0%)	1 (3.7%)	
White	7 (23.3%)	8 (29.6%)	
Other	4 (13.3%)	1 (3.7%)	
Missing	1 (3.3%)	0 (0.0%)	
Hispanic heritage, n(%)			1
Yes	1 (3.3%)	0 (0.0%)	
No	27 (90.0%)	27 (100%)	
Missing	2 (6.7%)	0 (0.0%)	
Annual household income, n(%)			0.28
\$0-\$50,000	19 (63.3%)	9 (33.3%)	
\$50,001-\$100,000	2 (6.7%)	5 (18.5%)	
More than \$100,000	5 (16.7%)	8 (29.6%)	
Missing	4 (13.3%)	5 (18.5%)	
Education level, n(%)			0.49
Some high school/ High school graduate	11 (36.7%)	9(33.3%)	
Some college	10 (33.3%)	7 (25.9%)	
College graduate	3 (10.0%)	2 (7.4%)	
Post-graduate degree	2 (6.7%)	6 (22.2%)	
Missing	4 (13.3%)	3 (11.1%)	
Years with HF, mean (SD)	7.5 (8.1)	7.3 (6.4)	0.95

continued ...

... Table 4.1 continued

Characteristic	Alexa+ (N=30)	Avatar (N=27)	P-value
Missing	5	8	
Number of medications to manage HF, mean (SD)	8.7 (4.0)	5.8 (3.4)	0.0075
Missing	2	1	
Visually impaired or blind, n(%)			0.11
Yes	4 (13.3%)	0 (0.0%)	
No	22 (73.3%)	25 (92.6%)	
Missing	4 (13.3%)	2 (7.4%)	
Type of mobile phone, n(%)			0.41
Basic	1 (3.3%)	2 (7.4%)	
Smart	25 (83.3%)	22 (81.5%)	
None	0 (0.0%)	1 (3.7%)	
Missing	4 (13.3%)	2 (7.4%)	
Uses phone to text, n(%)			1
Yes	25 (83.3%)	24 (88.9%)	
No	1 (3.3%)	1 (3.7%)	
Missing	4 (13.3%)	2 (7.4%)	
Uses phone for social media, n(%)			0.58
Yes	15 (50.0%)	17 (63.0%)	
No	11 (36.7%)	8 (29.6%)	
Missing	4 (13.3%)	2 (7.4%)	
Uses phone to browse the Internet, n(%)			0.23
Yes	24 (80.0%)	20 (74.1%)	
No	2 (6.7%)	5 (18.5%)	
Missing	4 (13.3%)	2 (7.4%)	
Confidence in using technology, n(%)			0.87
Very	11(36.7%)	12(44.4%)	
Somewhat	13 (43.3%)	10 (37.0%)	
Only a little	2 (6.7%)	2 (7.4%)	
Not at all	0 (0.0%)	1 (3.7%)	
Missing	4 (13.3%)	2 (7.4%)	

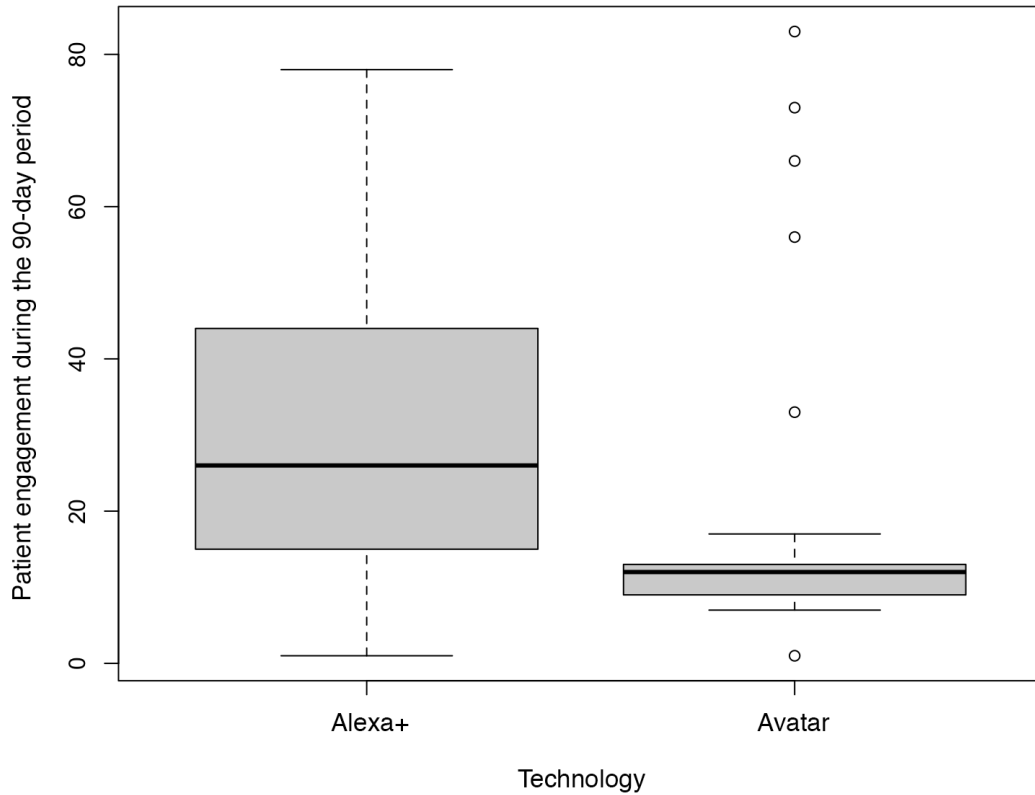


Figure 4.3: Box plot showing number of interactions in each study

4.3.2 Technology engagement

In both cases some patients did not complete the study. In particular, from the patients participating in the Alexa+ study, five patients decided to withdraw from the study, two patients had issues with their wifi connection, and two patients never responded to contact attempts. One participant of the Avatar study did not respond to any contact attempts. Thus, from the Alexa+ study we obtained information about the use of the conversational agent technology for 21 out of the 30 patients, and the Avatar study for 26 out of the 27 patients.

Figure 4.3 highlights the variations in the levels of engagement for patients participating in each study. For both technologies we see that there is a large range of values in the number of times that patients interacted with the conversational agent during the 90-day time period. While there are some patients in both studies that engaged with the conversational agent technology almost daily, the majority of participants used the technology a lot less. Furthermore, we observe a difference between the two technologies, with patients participating in the Alexa+ study appearing to interact more frequently with the technology. In particular, it is estimated that Alexa+ patients used the technology a mean of 31.8 times (standard deviation 22.9), while the Avatar patient used it a mean of 20.2 times (standard deviation 22.5).

4.3.3 Regression results

Based on the best subsets method, the highest adjusted R^2 value is obtained by the model presented in Table 4.2, which consists of six variables. The model has an adjusted R^2 of 28.9%. We see from the resulting coefficients that the older patients are linked to higher use of the technology (0.6974, P-value <0.05), while black patients used the technology fewer times compared to non-black patients of otherwise similar characteristics (-25.5295, P-value <0.005). Furthermore, patients that take an increased number of medications to manage HF, are associated with a lower use of the technology (-3.8529, P-value <0.05). Finally, patients that participated in the Avatar study completed the questionnaire is lower numbers (-27.0030, P-value <0.005) compared to patients of similar character-

Table 4.2: Linear regression model for predicting the number of times that the patient used the conversational agent technology.

Variable	Coefficient	95% CI		P-value
(Intercept)	39.5291	-0.5772	79.6354	0.0532
Age	0.6974	0.0272	1.3677	0.04189
Black	-25.5295	-40.6311	-10.4279	0.0016
Household income higher than \$100,000	2.3765	-12.9982	17.7512	0.75514
Number of medications to manage HF	-3.8529	-7.0922	-0.6136	0.02119
Confidence in using technology	7.4847	-7.0128	21.9822	0.30118
Avatar study participant	-27.0030	-44.8163	-9.1898	0.00411

istics that participated in the Alexa+ study. The variables for high household income and high confidence in using technology were also included in the model. Both had positive coefficients but were not statistically significant.

We also built two separate linear regression models, one for each study population. Both models consisted of the exact same variables, which were based on the ones selected for the model of Table 4.2. In particular, compared to the model of Table 4.2, we removed the variable showing whether a patient participated in the Avatar study, since this is no longer necessary with the populations being separate. Furthermore, we excluded the variable indicating whether the patient has a high household income because it was not statistically significant in the model of Table 4.2, and the smaller separate cohorts fewer variables are preferred. We selected to contain the variable showing confidence in technology, which has been identified as a concern of patients participating in similar telehealth studies [108, 136]. The resulting models are included in Table 4.3. The adjusted R^2 for the Alexa+ model is 38.1%, and for the Avatar 20%. The coefficient corresponding to the age of the patient is positive (0.7543 for the Alexa+, and 0.4373 for the Avatar), but not statisti-

Table 4.3: Linear regression model for each population separately.

Variable	Alexa+		Avatar	
	Coefficient	P-value	Coefficient	P-value
(Intercept)	75.9747	0.0257	8.4326	0.7578
Age	0.7543	0.0848	0.4373	0.3487
Black	-33.9386	0.0082	-24.6938	0.0148
Number of medications to manage HF	-7.1885	0.0047	-0.3584	0.8349
Confidence in using technology	-4.8618	0.6394	9.7999	0.3170

cally significant in either of the two models. Both models indicate that black patients used the technology fewer times compared to non-black patients of similar characteristics, with the coefficients being negative (-33.9386 for the Alexa+, and -24.6938 for the Avatar) and statistically significant. An increased number of medications has a negative effect in the number of interactions with the conversational agent in both models (-7.1885 for the Alexa+, and -0.3584 for the Avatar), but it is only statistically significant in the Alexa+ model. Finally, the coefficient for the variable showing confidence in technology is not statistically significant in either model. In particular, while in the model for the Avatar population the effect is positive (9.7999) as in the model of Table 4.2, for the Alexa+ population the effect is negative (-4.8618).

4.4 Discussion

4.4.1 Comparing the two technologies

Patients participating in the Alexa+ study engaged on average more with the conversation agent. This is highlighted by linear regression model, where we controlled for a number of patient characteristics (demographic, clinical, and technology-related). The in-

indicator variable identifying patients that participated in the Avatar study was selected to be included in the model by the best subsets method, and was negative and statistically significant. In particular, patients using the Avatar technology used the conversational day 27 fewer days on average during the 90-day study period, compared to the patients using the Alexa+ technology, after accounting for patient characteristics.

The circumstances under which the patients were enrolled, trained, and monitored were almost identical for the two studies, and both conversational agent types used the exact same script to interact with the patients. Thus, the difference in the levels of engagement is most likely attributed to the characteristics of each technology. The Alexa+ technology allows for patients to set up daily reminders to answer the questionnaire. This is not supported by the Avatar technology. Forgetting to interact with the system has been identified as a crucial factor of hindering telehealth uptake in previous studies [54]. Furthermore, the conversational agent using the Alexa+ technology, could potentially be easier to use since it is voice activated and the patient can interact with it by simply being in the same room. However, there is no clear evidence that using the Avatar technology was difficult for the patients, since the factor showing the confidence in using technology was not statistically significant. This result is also supported by the models focusing on each study population separately, which do not reveal a significant impact of technology experience on the number of interactions for either type of technology. In the literature, it has been suggested that confidence and experience with technology can be used as a selection criterion for patients participating in telehealth [108]. However, we do not find this to be an issue for this type

of technology. Thus, overall, the conversational agent technology seems to be easy to use, since confidence in using technology did not affect the levels of engagement.

4.4.2 Patient characteristics

Older patients were linked to higher levels of engagement. This agrees with findings from previous studies, where the age of the patient has been found to affect the level of adherence, with older patients using telehealth more regularly [130, 172]. Furthermore, we see that patients taking higher number of medications to manage HF tend to interact less with the conversational agents. The number of medications can be interpreted as a proxy for the severity of the HF condition. Thus, from the model, it seems that sicker patients interacted with the telehealth technology less frequently. This could be caused by a number of reasons, including physiological and psychological factors, which may have prevented the patient from using the corresponding technology. This finding highlights the importance of encouraging patients to use the telehealth systems, by underlying their role in helping them to manage their condition. Furthermore, it shows that it is important for future research to identify factors associated with the patient's health that are linked to low levels of utilization.

Finally, the only variable that was statistically significant in all three regression models was the indicator variable for black race. When combining both populations, black patients used the technology 25 fewer times on average during the study period. It is not clear what is causing black patients to engage with the technology less often. Excluding

other race variables, the variable for black race had a relatively strong correlation with the variable showing that the patient was married (-0.52), and moderate correlation with annual household income less than \$50,000 (0.24) and years with heart failure (-0.22). With the remaining variables there were weaker correlations. In order to investigate which socioeconomic factors might be driving this result, we rerun the best subsets approach after removing all race related variables from the data set. The model with the highest adjusted R^2 value (see Table F.1, Appendix F) was similar of that of Table 4.2. However, the variable for black race was replaced by the variable showing that the patient is a high school graduate or has some high school education, and the variable for high confidence in using technology was excluded from the model. The impact of education in this model was statistically significant, with patients with high school education or less using the technology about 18 fewer times compared to other patients with otherwise similar characteristics. Nevertheless, the impact of education was not as large as it was for the black variable. Furthermore, the adjusted R^2 for this model was nearly half of that of the original model in Table 4.2. Thus, this large difference in black patients may be an indication of other important socioeconomic or medical factors that are beyond the scope of our data and deserves further study.

4.5 Conclusions

In this chapter we studied the levels of telehealth engagement by HF patients, focusing on the use of conversational agent technology. Using linear regression we found that the

Alexa+ technology was used in higher rates than the Avatar technology. This difference in the levels of engagement was most likely attributed to the option that the Alexa technology offers to patients to set up daily reminder to answer the telehealth questionnaire. There was no indication that the patient's confidence in using technology affected the engagement with technology, which shows that conversational agents are not difficult to use. Other patient characteristics that were linked to the engagement levels included age, number of medications they take to manage HF, and race.

Chapter 5: An optimization model for multi-appointment scheduling in an outpatient cardiology setting

5.1 Introduction

In this chapter, we tackle the problem of outpatient scheduling in the cardiology department of a large medical center, in an effort to make access to care easy for patients, and thus ensure that they will go through the necessary treatment. Thus, this is a problem that focuses on facilitating tertiary prevention.

5.1.1 Motivation

Approximately 11% of the adult population in the U.S. is diagnosed with heart disease [149], which is also ranked first as a cause of death [69]. Receiving treatment on time is crucial in increasing the chances for survival [50]. It is critical to investigate ways of making access to care as effortless as possible for patients with a heart condition. This is expected to increase the willingness of patients to visit their physicians and go through the necessary treatment [44].

5.1.2 Background

We focus on appointment scheduling for outpatient interventional procedures (also known as outpatient programs) and elective surgery in cardiology. The outpatient programs that we study are the transcatheter aortic valve replacement (TAVR), the transcatheter mitral valve repair (TMVR), the patent foramen ovale (PFO) closure, valvuloplasty, and the Watchman. Examples of elective surgery that an outpatient could go through include the coronary artery bypass grafting (CABG), the ventricular assist device (VAD) implanting, heart valve surgery, heart transplant, and others.

Patients have to go through a number of steps including consultations, diagnostic tests, and treatments before they are able to go through one of the outpatient programs or elective surgeries described above. The steps that patients are required to go through depend on their history and condition. Figure 5.1 includes the steps that TAVR patients have to complete. More details about the steps included in each outpatient program or surgery can be found in Appendix G. We generated the procedure diagrams based on discussions we had with the scheduling staff and nurse practitioners in the University of Maryland Medical Center (UMMC) in Baltimore. We were not able to find information about the exact sequence of steps that outpatients have to follow in other hospitals. Nevertheless, the requirements in other hospitals were similar to those of UMMC [76, 79, 100, 105, 109, 176]. Thus, the model that we are studying is commonly used across different hospitals.

From Figure 5.1 we observe that not all TAVR patients will necessarily go through all of the steps appearing in the diagram. The steps that the patients have to visit depend

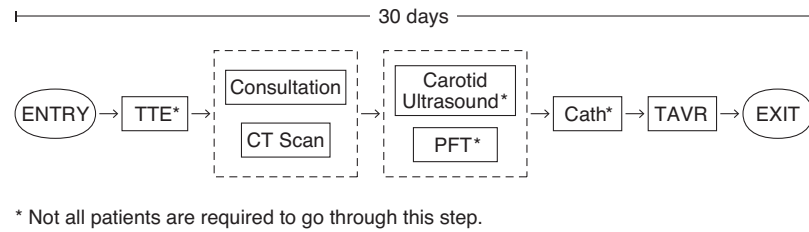


Figure 5.1: Procedure diagram for TAVR patients.

on their health and the procedures they have recently undergone. The dashed rectangles in the figure indicate that the procedures contained in them can occur in any order. The arrows indicate precedence between procedures or groups of procedures. Also note that no more than 30 days should elapse from start to finish, i.e., from the day that the patient gets referred to the hospital to the day that the patient goes through the TAVR procedure. This is important both for the health of the patient and because some of the tests have to be repeated if more than 30 days pass (e.g. history & physical, and blood tests [112]), which leads to unnecessary use of resources. Each step depicted in Figure 5.1 requires numerous resources to be available in order for the patient to pass through them.

Outpatients are patients who get treatment in the hospital without staying overnight or getting admitted. The patients we are studying get admitted only after going through the final procedure. This means that the patients have to travel to the hospital on multiple occasions. The UMMC treats patients throughout Maryland and the surrounding region. Thus, the patients may have to travel long distances to get to the hospital. Furthermore, they usually depend on someone else to drive them to and from the hospital. This complicates the scheduling procedure, and in some cases the patients may not show up for their appoint-

ments or they arrive late. Therefore, it is important to propose a scheduling approach that makes the visits to the hospital as convenient as possible for the patients.

5.1.3 Problem statement

Currently, appointments are scheduled manually without the support of a decision model. While the scheduling staff tries to generate schedules that will not cause unnecessary burdens on the patients, it can be time consuming to generate such a schedule, and the outcome may not be optimal. The resources required for each appointment are in many cases shared with other departments in the hospital, which means that the various departments are competing for the same resources. Each outpatient is scheduled separately. Different outpatient programs and surgeons have their own scheduling staff, who coordinate with the outpatients to book the appointments. The scheduling staff first talks to the patients to learn when they can come to the hospital. Then they call the corresponding labs to find out the availability of appointments. After booking all the required appointments, they inform the patient about the days and times of the appointments.

In this study, we propose an optimization model to help the staff decide how to schedule the appointments. The objective is to generate schedules that are more convenient for the outpatients. Furthermore, we investigate the effect that scheduling patients in groups would have in the quality of the resulting appointments. This could help distribute the available resources better since more information is available when additional patients are included in the optimization. A number of hospital settings schedule patients in groups

instead of one at a time. Examples include scheduling appointments for destination medical centers [140], for radiotherapy pre-treatment [21], and for care of neuromuscular diseases [80]. Scheduling patients in groups requires coordination between the scheduling staff of the various outpatient programs and surgeons. There is a big overlap in the resources required across the procedures that we study. If combining the scheduling of the outpatients leads to better outcomes for the patients, the hospital wants to encourage this collaboration. An additional advantage of grouping the patients is that the communication with the labs will become easier. The scheduling staff will not have to book appointments as often, since patients will be scheduled in batches. An additional derivative benefit, resulting from this scheme, is cost savings on the side of the hospital treating the patients. It can be time consuming every time that the scheduling staff has to find out the availability of each resource, given that there is no centralized way of doing this. Each lab and personnel has to be contacted separately. For the reasons discussed above, this is a direction that the hospital is interested in exploring.

5.1.4 Constraints

Our objective is to generate schedules that are convenient for the patients. The patients should not have to travel to the hospital more times than necessary. Furthermore, the patients should not have to spend too much time waiting in between appointments, because this may tire or stress them. The scheduling process must satisfy the following constraints:

- Once an appointment for a patient is set, it must not get canceled in order to accommodate another patient.
- The preference and the availability of the patient with respect to the different days of the week should be taken into consideration when scheduling the appointments.
- The patients have to complete all the required steps within the allowed time limit.
- The patient should not go through more steps than those required.
- Enough time must be provided for the patient to prepare (or recover) before (or after) a procedure.
- No more than the available resources can be used.

5.1.5 Contributions

The contribution of this research is threefold. First, to the best of our knowledge this is the first study that looks into multi-appointment scheduling in outpatient cardiology. In this work, we discuss the parameters and the constraints that need to be taken into account in such a problem and develop an IP formulation. We also provide the procedure diagrams including the steps that the outpatients have to go through. Second, we develop formulation improvements which help solve the IP significantly faster. Those types of improvements could be applied to other scheduling problems with a similar formulation approach. Third, we examine whether outpatients should be scheduled in groups, which requires the collaboration of different scheduling staff in outpatient cardiology. We investigate what is the

appropriate size of the group based on different levels of resource availability and external demand. Taking external demand into account is important in a hospital setting, since the various departments do not have complete control over all resources used by their patients.

The rest of the chapter is organized as follows. Section 5.2 provides a review of the existing literature relevant to this problem. Section 5.3 includes a description of the multi-appointment scheduling problem in outpatient cardiology. The formulation of the scheduling problem is presented in Section 5.4, which also includes a number of formulation improvements and discusses running times. Section 5.5 provides the computational experiments and the discussion of the results. Section 5.6 discusses the managerial insights. Finally, Section 5.7 states the main conclusions and provides directions for future research.

5.2 Literature review

This section discusses some of the relevant literature in outpatient scheduling. A thorough review of the existing outpatient appointment scheduling literature and suggested research opportunities can be found in [5, 23, 57]. We study scheduling outpatients to go through multiple procedures, which, due to resource or recovery constraints, have to take place on more than one days. While the majority of the outpatient scheduling research examines single appointments, a number of studies have looked at scheduling multiple appointments for the same patient [5]. In particular, the existing literature can be classified into one of the following groups: single appointments, combination appointments, or appointment series [5]. Combination appointments refer to multiple appointments booked for

the same day, while appointment series refers to appointments booked on more than one day for the same patient. However, appointment series usually refer to the same types of appointments scheduled on multiple days, since as part of the treatment, the patients have to make repeated visits. Examples include scheduling of chemotherapy [150, 163] or radiotherapy patients [36, 37], where a similar type of treatment is repeated on many days. Thus, our problem is better classified as a combination appointment even though the appointments can be scheduled on different days. An extensive literature review of multi-appointment scheduling for both inpatients and outpatients is provided in [98]. Our research considers the multidisciplinary scheduling group of problems, since the appointments scheduled include staff and resources from various parts of the hospital. A literature review on multidisciplinary planning can be found in [85], which discusses research on a number of settings, including outpatient clinics, emergency care, blood collection sites, etc.

A mixed integer program (MIP) formulation is presented in [90] for scheduling a set of patients to go through their path of required procedures in an ophthalmology clinic on a given day, where the order of the procedures is predetermined. The objective is to minimize the weighted sum of patient waiting time, resource use overtime, and congestion. Adaptive scheduling heuristics are used to solve the problem, where patients are transferred from more to less busy slots. Patients who have to go through radiotherapy pre-treatment are scheduled in [21]. A MIP formulation with multiple hierarchical objectives is proposed, in an effort to minimize the number of patients waiting longer than the waiting time targets. Each objective is added to the model separately, and its optimal value is passed as a

constraint to the next phase which includes the subsequent objective. Due to complexity, the problem is solved by passing initial solutions and not optimal solutions from one phase to the next. It is assumed that the sequence of procedures that the patients go through is known. Scheduling procedures in nuclear medicine is considered in [128], where there are strict constraints on the time that each step of the medical procedure takes place. Four different scheduling algorithms are taken into consideration including scheduling the patients as soon as possible, scheduling based on the day that the patient prefers to go to the clinic, and two algorithms that take into account the preference of the patient up to a point and then schedule them as soon as possible. A MIP formulation is developed in [9] for scheduling in a pathology laboratory as an effort to maximize the patient satisfaction, which is achieved by minimizing the completion time.

Scheduling procedures in nuclear medicine is also considered in [127], where an on-line scheduling algorithm and a stochastic online scheduling algorithm are proposed. The stochastic online scheduling algorithm consists of a two-stage stochastic program that also takes into account future patient arrivals when scheduling each new request for appointment. The future arrivals include patients that might request an appointment on the same day as the patient being scheduled requested. Scheduling chemotherapy appointments is studied in [60], during which each patient goes through three stages. The uncertainty of the type of appointments requested from new patients during a day and possible cancellations are dealt with by developing a template schedule based on historical data and the deterministic version of the problem. It is possible to update the template dynamically when

a new patient arrives who does not fit in the existing template. The authors in [86] study appointment scheduling in a cancer clinic, in an effort to minimize the weighted sum of the waiting time of the patients, the time that the resources are being idle, and the overtime. A stochastic IP is proposed, since the routes that each patient will follow are uncertain. The sample average approximation method is used in order to obtain the upper and lower bounds of the objective. The length of treatment and the course of the treatment of inpatients is predicted through a discrete time Markov model in [78]. A two-stage stochastic IP is proposed in [121] for scheduling patients in primary care. The patients go through a sequence of predetermined steps with stochastic duration. In the first stage the appointment times of all patients are scheduled, and in the second stage the service times in each stage are realized. The objective is to minimize the idle time of the physician and the waiting time of the patients. Scheduling outpatient surgeries is studied in [147], where the patients go through the pre-operation, the surgery, and the recovery stage. Each stage has stochastic duration. The authors propose simulation-based TABU search methods to solve the scheduling problem.

The objective of our study has similarities with research on scheduling appointments in rehabilitation and destination medical centers. Both types of problems aim to generate schedules that are convenient for the patients. Scheduling patients in destination medical centers means that the patients have to travel to the location of the hospital and stay in this location for the duration of their treatment. Thus, in [140] patients are scheduled in an effort to have them start their treatment as close to their start day as possible. Furthermore, the

time that the patients wait until all steps of their treatment are completed is also minimized, in order to avoid having patients spend too much time in a hotel. The problem is formulated as a MIP, and is solved using a hybrid particle swarm optimization algorithm. An IP for scheduling rehabilitation patients is proposed in [18]. Each appointment request is satisfied as it arrives. The problem is formulated as a multi-objective minimization problem, where the weight of each criterion is decided ahead of time. The eleven criteria taken into account in the objective include the number of extra visits the patient has to make to the clinic (in addition to the minimum number necessary), the time it takes until the first appointment of the patient takes place, and the number of unscheduled appointments. The formulation allows for a percentage of appointments in each discipline not to get scheduled. In the majority of the cases, the optimal solution of the problem is obtained within a few seconds. The number of visits that a child with a neuromuscular disease has to make to the hospital for rehabilitation is limited to one per year in [80]. Based on this constraint, an IP is proposed to schedule the appointments as well as decide on which children will visit the hospital on each day. The formulation allows for patients to have only a subset of the required appointments scheduled. The objective consists of five criteria, including the time the patients spend being idle, and the number of patients with complete or partial visits. The patients are scheduled in groups.

In this work, we aim to generate schedules that are convenient for the outpatients. In particular, due to the specifics of the outpatient cardiology setting we do not want to have patients travel to the hospital too many times or wait too long in between appoint-

ments. The majority of the research in outpatient multi-appointment literature has different objectives, with most studies focusing on decreasing the waiting time for the patients [21, 86, 90, 121, 127]. However, it is crucial to investigate this type of objective because it is more suitable to the case of non-urgent outpatients. Generating convenient schedules for those patients will help increase their willingness to go through the necessary treatment. Research on rehabilitation outpatient scheduling [18, 80] has the most similarities to our problem compared to other studies in the literature. Both of the cited studies formulate the problem using a multi-objective function. It can be difficult to determine the necessary weights of the objective function in a way that provides the hospital with the best schedule in every case. In our study, we propose providing the hospital with Pareto optimal solutions and allow them to decide which schedule is preferable. Thus, the weights do not have to be determined ahead of time, which gives more flexibility to the hospital to decide on the appropriate schedule. Furthermore, our method of finding the Pareto optimal solutions is much more general and complete than the weighted sum approach, because the fundamental problem here is that of trade-off analysis between the various objectives, and our solution provides precisely all the Pareto points corresponding to such trade-off analysis. The weighted sum approach is the so-called “scalarization method” for trade-off analysis that provides only one Pareto point, the one corresponding to the weights used [46]. Deciding on the weights ahead of time is not very easy or intuitive for the scheduling staff and may not lead to the desirable balance between the two components of the objective. In addition, the constraints of our problem are different from [18, 80] due to the characteristics of

our system. For example, we allow for recovery and preparation time when necessary, and we have a strict target day for completion. Finally, we investigate whether patients should be scheduled in groups by having different teams collaborate. This could help generate appointments of better quality in a setting where there are other departments in the hospital competing for the same resources. This is crucial, because in many hospital settings the resources are shared across multiple departments. To the best of our knowledge this has not been studied before in outpatient multi-appointment scheduling problems. In general, we see that only a small portion of the outpatient literature focuses on multi-appointment scheduling [5], which highlights the importance of investigating different aspects of this problem.

5.3 Problem description

This section discusses the assumptions made for solving the problem of multi-appointment scheduling and includes the description of the different elements of the formulation and the corresponding notation.

5.3.1 Assumptions

In order to model the multi-appointment scheduling problem we make the following assumptions.

1. *The duration of each process is deterministic.*

Some process steps may last for a longer or shorter time period than the duration

for which they were booked. Nevertheless, in this work, we are assuming that the duration of the appointments for each type of diagnostic test or treatment is fixed. This is the approach currently followed in the hospital when scheduling, since appointments are booked based on slots of a predetermined length. Since we want to provide a support tool for the scheduling staff in the hospital, we decided to solve the problem following the same approach. A deterministic duration is also assumed in [18, 80, 140]. The risk of assuming deterministic durations is that the patient may not finish a step in the expected time, and therefore not have enough time to go through a subsequent step. More complicated procedures (e.g. cardiac catheterization), which can have higher variability in duration due to their complexity, also require a long recovery time. This ensures that there will not be another procedure booked right after. Therefore, we assume that the duration is deterministic. In the experiments run, we use the maximum duration of a diagnostic test or procedure as the duration of the appointment.

2. *The steps that patients have to go through are determined as soon as they arrive.*

In reality, some diagnostic test might be added later, after finding out more about the patient's health, or some future test might get canceled because it was deemed that the particular procedure was not a good fit for the patient. Similarly, an entire series of steps might have to get canceled if it is deemed that the patient is not a good match for the final procedure at that point in time or in general. However, those cases are less frequent, and the combinations of all possible paths that the patient might end

up following in this case are many. Therefore, in order to get a simpler optimization model which is easier to solve, we make this assumption.

3. *The scheduling staff has enough time to book an appointment before the resource availability changes.*

In other words, when the scheduling staff obtains the available appointments they will have enough time to solve the optimization problem and call back each resource to book the appointments, without some other department being able to book these resources for their own patients in the meantime. Depending on the number of patients that are getting scheduled at the same time, solving the problem could take from a few seconds to a few minutes. We are assuming that the probability of another department booking appointments that overlap with the ones proposed by our model is very low, and thus there is no need to take this case into consideration.

5.3.2 Definitions

5.3.2.1 Time

Let \mathcal{D} denote the set of days and \mathcal{H} be the set of time slots or time units in the planning horizon. For example, if each slot corresponds to one hour, we would have $|\mathcal{H}| = 24 * |\mathcal{D}|$ because there are 24 hours in a day. The set of time slots \mathcal{H}^d denotes the time slots $h \in \mathcal{H}$ included in a day $d \in \mathcal{D}$, so in our example we would have $|\mathcal{H}^d| = 24, \forall d \in \mathcal{D}$. The length of each slot is set to be equal to the greatest common divisor of the appointment durations of

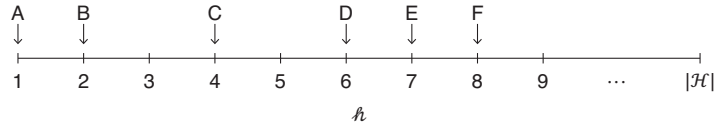


Figure 5.2: Example of patient arrivals during the time horizon.

all the procedures that patients could possibly go through in the system. Thus, the duration of each procedure can be expressed as an integer multiple of the defined time unit. We can schedule patients either one at a time, or in groups. Let \mathcal{T} denote the set of decision epochs in the planning horizon. In a decision epoch t , it is decided how to schedule any patients that arrived between decision epoch $t - 1$ and t , who have not been scheduled yet. Decision epochs do not take place at predetermined or fixed intervals. They depend on the arrival times of the last patient in the group. Function $o : (\mathcal{T}) \rightarrow (\mathcal{H})$ shows the time in the planning horizon that a specific decision epoch corresponds to. Figure 5.2 includes an example of the times that patients A through F were referred to the hospital. If patients are scheduled one at a time, then $o(1) = 1$. The first decision epoch corresponds to the arrival time of the first patient. On the other hand, if the patients are scheduled in groups of two, we have $o(1) = 2$. In other words, the decision epoch equals to the arrival time of the second patient. If patients are scheduled in groups of three, we get $o(1) = 4$, since the decision epoch equals to the arrival time of the third patient.

5.3.2.2 Patients

Let \mathcal{J} denote the set of patients that will be scheduled. There exists an amount of time within which a patient $i \in \mathcal{J}$ has to complete the program, which is denoted by \mathcal{L}^i . In other words, this is the maximum time that a patient is allowed to spend in the system. It is assumed that as soon as a patient is referred to the hospital and the history of the patient becomes available, the patient enters the system. The entry time is denoted by a_i . The planning horizon is set based on the latest it can take for a patient in the group being scheduled to exit the system without violating the allowed period of completion. A patient exits the system once the last procedure is completed, which is normally the main reason that the patient was referred to the hospital. For example, in the TAVR program, the final procedure is the TAVR being performed on the patient in a hybrid operating room.

5.3.2.3 Positions in system

Patients take various positions throughout their stay in the system. These positions can be categorized into two different types: *procedure* and *waiting positions*. A patient that is in a *procedure position* is a patient who is at a hospital going through a diagnostic test or a treatment. Patients who are in a *waiting position* might be in the hospital or not. A patient, who is in a *waiting position*, has already gone through a procedure and is expected to go through another one on the same day, is assumed to be waiting in the hospital. These types of positions are occupied by patients who are either waiting to recover from a previous

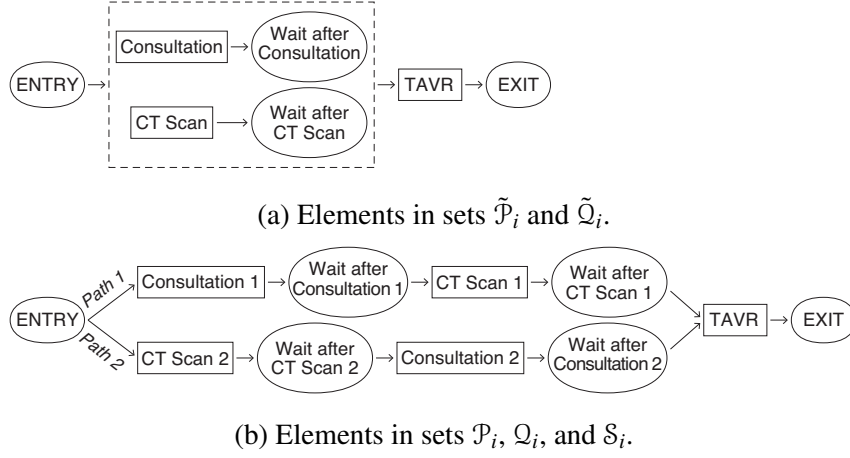


Figure 5.3: Example of paths followed by a TAVR patient i .

procedure or are waiting to go through their next appointment which might not be available right away due to capacity constraints. A patient who is in a *waiting position* is not using any hospital resources. Let $\tilde{\mathcal{P}}$ denote the set of *procedure positions* available in the hospital, and $\tilde{\mathcal{Q}}$ be the set of *waiting positions*. Note that for every element $\tilde{p} \in \tilde{\mathcal{P}}$ there exists an element $\tilde{q} \in \tilde{\mathcal{Q}}$ which is the *waiting position* that the patients will take after they complete procedure \tilde{p} . Also note that after the patients go through their last position in the system they go to a *waiting position* where they stay for the entire horizon, which is the *exit* position denoted by l . All patients that have reached this position are assumed to have exited the system. Set $\tilde{\mathcal{Q}}$ has one additional element ($|\tilde{\mathcal{Q}}| = |\tilde{\mathcal{P}}| + 1$), which is the waiting position *entry* which all patients take when they first enter the system before they go through any procedures and is denoted by b .

A patient entering the system will only visit a subset of the procedures (and their corresponding waiting positions) offered in the hospital. Let $\tilde{\mathcal{P}}_i$ and $\tilde{\mathcal{Q}}_i$ denote the sets of *procedure positions* and *waiting positions*, respectively, that a specific patient i has to visit,

where $\tilde{\mathcal{P}}_i \subseteq \tilde{\mathcal{P}}$ and $\tilde{\mathcal{Q}}_i \subseteq \tilde{\mathcal{Q}}$. An example of the procedures that a specific TAVR patient i may have to go through can be found in Figure 5.3a. In this case the elements appearing in the rectangles will be included in set $\tilde{\mathcal{P}}_i$, since they refer to procedures that patient i will go through, while those in the ovals will be part of the $\tilde{\mathcal{Q}}_i$ set, since the patient is waiting at those positions. For this example, the patient will follow one of the two paths presented in Figure 5.3b. The patient arrives in the system at position *entry*. Then the patient will either follow the first path in order to get a consultation and then do a CT scan or the second path in which the patient will first do a CT scan and then get a consultation. Finally, the two paths will merge into one and the patient will go through the TAVR procedure and then exit the system. It is important to point out that a patient who followed the first path and is going through a CT scan is in a different state in the system than a patient that followed the second path and is going through the CT scan. Therefore, multiple types of the same position are created, one for each path that a patient could follow. Let \mathcal{P}_i denote the set of all *procedures* in all possible paths that patient i could go through, and correspondingly let \mathcal{Q}_i be the set of all *waiting positions* in all possible paths that patient i could go through. Finally, let \mathcal{S}_i be the set of positions that a patient i may potentially visit, so $\mathcal{S}_i = \mathcal{P}_i \cup \mathcal{Q}_i$. Let $g : (\mathcal{S}_i) \rightarrow (\tilde{\mathcal{P}}_i \cup \tilde{\mathcal{Q}}_i)$, denote a function that returns an element $\tilde{s} \in (\tilde{\mathcal{P}}_i \cup \tilde{\mathcal{Q}}_i)$ for each argument $s \in \mathcal{S}_i$. Table 5.1 includes the elements that each of the sets defined above consists of, in the example presented in Figure 5.3. Finally, let $\mathcal{F}_{i,s}$ and $\mathcal{G}_{i,s}$ denote the set of positions right before and right after a position $s \in \mathcal{S}_i$ for patient i , respectively.

Table 5.1: Elements included in each set in the example illustrated in Figure 5.3.

Set	Elements
$\tilde{\mathcal{P}}_i$	CT scan, Consultation, TAVR
\mathcal{P}_i	CT scan 1, CT scan 2, Consultation 1, Consultation 2, TAVR
$\tilde{\mathcal{Q}}_i$	Entry, Wait after CT scan, Wait after Consultation, Exit
\mathcal{Q}_i	Entry, Wait after CT scan 1, Wait after CT scan 2, Wait after Consultation 1, Wait after Consultation 2, Exit
\mathcal{S}_i	CT scan 1, CT scan 2, Consultation 1, Consultation 2, TAVR, Entry, Wait after CT scan 1, Wait after CT scan 2, Wait after Consultation 1, Wait after Consultation 2, Exit

5.3.2.4 Availability, resources, and durations

For a patient to go through a procedure at a given time, the patient must be available to come to the hospital on that day, and the necessary resources must be available for the procedure to take place. Let A_i^d denote the availability of patient i to come to the hospital on day d . In particular, A_i^d is a binary parameter taking the value 1 if the patient can come to the hospital on day d , and 0 otherwise. Let \mathcal{R} be the set of all resources in the hospital that are required for the procedures to take place. These resources include equipment, labs, and staff. Let $P_{\tilde{p},r}$ denote the number of each resource type $r \in \mathcal{R}$ required for a procedure of type $\tilde{p} \in \tilde{\mathcal{P}}$ to take place. Let R_r^h denote the number of resources of type r that are available to be assigned to patients at time h . This number will change from one decision epoch to the next, since it will be updated based on the patients that got scheduled in the previous decision epoch and the demand from other departments in the hospital. Note that on weekends or during time in a weekday outside the 8am-5pm range, the availability of all resources is 0.

Table 5.2: Scheduling problem sets, function, and parameters.

<i>Sets</i>	
\mathcal{D}	Set of days in the planning horizon, indexed d
\mathcal{H}	Set of time slots in the planning horizon, indexed h
\mathcal{H}^d	Set of time slots belonging to the same day d , indexed h
\mathcal{T}	Set of decision epochs, indexed t
\mathcal{E}_i^d	Set of available appointment times for patient i on day d , indexed e
\mathcal{J}	Set of patients, indexed i
$\tilde{\mathcal{P}}$	Set of procedures, indexed \tilde{p}
$\tilde{\mathcal{P}}_i$	Set of procedures that patient i will visit, indexed \tilde{p}
\mathcal{P}_i	Set of procedure position states over all paths that patient i may visit, indexed p
$\tilde{\mathcal{Q}}$	Set of waiting positions, indexed \tilde{q}
$\tilde{\mathcal{Q}}_i$	Set of waiting positions that patient i will visit, indexed \tilde{q}
\mathcal{Q}_i	Set of waiting position states over all paths that patient i may visit, indexed q
\mathcal{S}_i	Set of position states over all paths that patient i may visit, indexed s, s'
$\mathcal{F}_{i,s}$	Set of positions preceding position s for patient i , indexed s, s'
$\mathcal{G}_{i,s}$	Set of positions subsequent to position s for patient i , indexed s, s'
\mathcal{C}	Set of steps required to reach the positions, indexed c
$\mathcal{K}_{i,c}$	Set of positions that can be reached by patient i after exactly c steps, indexed s, s'
\mathcal{P}_i^*	Set of procedure position states that will solely take place on a day, indexed p^*
\mathcal{R}	Set of resources, indexed r
<i>Functions</i>	
$o()$	Function mapping elements in \mathcal{T} to elements in \mathcal{H}
$f()$	Function mapping elements in \mathcal{H} to elements in \mathcal{E}_i^d
$g()$	Function mapping elements belonging in \mathcal{S}_i to elements in $\tilde{\mathcal{P}} \cup \tilde{\mathcal{Q}}$
<i>Parameters</i>	
R_r^h	Number of resources of type r available at time h
$P_{\tilde{p},r}$	Number of resources of type r required for a process \tilde{p} to take place
A_i^d	Binary indicating availability of patient i to visit the hospital on day d
a_i	Arrival time of the patient to the system, $a_i \in \mathcal{H}$
L_i	Number of time units within which patient i should complete the program
b	First position that patients take in the system, $b \in \mathcal{S}_i$
l	Last position that patients take in the system, $l \in \mathcal{S}_i$
$d_{\tilde{p}}$	Duration in time units of procedure \tilde{p}
$\omega_{\tilde{q}}$	Time units of recovery needed after a procedure, spent in the subsequent waiting position \tilde{q}
$\gamma_{\tilde{p}}$	Time units of rest required before procedure \tilde{p}
M	Upper bound for the time in a day that a patient can be in the hospital
N_i^j	Normalizing constant for patient i used in component j of the objective, $j = 1, 2$
λ	Trade-off parameter in the objective function, $\lambda \in [0, 1]$

Each procedure $\tilde{p} \in \tilde{\mathcal{P}}$ that a patient will go through has a duration $d_{\tilde{p}}$. Any resources that are allocated to the patient for a procedure \tilde{p} will be allocated to the same patient for the entire duration of the procedure. Every *procedure position* \tilde{p} is followed by a *waiting position* \tilde{q} , which is necessary to ensure that the patient has enough time to rest and recover from the procedure. Let $\omega_{\tilde{q}}$ be the time that a patient needs to recover from a preceding procedure \tilde{p} , or, in other words, the minimum time that the patient will spend in the *waiting position* \tilde{q} . Depending on the procedure, the recovery time could last up to a few days. Finally, let $\gamma_{\tilde{p}}$ denote the additional time required before a specific procedure \tilde{p} takes place. This is the case for procedures that require some preparation. For example, if the patient is not supposed to eat or drink anything for a few hours before the procedure. In those cases, in order to avoid stressing the patients further, we impose some additional rest time before the procedure.

5.4 Scheduling problem

This section describes the formulation used to solve the problem of multi-appointment outpatient scheduling. In Subsections 5.4.1 and 5.4.2, we present the decision variables, the objective function, and the constraints of the scheduling problem. The problem is formulated based on the notation discussed in Section 5.3 and included in Table 5.2. Subsection 5.4.3 describes the approach used to normalize the components of the objective function, and Subsection 5.4.4 includes an example for obtaining the Pareto optimal solutions. In Subsection 5.4.5 we include improvements of the initial formulation in order to decrease

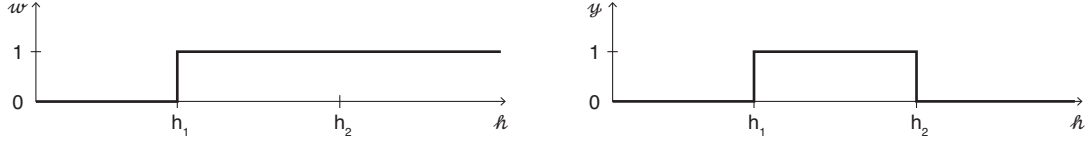


Figure 5.4: Difference between decision variables $w_{i,s}^h$ and $y_{i,s}^h$.

the time it takes to obtain an optimal solution.

5.4.1 Decision variables

The decision variables for the IP are presented below.

$$w_{i,s}^h = \begin{cases} 1, & \text{if patient } i \in \mathcal{J} \text{ arrives at position } s \in \mathcal{S}_i \text{ by time } h \in \mathcal{H} \\ 0, & \text{otherwise} \end{cases}$$

$$y_{i,s}^h = \begin{cases} 1, & \text{if patient } i \in \mathcal{J} \text{ is at position } s \in \mathcal{S}_i \text{ at time } h \in \mathcal{H} \\ 0, & \text{otherwise} \end{cases}$$

$$x_i^d = \begin{cases} 1, & \text{if patient } i \in \mathcal{J} \text{ visited the hospital on day } d \in \mathcal{D} \\ 0, & \text{otherwise} \end{cases}$$

$$x_{i,p}^d = \begin{cases} 1, & \text{if patient } i \in \mathcal{J} \text{ went through procedure } p \in \mathcal{P}_i \text{ on day } d \in \mathcal{D} \\ 0, & \text{otherwise} \end{cases}$$

$$u_i^d \equiv \text{time that patient } i \in \mathcal{J} \text{ arrived at the hospital on day } d \in \mathcal{D}$$

$v_i^d \equiv$ time that patient $i \in \mathcal{J}$ left the hospital on day $d \in \mathcal{D}$

Note that the decision variable $w_{i,s}^h$ shows whether a patient has arrived at a position by a specific time h . Once this variable takes the value 1 for a specific patient and position, it will take the value 1 for all subsequent times, since the patient has reached this position by all future times. This decision variable was first introduced in [14]. On the other hand, the decision variable $y_{i,s}^h$ only takes the value 1 if a patient is in position s at a specific point in time h . Figure 5.4 shows the values for these two types of variables. A patient is scheduled to go through a specific position from time h_1 to time h_2 . We can see from the figure that decision variable $w_{i,s}^h$ takes the value 1 for all times after h_1 . On the other hand, decision variable $y_{i,s}^h$ equals to 1 only for the times between h_1 and h_2 . Appendix H includes an example which illustrates the difference between the decision variables and the values they take.

5.4.2 The Integer Program

Below is the mathematical formulation of the IP. The hospital would have to run the following IP at every decision epoch $t \in \mathcal{T}$, in order to schedule all patients that have arrived since the last scheduling took place. The patients that have already been scheduled are not taken into account again in the decision making since it is not allowed to reschedule already scheduled patients. Nevertheless, the resources they occupy are updated to represent the availability at time t . However, when previously scheduled patients do not show up for an

appointment, they might be taken into account again in the decision making. In this case their appointments have to get rescheduled. In particular, if the appointment that the patient did not show up for can be rescheduled without affecting the timing of future appointments it can be rescheduled manually, since it is considered as a single appointment. If the no-show affects a combination of steps, then the patient is scheduled again through the IP. The IP follows:

$$\min \lambda \sum_{d \in \mathcal{D}} \sum_{i \in \mathcal{J}} \frac{1}{N_i^1} x_i^d + (1 - \lambda) \sum_{d \in \mathcal{D}} \sum_{i \in \mathcal{J}} \frac{1}{N_i^2} [(v_i^d - u_i^d) - \sum_{p \in \mathcal{P}_i} (d_{g(p)} - 1) x_{i,p}^d] \quad (5.1)$$

subject to:

$$w_{i,s}^h = 0, \forall h \in \mathcal{H} : h \leq a_i - 1, i \in \mathcal{J}, s \in \mathcal{S}_i \quad (5.2)$$

$$w_{i,s}^h = 1, \forall h \in \mathcal{H} : h \geq a_i, i \in \mathcal{J}, s = b \quad (5.3)$$

$$w_{i,s}^h = 1, \forall h \in \mathcal{H} : h \geq a_i + L_i, i \in \mathcal{J}, s = l \quad (5.4)$$

$$w_{i,s}^h = 0, \forall h \in \mathcal{H} : h \leq o(t), i \in \mathcal{J}, s \neq b \quad (5.5)$$

$$w_{i,s}^{h-1} \leq w_{i,s}^h, \forall \{h, h-1\} \in \mathcal{H}, i \in \mathcal{J}, s \in \mathcal{S}_i \quad (5.6)$$

$$w_{i,s}^h \leq \sum_{\substack{s' \in \mathcal{F}_{i,s}: \\ \{h - \max\{\omega_{g(s')}, \gamma_{g(s)}\}\} \in \mathcal{H}}} w_{h - \max\{\omega_{g(s')}, \gamma_{g(s)}\}}^{i,s'}, \forall h \in \mathcal{H}, i \in \mathcal{J}, s \in \mathcal{S}_i \cap \mathcal{P}_i \quad (5.7)$$

$$w_{i,s}^h = \sum_{\substack{s' \in \mathcal{F}_{i,s}: \\ \{h - d_{g(s')}\} \in \mathcal{H}}} w_{i,s'}^{h - d_{g(s')}}, \forall h \in \mathcal{H}, i \in \mathcal{J}, s \in \mathcal{S}_i \cap \mathcal{Q}_i \setminus \{b\} \quad (5.8)$$

$$w_{i,s}^h - \sum_{s' \in \mathcal{G}_{i,s}} w_{i,s'}^h \leq y_{i,s}^h, \forall h \in \mathcal{H}, i \in \mathcal{J}, s \in \mathcal{S}_i \quad (5.9)$$

$$\sum_{s \in \mathcal{S}_i} y_{i,s}^h \leq 1, \forall h \in \mathcal{H}, i \in \mathcal{J} \quad (5.10)$$

$$\sum_{i \in \mathcal{J}} \sum_{s \in \mathcal{S}_i \cap \mathcal{P}_i} y_{i,s}^h P_{g(s),r} \leq R_r^h, \forall h \in \mathcal{H}, r \in \mathcal{R} \quad (5.11)$$

$$x_i^d \leq A_i^d, \forall d \in \mathcal{D}, i \in \mathcal{J} \quad (5.12)$$

$$y_{i,s}^h \leq x_i^d, \forall d \in \mathcal{D}, h \in \mathcal{H}^d, i \in \mathcal{J}, s \in \mathcal{S}_i \cap \mathcal{P}_i \quad (5.13)$$

$$x_i^d \leq \sum_{h \in \mathcal{H}^d} \sum_{s \in \mathcal{S}_i \cap \mathcal{P}_i} y_{i,s}^h, \forall d \in \mathcal{D}, i \in \mathcal{J} \quad (5.14)$$

$$y_{i,s}^h \leq x_{i,p}^d, \forall d \in \mathcal{D}, h \in \mathcal{H}^d, i \in \mathcal{J}, p \in \mathcal{P}_i, s = p \quad (5.15)$$

$$x_{i,p}^d \leq \sum_{h \in \mathcal{H}^d} y_{i,s}^h, \forall d \in \mathcal{D}, i \in \mathcal{J}, p \in \mathcal{P}_i, s = p \quad (5.16)$$

$$u_i^d \leq (h - |\mathcal{H}^d| * (d - 1)) y_{i,s}^h + M(1 - y_{i,s}^h) - M(1 - x_i^d), \forall d \in \mathcal{D}, h \in \mathcal{H}^d,$$

$$i \in \mathcal{J}, s \in \mathcal{S}_i \cap \mathcal{P}_i \quad (5.17)$$

$$v_i^d \geq (h - |\mathcal{H}^d| * (d - 1)) y_{i,s}^h, \forall d \in \mathcal{D}, h \in \mathcal{H}^d, i \in \mathcal{J}, s \in \mathcal{S}_i \cap \mathcal{P}_i \quad (5.18)$$

$$w_{i,s}^h, y_{i,s}^h, x_i^d, x_{i,p}^d \in \{0, 1\}, \forall d \in \mathcal{D}, h \in \mathcal{H}, i \in \mathcal{J}, p \in \mathcal{P}_i, s \in \mathcal{S}_i \quad (5.19)$$

$$u_i^d, v_i^d \in \mathbb{Z}^+, \forall d \in \mathcal{D}, i \in \mathcal{J} \quad (5.20)$$

The objective function (5.1) minimizes the linear combination of the number of times that the patients have to visit the hospital, and the time that the patients spend in the hospital waiting for their next appointment. The first component of the objective has weight λ , and is estimated based on the total number of visits to the hospital over all patients. For each patient, the number of visits is normalized to take a value between 0 and 1. This is achieved by dividing the number of visits of each patient by a constant N_i^1 . More details about how the value of the normalizing constant is chosen are included in Subsection 5.4.3. The

second component of the objective has weight $(1 - \lambda)$, and corresponds to the total time that the patients spent in the hospital not going through a procedure, or in other words the time spent in the hospital in-between procedures. Similarly to the first component, the total idle time for each patient is normalized by dividing by a constant N_i^2 . We plan to provide the hospital with multiple schedules to choose from. Therefore, in each problem instance we estimate the Pareto optimal solutions based on various values of λ . Varying λ in this way allows us to obtain the convexification of the Pareto points boundary (see [46]), which is much better than providing the solution for a single value of λ . Such an example is discussed in Subsection 5.4.4.

Constraint (5.2) makes sure that the patients will not reach any position in the system before they get referred to the hospital. Constraints (5.3), and (5.4) enforce that patients will visit the first and the last positions in their path by their entry time and at most after spending the maximum allowed time in the system respectively. Constraint (5.5) states that patients who are referred to the hospital cannot go through any procedure before the decision epoch following their arrival. Constraint (5.6) guarantees that once a patient has reached a position, this position will have been reached in all future times by this patient. Constraint (5.7) enforces a recovery and preparation time before the patient can move to the next procedure. Similarly, constraint (5.8) imposes that a patient will move on from a procedure to the subsequent *waiting position* exactly after time equal to the duration of the procedure. Constraint (5.9) ensures that a patient is in a specific position, when the patient has reached the current position but none of the subsequent positions. Constraint (5.10)

makes sure that a patient is at most at one position in the system at all times. Constraint (5.11) verifies that no more than the available resources are used at each point in time. Constraint (5.12) enforces that all appointments are scheduled on days that the patient is able to come to the hospital. Based on the discussions we had with the hospital, we decided to consider availability based on the day and not the time. Since the hospital tries to fit as many procedures as possible on a single day, we decided that patients are available if they are available all day. However, if necessary, availability per time can be easily introduced to the IP by changing constraint (5.12) to $y_{i,s}^h \leq A_i^h$, where A_i^h is the availability of the patient in each time slot h .

Constraints (5.13) and (5.14) capture whether a patient is scheduled to be in the hospital on a specific day. Similarly, (5.15) and (5.16) capture whether a patient is scheduled to go through a specific procedure on a specific day. Constraints (5.17) and (5.18) capture the arrival and departure times of each patient on each day. Since this is a minimization problem and variable u_i^d has a negative sign, the variable will take the largest value possible. Thus, $u_i^d \leq (h - |\mathcal{H}^d| * (d - 1)) y_{i,s}^h$ ensures that variable u_i^d will equal the time of day d that the patient is scheduled for the first procedure of the day. If a patient is not scheduled for procedure p on day d , but is scheduled for a different procedure, constraint (5.17) becomes $u_i^d \leq M$ for procedure p . This ensures that u_i^d will equal to the start time of a procedure that the patient is scheduled to go through on that day. This requires a large enough M . On the other hand, if the patient is not scheduled for any procedure on day d , constraint (5.17) becomes $u_i^d \leq M - M \Rightarrow u_i^d \leq 0$ for all procedures. Since v_i^d has a positive sign in

the objective, it will take the smallest value possible. This corresponds to the time that the patient finished with the last procedure for the day. Constraints (5.19) and (5.20) define the binary and the nonnegative integer decision variables of the problem respectively.

Some of the constraints introduced above either come from, or are based on, constraints from [13, 14]. Constraints (5.6) and (5.7) were used in [13, 14], and ensure connectivity between the positions and connectivity in time. Constraint (5.8) is similar to (5.7) but with an equal instead of a less than or equal sign. We adapted this type of constraint to ensure that a patient will spend time in a procedure exactly equal to the duration of the appointment. Constraint (5.11) has been extended to include the number of resources required for a procedure to take place. The remaining constraints and objective functions were created for the purpose of this problem.

5.4.3 Choice of normalizing constants

The two components of the objective are estimated based on different metric units. The first component refers to the number of visits to the hospital, and the second to the total idle time during a patient's visits to the hospital. The idle time component tends to get larger values, which effectively gives this component a larger weight in the objective. Therefore, it is important to normalize the two components. For every patient getting scheduled, each component of the objective will take values between 0 and 1 after the normalization. This helps achieve a better balance between the two components, and avoids the well know pitfall of different dynamic ranges (i.e. ranges of values) between two or more objectives

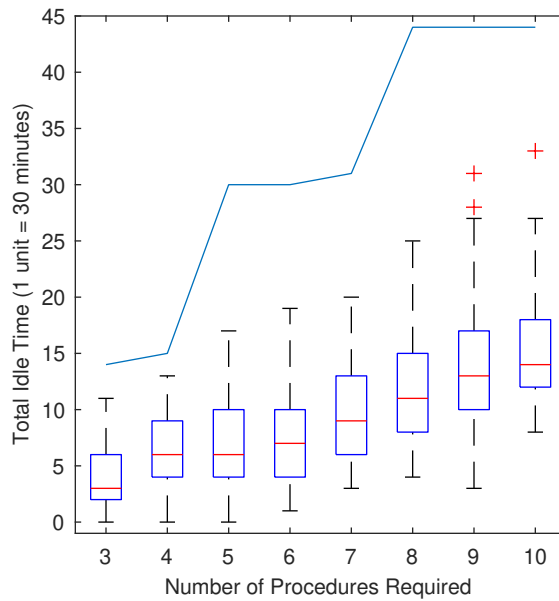


Figure 5.5: Idle times observed per number of procedures required.

in trade-off analysis.

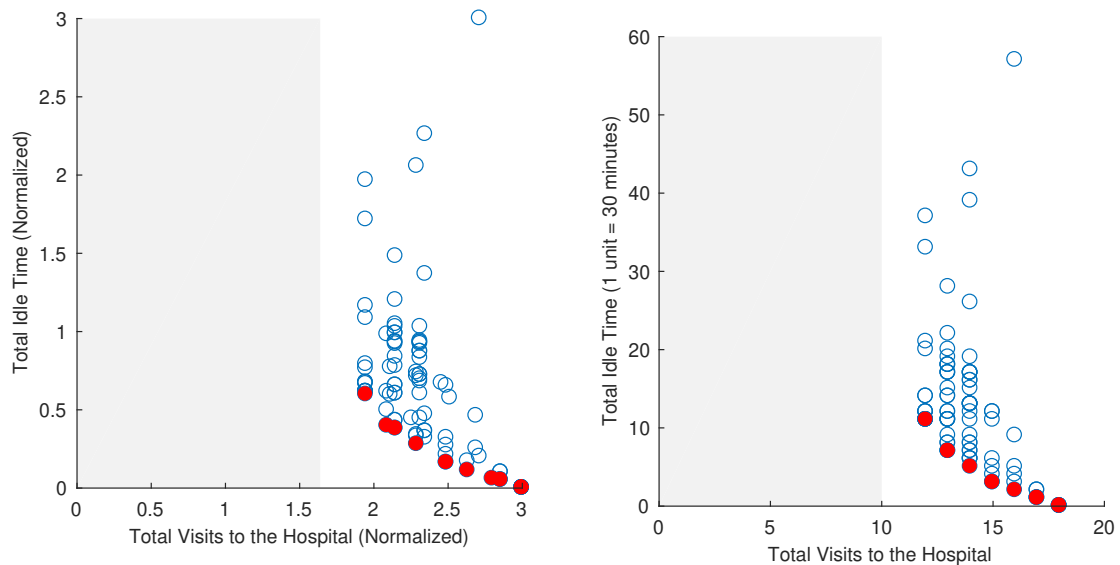
In the case of the number of visits to the hospital we achieve this by dividing the total number of visits that a patient has to make to the hospital with the maximum number of visits that the patient could make to the hospital (i.e., the number of procedures required). With the second component of the objective we want to use a similar approach when normalizing. However, in the worst case scenario, where the patients have to wait in the hospital for the longest time possible, the total wait time for each patient becomes a very large number. If we divide the total idle time for each patient by the maximum possible wait time that this type of patient could spend in the hospital, we obtain a very small number. The reason is that the worst case scenario never occurs in reality. Therefore, the first component of the objective would effectively have a larger weight. In an effort to decrease the value of the

normalizing constant in the second component of the objective, we ran a number of experiments where the objective only focused on minimizing the number of visits to the hospital (i.e. $\lambda = 1$). For each patient, we estimated the total idle time in the hospital. The patients were grouped based on the number of required procedures they have to go through. The results are presented in Figure 5.5. The line at the top of the figure shows the maximum idle time for each group in the worst case scenario. From the box plots we can see that the actual idle times are considerably lower than the longest possible idle time. Therefore, the normalizing constant for each type of patient is set equal to the longest idle time observed in the experiments.

5.4.4 Pareto solutions

Our objective consists of two components, which are incompatible with each other. A Pareto optimal solution ensures that in order to improve one of the components, the other will have to become worse. The hospital should be the one to choose between schedules that provide Pareto optimal solutions. Thus, the scheduling staff will select the schedule that provides the desirable balance (or compromise) between the two components.

An example of the different solutions provided when solving a specific scheduling problem is presented in Figure 5.6. In this example, three patients are getting scheduled simultaneously. In order to obtain the different solutions, we solved the IP using different values of λ (i.e., $\lambda \in \{0, 0.1, \dots, 1\}$). Furthermore, we used different time limits, after which the IP provided the best solution found up to that point. We also allowed enough time for the



(a) Normalized values of the two objective function components.

(b) Values of the two objective components.

Figure 5.6: Pareto optimal solutions (in red) in example of scheduling 3 patients simultaneously.

IP to reach optimality in some of the experiments. Note that in cases where the solver is not allowed enough time to prove that a proposed solution is optimal (i.e., to reach optimality), we subsequently cannot prove that a solution is Pareto optimal. Nevertheless, since enough time was allowed in this particular example, we have generated Pareto optimal solutions.

The filled red points in Figure 5.6 are the Pareto optimal solutions. The gray areas in both graphs indicate values that cannot be part of the solution, since there is a minimum number of visits that a patient has to make to the hospital. Figure 5.6a shows the values for each component of the objective. The y and the x axis of the graph range from 0 to 3, since for each of the 3 patients getting scheduled both components of the objective take at most the value 1. Figure 5.6b includes the same solution without normalizing the two components of the objective.

It can be observed from Figure 5.6 that there exists a trade-off between the two components of the objective. As it was expected, low values of idle time are achieved when the patient makes many visits to the hospital. On the other hand, the time spent at the hospital while waiting increases as the number of visits to the hospital decreases. If the hospital is more interested in obtaining schedules where the patients visit the hospital few times, they could choose a schedule that corresponds to 12 visits and 11 time units of wait in total for the three patients being scheduled. Another option would be to choose a schedule that corresponds to 13 visits and 7 time units waiting time in the hospital in total. The second schedule proposed might be preferable, since the hospital would require one additional visit from one of the three patients, but save four time units of wait, which corresponds to two hours. Nevertheless, the hospital will have to decide whether this is indeed preferable.

5.4.5 Formulation improvements

We make improvements to the IP presented in Section 5.4.2 in order to help in solving it faster. The improvements guarantee that the resulting IP will provide the same solutions as the initial formulation. First, we ensure that the big M will take the smallest possible value, which helps the IP to be solved faster. Second, we introduce valid inequalities. These are constraints that eliminate some non-integer solutions, which are feasible in the initial formulation. However, none of the integer solutions are eliminated. The improvements that we introduce are based on the structure of this particular problem.

Valid inequalities have been used before in the outpatient scheduling literature [142].

In [142], the valid inequalities have to do with the fact that the total resource demand on a given day cannot be higher than the available capacity, and that a procedure cannot be scheduled if none of the resources are used by this procedure on a specific day. The authors use Bender's decomposition, and their objective function only depends on the day that a specific procedure is scheduled. The formulation approach and constraints are different to the IP proposed here, which means that we use different valid inequalities.

As we described in Section 5.4.2, parameter M has to be large enough to ensure that it will not be smaller than a potential appointment time. At the same time, for computational efficiency M has to take the smallest possible value. One option is to set M equal to $|\mathcal{H}^d|$, since all appointments are completed by the end of the day, and there are $|\mathcal{H}^d|$ time units in a day. Nevertheless, we achieve an even stricter bound by setting different M values for different days and different patients. So in fact M becomes $M_i^d, \forall d \in \mathcal{D}, i \in \mathcal{J}$.

We know the available resources and the procedures that each patient is going to go through. Thus, we can estimate the earliest and the latest time on each day that each patient could potentially be scheduled to go through a procedure. We generate set $\mathcal{E}_i^d = \{0, 1, \dots, E\}$ for each patient on each day. We define the earliest time that the patient could be in the hospital as $e = 1$, and the latest time as $e = E$. For times in a day that a patient will definitely not be in the hospital, we have $e = 0$. If the patient cannot be scheduled for any procedure on a day, we get $\mathcal{E}_i^d = \{0\}$. Let $f : (\mathcal{H}) \rightarrow (\mathcal{E}_i^d)$ denote a function that returns the order in a day for each argument $h \in \mathcal{H}$. If h corresponds to a time outside the appointment range it returns 0. For example, consider the case where a patient could only be at the

hospital for any appointment from 8am to 1pm on a specific day. This corresponds to $h = 8, 9, \dots, 13$, assuming that this is the first day in the planning horizon and the time unit is in hours. The corresponding set \mathcal{E} for the patient on this specific day, would include elements $\{0, 1, 2, \dots, 6\}$, where $e = 1$ corresponds to $h = 8$, $e = 2$ corresponds to $h = 9$, etc. In addition, $e = 0$ corresponds to all h on that day that the patient could not possibly be at the hospital (e.g. 4am). Using this new information obtained from preprocessing, constraints (5.17) and (5.18) can be replaced by constraints (5.21) and (5.22), where $M_i^d = |\mathcal{E}_i^d| - 1$. Through this change in the formulation, we obtain much smaller M values.

$$u_i^d \leq f(h)y_{i,p}^h + M_i^d(1 - y_{i,p}^h) - M_i^d(1 - x_i^d), \forall d \in \mathcal{D}, h \in \mathcal{H}^d, i \in \mathcal{J}, p \in \mathcal{P}_i \quad (5.21)$$

$$v_i^d \geq f(h)y_{i,p}^h, \forall d \in \mathcal{D}, h \in \mathcal{H}^d, i \in \mathcal{J}, p \in \mathcal{P}_i \quad (5.22)$$

$$\sum_{s \in \mathcal{K}_{i,c}} w_{i,s}^h \leq 1, \forall h \in \mathcal{H}, i \in \mathcal{J}, c \in \mathcal{C} \quad (5.23)$$

$$\sum_{h \in \mathcal{H}} \sum_{\substack{s \in \mathcal{S}_i \cap \mathcal{P}_i: \\ g(s) = \tilde{p}}} y_{i,s}^h = d_{\tilde{p}}, \forall i \in \mathcal{J}, \tilde{p} \in \tilde{\mathcal{P}}_i \quad (5.24)$$

$$(v_i^d - u_i^d) \geq \sum_{p \in \mathcal{P}_i} (d_{g(p)} - 1)x_{i,p}^d, \forall d \in \mathcal{D}, i \in \mathcal{J} \quad (5.25)$$

$$x_{i,p^*}^d + x_{i,p}^d \leq 1, \forall d \in \mathcal{D}, i \in \mathcal{J}, p^* \in \mathcal{P}_i^*, p \in \mathcal{P}_i : p \neq p^* \quad (5.26)$$

The time it takes to solve the IP can be decreased further by introducing valid inequalities (5.23) through (5.26). Let \mathcal{C} denote the set including the number of steps required for patients to reach any position in their path. Let $\mathcal{K}_{i,c}$ denote the set including all positions that could be possibly reached by patient i after exactly c steps. Valid inequality (5.23) states that at most one position will be reached among those requiring exactly c steps to be reached by patient i . This is similar to the antichain inequality used in [13]. Valid inequality (5.24) states that the time spent over all procedures of the same type will equal to the duration of this specific procedure. Valid inequality (5.25) has to do with the fact that the time that patients spend in the hospital on a given day is greater or equal to the duration of the procedures that they go through. Let \mathcal{P}_i^* denote the set of *procedure positions* for a patient i , where each *procedure position* included in the set will solely take place on a day. In other words, the patient will not go through other procedures on the same day if he goes through a procedure in \mathcal{P}_i^* . These are procedures that might require long preparation and/or recovery times. Valid inequality (5.26) states that all patients can either go through a procedure in \mathcal{P}_i^* or any other procedure on a given day, but not both.

5.4.5.1 Resulting running times

We ran experiments of scheduling 60 patients, where one patient was scheduled at a time, in order to see how the proposed formulation improvements affected the running

times. The maximum time that the solver was allowed to run was set to 1500 seconds. If by that time no optimal solution was found the solver stops and returns the best solution obtained up to that point in time. This limit was selected due to our 3rd assumption, which states that “*The scheduling staff has enough time to book an appointment before the resource availability changes*”. Therefore, we need to impose a limit to the time that we allow the IP to run. We notice that the solver finds the optimal solution relatively fast, but it takes a long time to prove optimality. In other words, by limiting the time to 1500 seconds we might still get an optimal solution but it is not proven that it is optimal. In Section 5.5 we ran the simulation experiments where we schedule patients in groups of 2 up to 5 patients. This complicates the problem and it takes longer for the IP to run. Nevertheless, within the 1500 second limit all IPs solved in the experiments had enough time to go through the presolve section of Gurobi and generate a solution, even through it was not proven to be optimal. Therefore, 1500 seconds seems to be reasonable time limit for our problem.

All experiments were coded in Java 8. We used the Gurobi 7.5 [58] optimization solver through Java in order to solve the IP. Experiments were run on a computer with an 2.9 GHz Intel Core i5 processor and 8 GB 1867 MHz memory.

Figure 5.7 includes the running times of the initial formulation (IF) and the final formulation (FF), after introducing improvements (5.21) through (5.26). For all values of λ the final formulation, including all of the proposed improvements, performed considerably better than the initial formulation. We use the Wilcoxon rank sum test, which is a nonparametric test, in order to test whether the initial and the final formulations have statistically

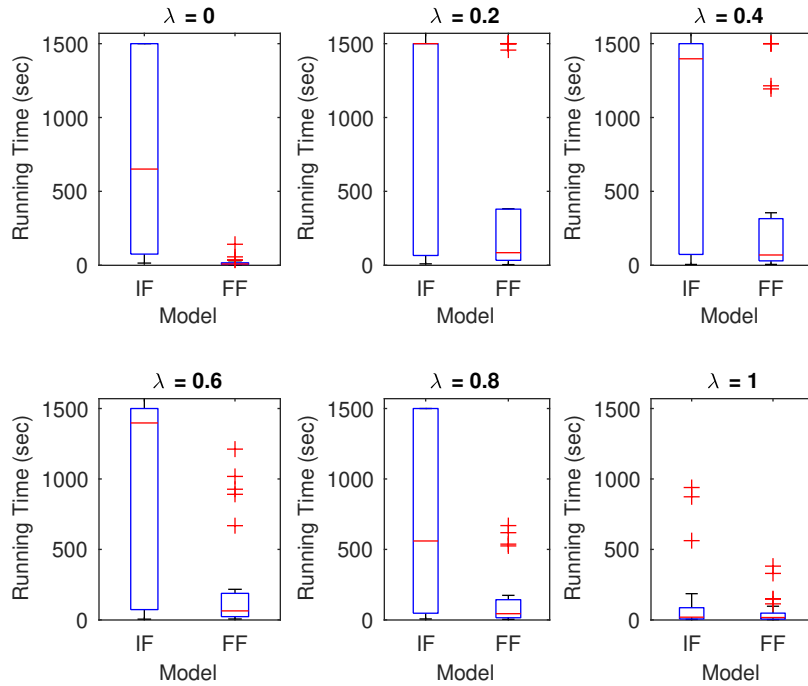


Figure 5.7: Running times of initial and final formulation.

Table 5.3: Results of the Wilcoxon rank sum test (comparing each model with the IF).

Model	$\lambda = 0$	$\lambda = 0.2$	$\lambda = 0.4$	$\lambda = 0.6$	$\lambda = 0.8$	$\lambda = 1$
IF + (5.21, 5.22)	0.3853	0.0597	0.4917	0.4988	0.1975	0.4893
IF + (5.24)	0.2381	0.0241	0.2193	0.3127	0.0168	0.4768
IF + (5.25)	0.0000	0.0077	0.0208	0.0344	0.0110	0.2491

different running times. The null hypothesis states that they are samples from distributions with equal medians. The resulting p-values reject the null hypothesis at the 5% level, with the exception of $\lambda = 1$. The scheduling problem solved already fast for $\lambda = 1$, so adding the valid inequalities did not significantly change the running time.

Figure 5.8 presents the results of experiments ran, where proposed improvements in the formulation were added separately in the initial formulation (IF). While all formulation

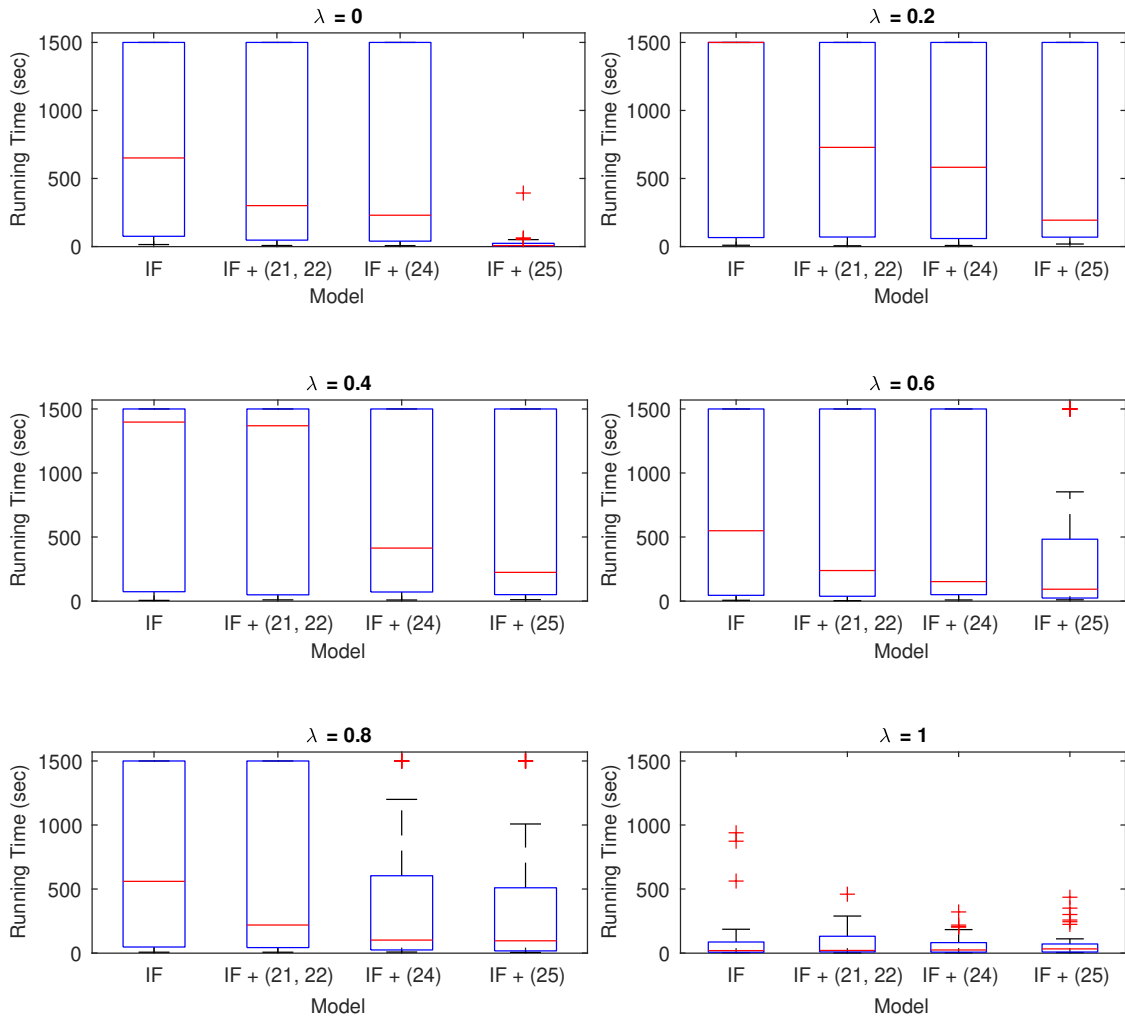


Figure 5.8: Running times after separately introducing improvements to the formulation.

improvements seem to provide faster running times in all cases, valid inequality (5.25) is the one with the largest proportion of gains in running time. Table 5.3 includes the resulting p-values of the Wilcoxon rank sum tests. Note that no multiple testing procedure has been used. We see that valid inequalities (5.24) and (5.25) rejected the null hypothesis of equal medians for at least some values of λ . However, introducing inequalities (5.21, 5.22) to the initial formulation did not result in statistically different running times. Nevertheless,

because we see an improvement in the running times even though it is not significant at the 5% level, we decided to keep the aforementioned improvements in the formulation.

5.5 Numerical experiments

In this section, we include the results of the simulation experiments. First, we conduct benchmark analysis. Second, we investigate under which circumstances it is better to group outpatients together when scheduling, and the gains obtained in those cases.

5.5.1 Simulation

Due to the lack of historic data including the availability of resources over time and information about the outpatients, we make a number of assumptions regarding the distributions of the data.

5.5.1.1 Outpatients

The outpatients usually get referred to the hospital from different physicians, so the referral times are independent from one another. Therefore, we assume that outpatients get referred to the hospital following a Poisson distribution [56, 85]. In particular, outpatients get referred to the hospital only on days Monday through Friday, and during the 8am-5pm time range. Based on discussions we had with the hospital personnel we know that on average 60 outpatients per month go through cardiology programs or elective surgery. About 10 patients per month go through the TAVR program, 4 through the TMVR, 4 through

the Watchman, 1 through the PFO closure, 1 through the Valvuloplasty, and 40 through elective surgery. Each new outpatient that arrives gets assigned to one of the aforementioned outpatient programs or to elective surgery based on the probabilities generated from the corresponding average numbers discussed above. Then, the combination of required steps is determined. Each combination is equally likely to be required for an outpatient of a specific condition. Finally, the outpatients are assigned the days that they are able to come for an appointment to the hospital within the planning horizon. We are assuming that with probability 0.1 a patient will not be able to come to the hospital on a given day. We were not able to find information about the real availability of the patients. We chose a non-zero probability to illustrate that our formulation takes into account the availability of the patient. However, the number is low enough to avoid infeasible solutions. We assume that the outpatients will make the effort to come to the hospital unless there are exceptional circumstances that makes them unavailable. This rare case is captured by this low probability.

5.5.1.2 Durations

Table 5.4 includes the duration of each procedure and the minimum required recovery time after a procedure. Those times are maximum estimations of the durations, and are based on information found online and discussions we had with the staff in the hospital. These durations are used to illustrate the performance of the system. However, they can be easily adjusted if the real numbers from the hospital are different. Based on these durations

Table 5.4: Procedure durations and recovery times.

Type	Procedure	Duration	Recovery Time
Common	TTE [67]	30 mins	0 mins
	CT scan [102]	30 mins	0 mins
	Carotid Ultrasound [101]	30 mins	0 mins
	PFT [93]	30 mins	30 mins
	PREP [164]	2 hours	1 hour
	TEE [160]	1.5 hours	24 hours
	Cath [66]	1.5 hours	72 hours
TAVR	Consultation	1.5 hours	30 mins
	Procedure [162]	2.5 hours	(admitted)
TMVR	Consultation I	1 hour	30 mins
	Consultation II	30 mins	0 mins
	Procedure [165]	2.5 hours	(admitted)
PFO closure	Consultation	1 hour	30 mins
	Procedure [24]	2 hours	(admitted)
Valvuloplasty	Consultation	1 hour	30 mins
	Procedure [82]	1.5 hours	(admitted)
Watchman	Consultation	1 hour	30 mins
	Procedure [49]	1.5 hours	(admitted)
Surgery	Consultation	1 hour	30 mins
	Procedure [65]	4 hours	(admitted)

we determine the length of the time unit in the scheduling problem. A time unit is equal to 30 minutes, since all durations and recovery times are multiples of 30 minutes. We choose 30-minute slots for this simulation, because we have no data available showing the length of the slots used in the hospital. The parameters of the IP can be easily adjusted to include slots of different length, as for example 15 minute slots. Thus, the scheduling staff can change the slot length if necessary in the future. In addition to the times presented in Table 5.4, we assume that the patients will spend some time after they enter the system but before

they go through any procedures. This time is set equal to 48 hours and it represents the time it takes for the hospital to learn about the patients and decide on the procedures that they will follow. Some procedures require some preparation time, where the patient usually is not allowed to eat or drink for some time. Those procedures are the TEE, the Cath, and all the procedures where the patient gets admitted afterwards.

5.5.1.3 Scenarios

In the beginning of each simulation we generate the initial resources available. We consider scenarios of different initial availability. In particular, low initial availability corresponds to 30% of the appointments of each resource being free. High availability corresponds to 50% of the appointments being free. The slots of each physical resource are grouped in blocks that equal to the maximum duration of all the procedures that this resource may participate in. In the case of personnel, the slots are grouped in blocks equal to half-days. This way we avoid having fragmented availability of resources. Each block is free with probability 0.5 or 0.3, depending on the scenario. The total number of each type of resource present in the hospital can be found in Appendix I. The available resources are updated during the simulation, as *external demand* and new cardiology outpatients arrive.

The *external demand* arrives following a Poisson distribution during working hours on weekdays. We consider different arrival rates (low and high) of *external demand*. The arrival rates depend on the number of blocks of slots present in the hospital for each resource. In the case of high levels of *external demand* about 14% of the blocks will be occupied in

the entire planning horizon. When there are low levels of *external demand* 7% of the blocks present in the hospital will be occupied. Based on these numbers we produce the interarrival times of *external demand* for each type of resource. Thus, resources that can treat higher number of patients during a fixed time also have higher rates of *external demand*. In other words, we assume that a resource is present in higher numbers in the hospital because there is also higher demand for this resource.

We investigate four different scenarios based on the initial resource availability and *external demand*. Scenario 1 considers an environment with low availability of resources and high external demand. Scenarios 2 and 3 consider the cases of low resource availability and low external demand, and high resource availability and high external demand respectively. Scenario 4 corresponds to a setting with high availability of resources and low external demand.

5.5.1.4 Simulation components

The parameters described in Subsections 5.5.1.1 through 5.5.1.3 are used as an input in the simulation. Figure 5.9 shows the steps followed in our simulation.

1. Based on the scenario we are in, we generate the availability of each type of resource during the planning horizon. Furthermore, we generate the list of cardiology outpatients that are going to get referred to the hospital, which includes the referral time, the steps that they have to complete, and their availability (as discussed in Subsection 5.5.1.1). Similarly, depending on the scenario, we generate the external demand,

which is a list of resource types and the times that they are requested. Finally, we set the group size (i.e. how many outpatients are scheduled together in each decision epoch).

2. Next we run the simulation, where we schedule appointments for cardiology outpatients and external demand. Based on the referral times of the last outpatient in each group (i.e., if the group size is four, the referral times of the 4th, 8th, 12th outpatient, etc.), and the arriving times of external demand we generate *events*. During an *event* we either solve the IP, if the last outpatient in a group has arrived, or an abbreviated version of the IP, which simply schedules the external demand, if an external demand has arrived. Thus, the IP presented in Section 5.4.2 is solved $\lceil \frac{\text{\# of outpatients}}{\text{\# of outpatients in each group}} \rceil$ times in each simulation. After each *event* we update the available resources based on the schedule resulting from the corresponding IP. Once the last *event* is executed, the simulation terminates.

As we see from the above, all of the random factors in the system are generated in the first step. This allows us to rerun the second step multiple times using the same input, but with a different group size or λ value each time. Thus, we are able to compare the change in the objective value and the resulting schedules in the same setting. To get different input we use different seeds, which allows us to run multiple simulations and estimate the average effects.

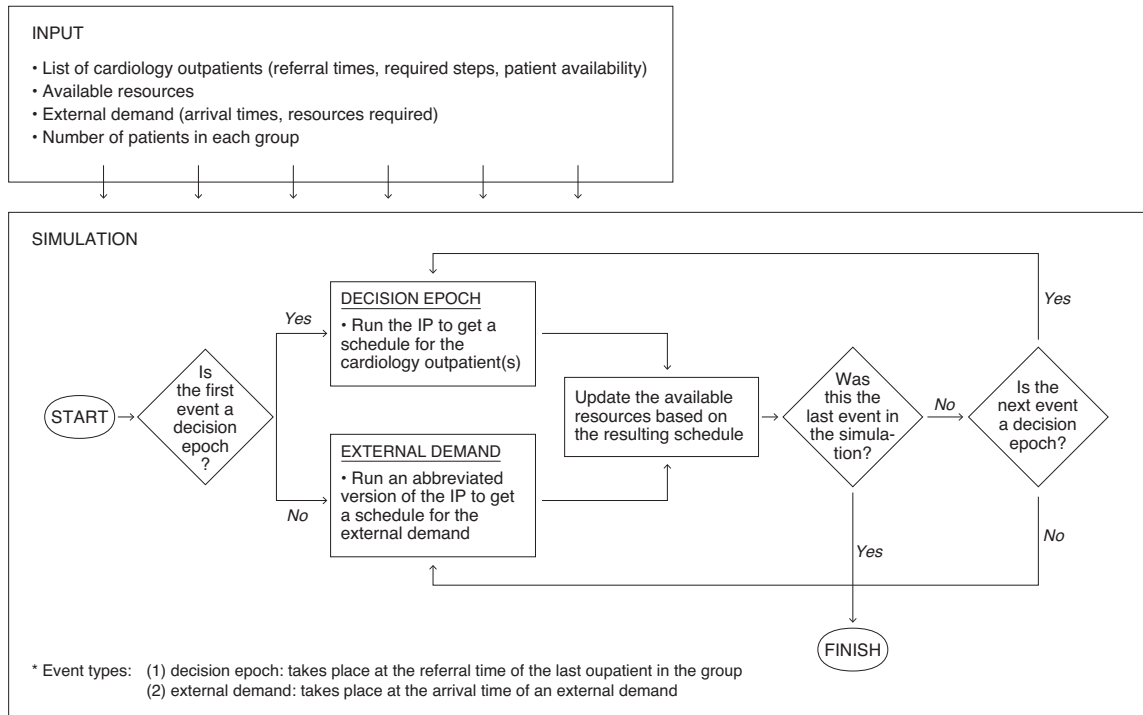


Figure 5.9: Simulation diagram and corresponding input.

5.5.2 Numerical results

This section presents the numerical results. We use five different seeds in the simulations. For each seed, we run the simulation once for each combination of: scenario, $\lambda = \{0, 0.2, \dots, 1\}$, and group size (we consider sizes 1 through 5).

5.5.2.1 Benchmark analysis

Based on the results from the simulations we conduct a benchmark analysis. First, we estimate the number of visits and the time spent waiting in between appointments for different types of patients in the ideal case, where there are no resource restrictions. In total,

Table 5.5: Average visits and time spent waiting when there are no resource restrictions.

Number of steps required:	3	4	5	6	7	8	9	10
Average Visits	2	2.34	3.01	3.56	4.25	5	5	5
Average Idle Time	0.67	2.5	2.67	3.56	3.5	4.5	4.5	6

we have 88 types of patients in our setting. Each type has a unique set of steps they have to complete. For example, TAVR patients can be classified into 16 different types. However, a TAVR patient that has to go through 3 procedures is expected to behave differently from a TAVR patient that has to go through 7 procedures. For that reason we categorize patients based on the number of steps they are required to go through and not the condition they have. Table 5.5 includes the average number of visits and the units of time spent waiting when there are no resource restrictions. We use $\lambda = 0.8$ to estimate the results. We can see that patients with more requirements make more visits to the hospital and spend more time waiting in between appointments, even when there are no resource restrictions.

Next, for each scenario, we estimate the average number of visits and the idle time based on the optimal schedules generated from the IP. We assume that $\lambda = 0.8$ in order to compare the results with the best case scenario presented in Table 5.5. Figure 5.10 includes the average change in the values included in Table 5.5. Note that the values presented in the figure are not integer because they correspond to the average over many patients of each type. We see that in most cases Scenario 1 has the largest increase in the number of visits and the idle time. This was expected, since Scenario 1 has the fewest available resources. The opposite effect is observed for Scenario 4. We also see that as the number of requirements increases the patients are more likely to visit the hospital more times than the

minimum required. The same is true for the time they spend waiting. This was expected, because when there are limited resources it is harder to create convenient schedules for patients that have more requirements. Nevertheless, there is no indication that the proposed IP benefits some patients more than others. On average, the extra visits that patients have to make are less than 1 for all types of patients. The additional waiting time is less than 2 hours on average. Thus, we do not observe a large variation between the different types of patients.

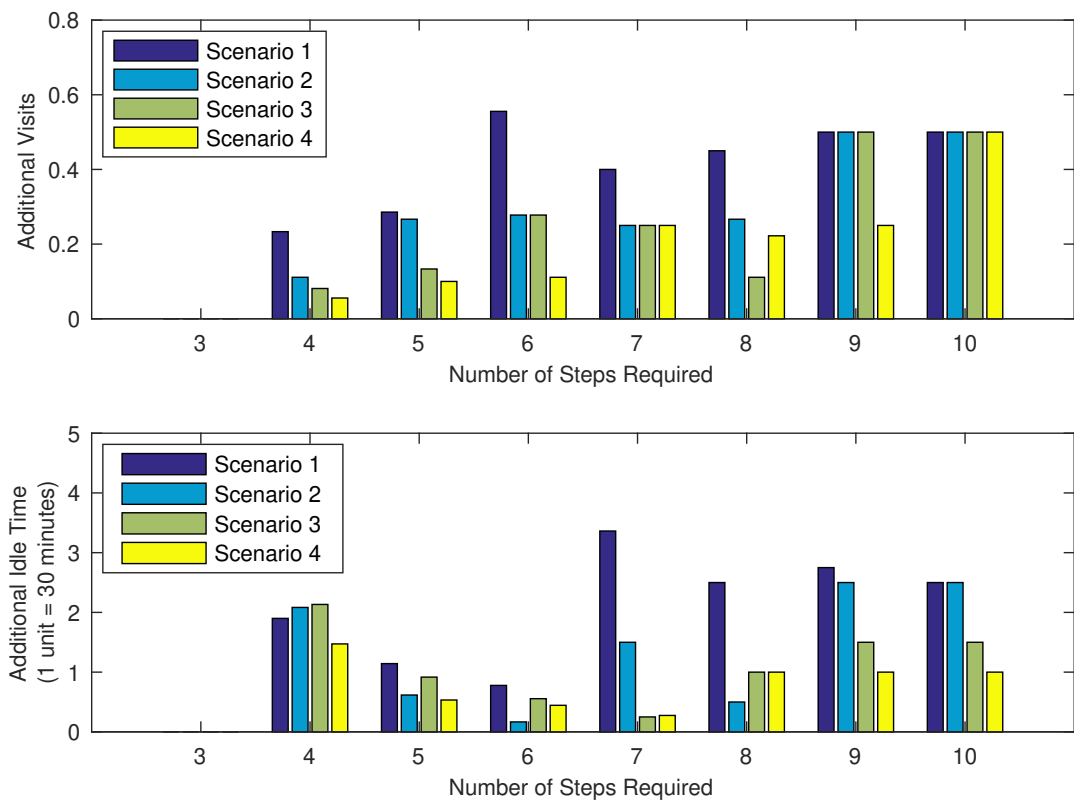


Figure 5.10: Additional visits and additional idle time spent in the hospital on average, compared to the *no resource restrictions* setting.

5.5.2.2 Scheduling in groups

Initially we schedule one patient at a time and then we schedule patients in groups of two to five patients. Patients are grouped together based on the order that they were referred to the hospital. Thus, we are able to compare the total objective value at the end of the month for each case.

Table 5.6 includes the percentage of group scheduling cases where the objective value increased, decreased, or there was no change observed compared to the baseline case of scheduling one patient at a time. It also includes the percentage of cases where an infeasible solution was obtained. Each column is based on the experiments of a particular group size, which includes the 6 λ values taken into account, and the 4 Scenarios, using 5 different seeds. In other words, in each column we have 120 objective values to compare with the case of grouping 1 patient at a time. Each objective value is compared to the corresponding objective value (same λ , Scenario, and seed) in the setting of scheduling one patient at a time. Thus, the percentages of each column show in which portion of the 120 objective values there was an increase, decrease, no change, or we got an infeasible solution. We see that over 60% of the cases performed better when scheduling patients in groups of two instead of one at a time. However, in about 8% of the cases there was an increase in the objective value. The increase in the objective value when scheduling in groups can be the result of missed opportunities, since we have to wait before scheduling a patient. One situation is that the day that a convenient combination of resources was available for the patient has passed when we finally scheduled the patient. Another case is that the external

Table 5.6: Type of change observed in the objective value after scheduling patients in groups.

Outcome	2 per group	3 per group	4 per group	5 per group
No Change	28.33%	29.17%	21.67%	27.5%
Increase	8.33%	15.83%	25%	34.17%
Decrease	63.33%	51.67%	45.83%	35%
Infeasible	0%	3.33%	7.5%	3.33%

demand occupied the resources that would have otherwise been occupied by the patient. We observe that as the number of patients getting scheduled simultaneously increases, there is a smaller percentage of cases where a decrease in the objective value was observed. On the other hand, there were more cases of increase in the objective value. The cause of this is that patients getting scheduled in groups of a larger size, usually have to wait longer to get scheduled and therefore have a higher chance of missing a good opportunity. Thus, while scheduling patients in groups provides us more information about patients, waiting too long can have a negative effect. Finally, in the cases of groups of three patients or more, we can observe that there is a chance of getting an infeasible solution. This means that of all the patients scheduled during the month we are taking into consideration, at least one patient was not able to complete all steps in the required time. For those patients it would take more than 30 days to go through all the required steps.

Table 5.7 presents the results included in Table 5.6 separately for each value of λ . The chance of getting an infeasible solution does not seem to depend on the value of λ , based on the results included in Table 5.7. Nevertheless, we can observe that the chance of increase or decrease in the objective value can differ considerably for different values of λ . For example, for $\lambda = 0$ we can see that for all group sizes in the majority of the cases the

Table 5.7: Type of change observed in the objective value for different values of λ when scheduling in groups.

λ	Outcome	2 per group	3 per group	4 per group	5 per group
0	No Change	100%	95%	90%	95%
	Increase	0%	0%	0%	0%
	Decrease	0%	0%	0%	0%
	Infeasible	0%	5%	10%	5%
0.2	No Change	65%	65%	35%	35%
	Increase	0%	0%	20%	25%
	Decrease	35%	35%	40%	35%
	Infeasible	0%	0%	5%	5%
0.4	No Change	5%	0%	0%	0%
	Increase	10%	20%	50%	50%
	Decrease	85%	80%	45%	45%
	Infeasible	0%	0%	5%	5%
0.6	No Change	0%	0%	0%	0%
	Increase	5%	35%	40%	75%
	Decrease	95%	60%	55%	25%
	Infeasible	0%	5%	5%	0%
0.8	No Change	0%	0%	0%	20%
	Increase	10%	20%	20%	10%
	Decrease	90%	75%	70%	65%
	Infeasible	0%	5%	10%	5%
1	No Change	0%	15%	5%	15%
	Increase	25%	20%	20%	45%
	Decrease	75%	60%	65%	40%
	Infeasible	0%	5%	10%	0%

objective value does not change, excluding the few cases with infeasible solutions. However, for $\lambda = 0.2$ or $\lambda = 0.4$ it seems to make sense to schedule patients in groups of two or three patients, since in most cases the objective value decreases. For $\lambda = 0.8$ the results suggest that we could use even larger groups of patients when scheduling. Nevertheless, as we discussed in Subsection 5.4.4, the hospital will be provided with Pareto optimal so-

lutions to choose from. This requires using multiple values for λ , when scheduling the same group of patients, in order to obtain multiple solutions. Therefore, since we have to decide on the size of the group ahead of time, we should select a size that provides good enough results for all values of λ . Therefore, based on Table 5.7 a good choice seems to be scheduling patients in groups of two or three in order to avoid the increases in the objective value cancel out any potential decreases.

When scheduling one patient at a time, the patients get informed quickly about their appointments. However, when grouping the patients together, the patients have to wait until the arrival of the last patient in the group in order to get scheduled. This means that patients may have to wait up to a few days in order to find out about their appointments. The patients prefer to learn their schedule as early as possible, in order to be able to plan ahead. Figure 5.11 presents an example of the hours that patients arriving over a month had to wait for each group size. As expected, for smaller group sizes the patients are more likely to wait for a shorter period of time. Also it appears that when scheduling patients in groups of two or in groups of three patients, the wait time is approximately the same. On the other hand, for groups with size four and five we can observe a considerable increase in the wait time.

The level of change in the objective value for each Scenario is presented in Table 5.8. The results were estimated after excluding the cases where an infeasible solution was obtained. In particular, all of the infeasible cases occurred under Scenario 1, where there is low availability of resources and high external demand. Infeasible solutions appeared in

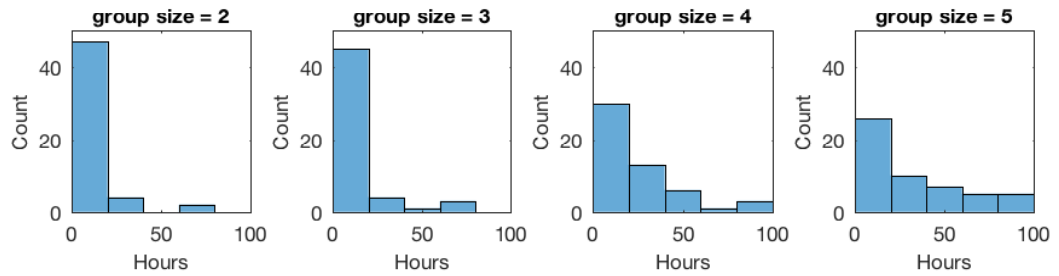


Figure 5.11: Wait time in hours from the time the patients got referred to the time that the appointments were scheduled.

Table 5.8: Amount of change observed in the objective value for each Scenario.

Scenario	Measure	2 per group	3 per group	4 per group	5 per group
1	Mean Change	-0.43	-0.21	-0.1	-0.07
	Mean Pct. Change	-2.33%	-1.57%	-0.93%	-0.93%
2	Mean Change	-0.14	-0.13	-0.03	-0.03
	Mean Pct. Change	-0.44%	-0.45%	-0.05%	-0.15%
3	Mean Change	-0.12	-0.13	-0.04	-0.04
	Mean Pct. Change	-0.73%	-0.74%	-0.32%	1.44%
4	Mean Change	-0.05	-0.12	-0.16	-0.10
	Mean Pct. Change	-0.15%	-0.39%	-0.59%	-0.24%

two out of the five seeds used in the simulation. In each case there was one infeasible group across all the groups getting scheduled. The bold entries in Table 5.8 indicate the largest percentage improvements across all group sizes for each scenario. In Scenario 1 the highest percentage of decrease was observed when scheduling in groups of two patients. Since Scenario 1 also included infeasible solutions, it seems that having groups of two patients is a reasonable choice in a setting with low initial availability and high external demand. In an environment with big competition for resources, it is best not to risk waiting too long to schedule the appointments of the patients. Scenarios 2 and 3 seem to behave in a similar

Table 5.9: Change in the objective value and the wait time to find out about the appointments.

From size	To size	Wait Increase (in hours)	Pct. Change in Objective value			
			Scenario 1	Scenario 2	Scenario 3	Scenario 4
1	2	4.77	-2.33%	-0.44%	-0.73%	-0.15%
2	3	6.19	0.78%	-0.01%	-0.01%	-0.24%
3	4	8.5	0.65%	0.40%	0.42%	-0.20%
4	5	4.45	0.00%	-0.10%	1.77%	0.35%

manner with each other. They both appear to have the highest percentage of decrease when the patients are scheduled in groups of three, but they only perform slightly better compared to scheduling patients in groups of two. Finally, Scenario 4 gives better results when scheduling in groups of four patients. As was expected, when there are many resources available, and not a lot competition caused by the external demand, it is possible to wait for more patients to arrive before scheduling without worrying that the appointments are going to get booked. The results in Table 5.8 show that the scheduling staff could adjust the size of the groups if they have information about the availability of resources and the expected rate of external demand in the next few weeks. Nevertheless, if it is not possible to get an estimate of the state of the system regarding the resources and the demand, the hospital could schedule the patients in groups of two or three based on the results obtained from the simulations. The exact group size should be determined by the hospital depending on the likelihood of getting each Scenario and on their willingness to risk.

Table 5.9 shows the increase observed in the average time it takes for the outpatients to find out about their appointments, and the percentage of change observed in the objective. We consider the different group sizes separately, but in each case the size of the group

increases by 1 patient. We see that the smaller increase in the time it takes to find out the appointments is observed when going from a group size of 1 to a size of 2, and from a group size of 4 to a size of 5. Furthermore, the only transition to a larger group size that leads to a decrease to the objective value in all of the scenarios studied is increasing the group size from 1 patient to 2. Thus, from the above we see that having a group of two patients seems to improve the objective value, while at the same time not considerably increasing the time it takes for outpatients to get informed about their appointments.

While the results show that there are gains in grouping patients when scheduling, the percentages of decrease in the objective value are small. We use an example from the simulations to illustrate. The example is in a Scenario 2 setting, where $\lambda = 0.8$. During the month of the simulation 54 patients were scheduled. When scheduling each patient separately, there were 196 visits to the hospital with a total wait time of 248 time units (124 hours). If we scheduled in groups of two patients, the total objective value in this example decreased by 0.29%. The resulting schedule corresponded to 195 visits to the hospital and a wait of 248 time units. In other words, a decrease of 0.29% corresponded to one less visit to the hospital across all patients. On the other hand, if we scheduled in groups of three patients there was a decrease of 1.45% in the objective value, which corresponded to a schedule of 193 visits and 251 time units of waiting. Thus, compared to scheduling one patient at a time, there were three fewer visits to the hospital but the wait time increased by one and a half hours. We can see from the examples above that the improvements to the final schedule are relatively small, and are expected to affect only a few patients among

Table 5.10: Amount of change observed in the objective value.

Measure	2 per group	3 per group	4 per group	5 per group
Mean Percentage Change	-1.11%	-4.01%	-1.85%	-1.37%

those getting scheduled.

5.5.2.3 Scheduling in a larger department

Based on the results presented in Subsection 5.5.2.2, we see that only a small number of patients will get an improved schedule when scheduling in groups in our outpatient cardiology setting. In this section, we investigate the effect of scheduling in groups in a department treating a larger number of outpatients each month. In order to study this, we increased the average number of outpatients referred to the cardiology department by 50%. All other input parameters remain the same based on the description of Subsection 5.5.1. This allows us to investigate the effect of scheduling in groups in a larger department.

We ran experiments for $\lambda = 0.8$. The change observed in the objective value compared to scheduling one patient at a time is included in Table 5.10. The results show that the largest decrease is observed when scheduling in groups of 3 patients. Furthermore, the patients had to wait for a shorter time period in order to find out about their scheduled appointments. For example, the average time was around 10 hours in the original setting (smaller department) when scheduling in groups of 3 patients. In this setting, where we consider a larger department, the average time decreased to about 6 hours. This was expected, because patients arrive more often, and therefore the groups are completed in higher

rates.

Let us consider a specific example in this setting. In total, 88 cardiology outpatients were referred to the hospital during the course of one month. In this case, scheduling one patient at a time leads to 316 total visits and 165 hours of waiting in the hospital between appointments. Scheduling in groups of three patients at a time leads to 303 visits to the hospital and 164 hours of waiting in the hospital. In other words, there were 13 fewer visits in the hospital in this case. Thus, the experiments show us that in larger departments there are greater gains obtained when scheduling in groups, since more patients are affected by the improved schedules. Furthermore, in a larger department the patients do not have to wait as long on average to find out about their schedule.

5.6 Implementation and managerial insights

This study resulted from discussions we had with the procedural director of the heart and vascular center, who identified the outpatient procedures as an area of interest. However, the proposed IP was not used in the hospital. Nevertheless, in this work we provide the decision tool and an initial analysis of the expected outcomes. This information can be used in the future if the hospital decides to go forward with this scheduling approach. In this section we discuss the implementation requirements for using such a tool and provide some managerial insights.

The implementation requirements refer to a) the deployment environment, and b) information exchange.

With regards to a), the hospital must have access to a solver (e.g. Gurobi, CPLEX, etc.) coupled with a suitable platform to allow the scheduling staff to provide information about outpatient availability, required steps, and resource availability. With regards to b), information sharing between different members of scheduling staff will facilitate scheduling patients in groups by gradually inputting information about patients, until the group is complete. In addition, shared information between scheduling and lab staff facilitates the procedure of determining the availability of resources in advance of each appointment and scheduling accordingly while at the same time considering patient convenience.

The proposed IP can help generate schedules that are convenient for the patients. Especially as the number of procedures that the patient has to go through increases it becomes very complicated to schedule the appointments manually. By providing multiple schedules to choose from, the scheduling staff will be able to choose the one that best fits the needs of each specific patient. Finally, we see that grouping patients when scheduling provides better schedules. The improvements only affect a small number of patients in the case of our outpatient cardiology setting. However, in the case of a slightly larger department, which treats more outpatients each month, the results showed that an increased number of outpatients gets positively affected by scheduling in groups. Furthermore, in a larger department the outpatients would not have to wait as long to find out about their appointments. Thus, having groups within the same department collaborate when scheduling can lead to improvements that benefit the outpatients. Additionally, scheduling in groups means that the staff responsible for scheduling the appointments will not have to contact the various re-

sources as often to find out about the availability, since there are fewer decision epochs in each month. Considering that this will also be done collaboratively with other members of the scheduling staff means that this option will save them time during the course of the month.

5.7 Conclusions

In this chapter we discussed the problem of multi- appointment scheduling in outpatient cardiology. We generated the procedure diagrams including the steps that the patients have to go through in order to be able to complete the procedure they were referred to the hospital to have. Each step was linked to the corresponding resources that need to be available for the patient to be able to go through the step. We proposed an IP formulation, in order to support the staff in making appointment scheduling decisions, which are currently done manually. We identified the objective of the problem as minimizing the combination of the number of visits that the patients make to the hospital and the time the patients spend in the hospital in-between appointments. The formulation allows for patients to be scheduled either one at a time or in groups. The scheduling staff will be provided with Pareto optimal solutions to choose from when deciding on which appointment to book for the patients. We discussed improvements to the initial formulation and added valid inequalities to the IP in order to decrease the time it takes for the solver to find an optimal solution and prove that it is optimal. Through the suggested improvements the running time of the IP decreased significantly. Finally, we investigated the advantages of scheduling patients in groups. We

considered various hospital settings based on the initial availability of resources and the rate of external demand. Since many of the resources used by the cardiology outpatients are shared across many departments in the hospital, it is crucial to take into account the external demand generated by the patients in those departments. The results varied for different levels of initial resources and external demand. In particular, when more resources were available there were better results obtained for larger sizes of groups. On the other hand, when fewer resources were available there was a risk of obtaining infeasible solutions when scheduling in large group sizes. Also, there was a larger decrease in the number of visits and the wait time for smaller group sizes. Nevertheless, the improvements observed across the various settings were on the level of few visits or time units. Thus, while on average there are improvements in scheduling in groups, those improvements were not major and expected to affect only a small portion of the patients getting scheduled in our cardiology outpatient setting. Additional experiments showed that in departments that treat an increased number of outpatients, scheduling in groups positively affects a larger portion of patients.

5.7.1 Limitations and future research

One limitation of this work is that we do not have access to data from the hospital. For that reason we were not able to generate a simulation model that can be validated to match the current system. This did not allow us to make comparisons between the schedules that the scheduling staff currently generates and the schedules resulting from the proposed

IP. Furthermore, while we were able to conduct some initial analysis about scheduling patients in groups, this could be examined further. Future directions of this research could investigate ways of getting a good estimate of the state of the system. This refers to the levels of available resources and the rate of external demand. Based on historical data, it could be possible to make predictions about how the availability of resources will change within the scheduling horizon. Thus, the scheduling staff would be able to decide on the size of the groups and adjust them if necessary.

The second limitation of this work is that we assume a number of parameters to be deterministic. We assume that each appointment that the outpatient goes through will start on time, and will not take longer than the duration that it was booked for. However, in reality this might not be the case. Having considerable delays in the system may not allow the patient to go through all necessary steps booked for a specific day. Therefore, future research could investigate how to schedule the outpatients after taking into account this variability in the system. A robust schedule to uncertainty can be achieved by simulating multiple scenarios of the duration of the individual procedures and formulating a stochastic programming model. In this case, the objective of the problem is to minimize not a deterministic value of the number of visits or idle time, rather than a stochastic measure thereof, such as their average or worst case values according to the underlying statistical distribution.

Chapter 6: Conclusions

The U.S. is leading in healthcare expenditures worldwide, both based on per capita expenses [73], and based on the percentage of the country's GDP corresponding to healthcare related expenses [72]. However, increased expenditures do not seem to translate to a healthier population in the U.S. [39]. Prevention, which includes actions that prevent diseases from occurring, detect diseases at an early stage, and manage diseases that have been diagnosed, plays a crucial role in improving the health of people. In this dissertation, we study four problems that facilitate disease prevention in the U.S., with two problems at the public health level followed by two at the healthcare provider level. A summary of each study, including contributions and future directions, is presented below.

In Chapter 2, we use U.S. state level data to identify factors that impact MMR vaccination rates. The MMR is the most commonly used vaccine for measles prevention. With some parents choosing not to vaccinate their children, there have been a number of measles outbreaks in the U.S. in recent years. In the U.S., students are required to get vaccinated in order to be able to attend school. However, a number of exemptions are allowed. Medical exemptions are allowed in all 50 states and the District of Columbia. Nevertheless, some states also allow for religious as well as personal belief exemptions. Our data cover a period

of seven years, during which, the measles outbreak in Disneyland took place. This specific outbreak was covered extensively in the news at the time. In this study, we investigate the impact of state level vaccination exemption policy, and of the highly publicized Disneyland measles outbreak on MMR vaccination rates of young children (19-35 months old).

We try a number of approaches to select the socioeconomic controls for our linear regression model, in order to demonstrate the influence that different socioeconomic factors can have on the outcomes of interest (i.e., the impact of exemption policy, and the Disneyland outbreak). First, we use an *econometric* approach, where the socioeconomic controls are selected based on past research findings. Second, as sensitivity analysis on the coefficients of interest, we use a number of approaches including variable selection methods, principal component analysis, and indices summarizing socioeconomic controls of each dimension (i.e., education, economy, and community). The results show a consensus across all modelling approaches that allowing personal belief exemptions in a state is linked to lower vaccination rates. However, depending on the modelling approach followed, the impact ranges from -0.74 to -0.99 percentage points. On the other hand, the results on the impact of the Disneyland outbreak on the vaccination rates during the subsequent year are not conclusive, since different modelling approaches yield different results.

Previous studies have linked personal belief exemptions to lower vaccination rates in children attending kindergarten [122, 151]. Through this study, we show that the impact of personal belief exemption is similar for children younger than 3 years old, who do not necessarily attend school. This underlines the significance of vaccination exemption poli-

cies, since young children have a higher risk of serious complications from measles [175]. Furthermore, to the best of our knowledge, this is the first study that looks into the impact of the Disneyland outbreak on vaccination rates at a national level. The fact that there is no clear impact, shows that even though most parents found out about the dangers of the disease during that time, this did not necessarily change their decision about vaccination. Finally, through this study we highlight the importance of carefully selecting socioeconomic controls, and reporting the resulting models in detail, since including a single control can change the outcome considerably. Future research could focus on identifying additional factors that impact vaccination rates, including, for example, vaccination campaigns, and the level of anti-vaccination activity in an area. Our models only explain up to 31% of the variation in state level vaccination rates, which shows that there are other factors that we could not control for. Furthermore, other sources of data could provide better estimates of the actual MMR vaccination rates in an area. In our study, MMR vaccination rates are based on survey data. However, relatively large fluctuations in the same state from one year to the next indicate that the rates may not be as accurate. A different approach for estimating vaccination rates of various geographical areas could be based on insurance claims data.

In Chapter 3, we study the cost behavior of various types of chronic conditions. Chronic conditions are common in the U.S., with about half of the adult population having at least one chronic condition, and one in four adults having multiple (two or more) chronic conditions [171]. Annual expenditures as well as different cost components (outpatient, inpatient

and other services) are known to be higher for those with chronic diseases [10, 30, 51, 153]. Furthermore, individuals with chronic conditions make more frequent outpatient [139], and emergency department visits [133]. The cost of each type of condition can be used as an indication of how difficult it is to treat, and by extension its severity. With many people suffering from multiple chronic conditions, it is crucial to understand how each type of condition interacts with other chronic conditions that are present in the same individual. Thus, in this study, we estimate the additive cost of chronic diseases and study their cost patterns.

We use gamma regression with a log link to model the relationship between healthcare costs and the chronic conditions that are present in the same person. In particular, we use a cost hierarchy, where the cost of each condition is modeled as a function of the number of other more expensive chronic conditions that the individual has. The analysis is based on insurance claims data, from which we obtain annual healthcare costs and diagnoses of individuals. Based on the results of the regression, we estimate the cost contribution of each type of chronic condition dependent on the number of more expensive conditions that are present. We characterize the resulting cost patterns based on the average value (and corresponding variance), and the slope of the cost contributions. We use clustering techniques to group together conditions that behave in a similar manner. The results show that for the majority of the chronic conditions, their cost contribution increases with the number of other more expensive conditions that are present. This illustrates that these conditions impose an additional burden to the treatment of other conditions when they are

present in a patient. Examples in this category include obesity, asthma, congestive heart failure, hypertension, and bipolar disorder. On the other hand, for some chronic conditions, the cost contribution does not increase or sometimes decreases as the number of more expensive conditions that the patient has increases. This means that those conditions either do not add more complexity to the treatment of other conditions, or the individual does not get the necessary treatment for other conditions when they are present. Examples include back problems, allergies, Parkinson's disease, dementia, and malignant neoplasm.

The majority of previous studies analyzing the cost of combinations of chronic conditions has focused on a small number of conditions [45, 104]. In [38], the authors expand their analysis to 10 conditions, but limit the number of possible combinations to two at a time. Through our proposed methodology, we increase the number of chronic conditions taken into account to 69, and manage to study the cost contribution of conditions when an increased number of other conditions are present. This allows us to build a comprehensive picture of the chronic cost burden. The proposed methodology and the resulting estimates of chronic cost burden can be used for policy and program designs, since they can help estimate the effect of interventions on the healthcare cost of patients with specific chronic conditions, and make better healthcare cost predictions for people with chronic conditions. Future research could focus more on the cost contribution of chronic conditions in individuals with multiple chronic conditions, after taking into account socioeconomic factors linked to the individual. Those could include factors like gender, income, education level, and others. It would be interesting to see to what extent the cost behavior of each condition

changes based on these socioeconomic factors.

In Chapter 4, we study the use of conversational agents in patients with heart failure. The management of heart failure relies a lot on self-care, which includes taking medications, controlling salt and fluid intake, and checking for symptoms such as weight increase or swelling in ankles. A number of telehealth technologies have been developed in the past, in order to help patients with heart failure to manage their condition [7, 48, 81, 87, 97]. Telehealth technologies provide frequent updates to the patients' physicians, which allows them to intervene when necessary. Some factors that have been found to negatively influence telehealth adoption include difficulties with using the technology, or not remembering to use it every day [54]. Conversational agents that use speech, can make the use of the telehealth technology easier, since they allow patients to answer questions about their symptoms using their voice. In this study, we compare two types of conversational agent technologies, and investigate which patient's characteristics are important factors in determining the patient engagement.

Over a period of 90 days, thirty patients with heart failure used the conversational agent that was based on Amazon's Alexa technology, and thirty different patients used the conversational agent that utilized an avatar to ask the questions, thus, combining sound and image. We obtained demographic information about the patients through a survey, and from electronic health records. We use multiple linear regression, in order to model the relationship between the number of times that a patient used the conversational agent during the 90 days, and the patient's characteristics. The results show that patients participating

in the Alexa survey completed the questionnaire more often than in the Avatar study. This could be explained by the fact that the Alexa technology allows patients to set-up daily reminders. Furthermore, older patients, and non-black patients engaged with the conversational agent technology more often, while patients that are prescribed an increased number of medications to manage heart failure were linked to lower levels of engagement. On the other hand, confidence in using technology did not have a statistically significant effect on patient engagement.

In this work, we compare two types of conversational agent technologies, that follow identical questionnaire scripts, and are used by two similar groups of heart failure patients. The difference in patient engagement highlights that even small changes in the design or capabilities of the technology can considerably influence the adoption levels. Furthermore, to the best of our knowledge, this is the first study that examines factors that influence conversational agent technology uptake in patients with heart failure. Future research could investigate to what extent engagement and compliance influence health results, through the use of electronic health data. This would provide information on hospitalizations and health complications, which would provide an insight on the value obtained from the use of conversational agent technology.

In Chapter 5, we study the problem of appointment scheduling for patients who are referred to the cardiology department of a large medical center in order to go through an elective procedure. Those patients have to go through a number of diagnostic tests and/or treatments before they are ready to complete the elective procedure. Because those patients

are not admitted to the hospital until after they complete the elective procedure, they have to visit the hospital every time they have an appointment. This can be complicated for the patients, since they could live a long distance from the hospital and they usually depend on someone else to drive them to the hospital. In an effort to make the visits to the hospital as effortless as possible for the patient, we develop an IP to help the scheduling staff in deciding on the day and time of each patient's appointments.

Our objective is to book appointments that minimize the number of visits that the patients have to make to the hospital as well as the time that the patients have to spend in the hospital waiting in between appointments. The goal is to provide the scheduling staff with all Pareto optimal solutions to choose from. We develop an IP formulation that takes into account the available resources and the availability of the patients on each day, and provides the optimal solution. At the same time, it is ensured the patients will be able to complete all of the required steps on time. In addition to the IP formulation, we propose a number of improvements to the formulation in order to obtain an optimal solution faster. The improvements include formulation changes based on information obtained through preprocessing as well as inclusion of valid inequalities to the formulation. Through these improvements, we manage to decrease the running times considerably. Finally, we investigate the value of scheduling patients in groups under various scenarios, which vary based on the availability of resources and the demand. We conclude that in scenarios where more resources are available there are better results obtained for larger sizes of groups. On the other hand, when fewer resources are available there was a risk of obtaining infeasible solutions when

scheduling in large group sizes. However, the improvements only affect a few patients. The results show improvements in the total objective value over a period of one month, ranging from 0.45% to 2.33% on average, depending on the scenario taken into account.

To the best of our knowledge, this is the first study that looks into multi-appointment scheduling in outpatient cardiology. Through this work, we provide the procedure diagrams, parameters, and constraints that need to be taken into account in such a problem and develop an IP formulation. Furthermore, we propose formulation improvements, which could potentially be applied to other scheduling problems with a similar formulation approach. Finally, we examine whether outpatients should be scheduled in groups, which looks at the problem of different departments in the hospital competing for the same resources. In future research, if hospital data become available, it would be possible to estimate the gains from moving from manually scheduling appointments, to using the proposed optimization model. Furthermore, it could be possible get estimates of the state of the system (i.e., availability of resources, and levels of external demand), and based on historical data, make predictions about how the availability of resources will change within the horizon. Thus, the scheduling staff would be able to decide on the size of the groups and adjust them accordingly.

The studies included in this dissertation show the range of problems associated with disease prevention in the U.S. Those span from understanding the impact of health policies, and identifying areas that require prevention interventions at the public health level, to helping patients manage their health, and making treatments as effortless as possible at the

provider level. Data analytics, and mathematical modelling techniques can play a crucial role in better understanding the underlying issues, and providing efficient solutions.

Appendix A: Summary statistics for variables used in the MMR study

Table A.1: Summary statistics for all non-binary variables in dataset.

Variable	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
MMR rates	83.40	89.80	91.70	91.59	93.50	98.60
American Indian/Alaska Native	0.00	0.20	0.40	1.46	0.90	14.20
Asian	0.50	1.40	2.50	3.92	4.20	38.80
Black	0.00	3.00	7.00	10.84	15.10	50.20
Hispanic	1.00	4.60	9.00	11.22	13.20	48.20
Native Hawaiian/Pacific Islander	0.00	0.00	0.00	0.27	0.10	9.70
White	21.70	58.10	73.10	69.55	81.50	94.50
Multiracial	0.90	1.80	2.10	2.69	2.50	21.20
Economy Dimension	34.21	48.27	53.20	53.19	58.30	69.54
Jobs	2.200	4.300	5.500	5.848	7.200	13.700
Wages	35225	43966	48485	50334	55847	70538
Poverty	8.20	12.10	14.60	14.76	17.20	24.20
Income Inequality	3.71	4.32	4.63	4.70	4.96	7.40
Access To Banking Services	2.400	3.810	4.370	4.449	4.800	8.110
Affordable Housing	51.20	62.40	67.10	66.39	70.34	79.55
Education Dimension	23.79	45.32	50.70	50.23	54.93	66.50
Preschool Enrollment	29.30	41.40	45.80	46.53	50.10	86.36
High School Graduation	56.00	75.50	80.40	79.65	85.30	93.00
Postsecondary Education	23.29	33.30	36.95	37.05	40.80	59.70
Health Insurance Coverage	3.457	11.004	13.829	14.134	17.072	25.483
Access To Medical Care	157.4	216.2	251.9	270.6	285.1	1025.4
Community Dimension	37.61	48.85	53.84	54.00	59.24	76.93
Volunteering	16.68	23.93	27.13	27.86	31.70	45.58
Youth Disconnection	7.20	11.48	13.43	13.46	15.60	20.74
Violent Crime	99.3	255.0	336.3	376.1	454.8	1348.9
Access To Healthy Food	1.200	1.740	1.990	2.104	2.270	5.600

Appendix B: Extended diagnosis codes used in the chronic conditions study

In this appendix, we describe the process of including additional ICD-9 diagnosis codes to the existing hipxchange algorithm.

We selected the first 3 digits of the ICD-9 (International classification of diseases, Ninth revision) diagnosis codes included in the hipxchange list [94]. This resulted to 396 unique numbers. We went through each of the 396 codes in [74] and added necessary codes that were not included in the initial list.

In particular, a shorter code was added only if all extensions of that code were included in the hipxchange list and classified as the same condition. On the other hand, a longer code was included only if its first set of digits (non-billable code) was included in the hipxchange list. Note that code 3020 (Ego-dystonic sexual orientation) was changed from sleep disorders to sexual and gender identity disorders, which is a subsection of the personality disorder.

In total 640 additional codes were added to the initial hipxchange list. In particular, the codes added for each condition are included in Table B.1.

Table B.1: Additional ICD-9 codes.

Chronic Condition Category	Codes
Allergy, ENT and other upper respiratory disorders	4783, 477, 476, 474, 4741, 473, 472, 3890, 3860, 3811, 3812
Anemia and other non-cancer heme disorders	2898, 28741, 28749, 286, 2852, 284, 283
Aneurysm	4477, 4432, 441, 442, 4428
Anxiety disorders	3075, 3000, 3002, 308
Asthma, COPD, other chronic lung disease	516, 5166, 495, 493, 4930, 4931, 4932, 4938, 4939, 492, 491
Coronary atherosclerosis	413, 411, 41402, 41403, 41404, 41405, 41407
Back problems	722, 7221, 7223, 7225, 7227, 7228, 7229, 721, 7214, 7219, 7208
Behavior disorders	318, 314, 315, 3150, 3153, 3140, 312, 3120, 3121, 3122, 3123, 3072, 299, 2990, 2991, 2998, 2999
Bipolar disorder	2960, 2961, 2964, 2965, 2966, 2968, 2969
Cerebrovascular Disease	3466, 4381, 4382, 4383, 4384, 4385, 4388, 435, 434, 433, 432
Congestive heart failure	428, 4282, 4283, 4284
Other central and peripheral nervous system disorders	3382, 337, 3372, 336, 335, 3351, 3352, 334, 330, 046, 0467, 952, 9520, 9521, 3597, 3583, 356, 355, 354, 353, 348, 3470, 3471
Congenital Heart Disease	747, 7471, 7472, 7474, 7478, 7468, 745, 7451, 7456
Non-cardiac congenital disorder	754, 759, 758, 757, 7573, 756, 7561, 7565, 7568, 755, 7550, 7551, 7552, 7553, 7555, 7556, 7543, 7544, 7545, 7546, 7547, 7548, 753, 752, 7521, 7524, 751, 7516, 750, 7501, 7502, 749, 7490, 7491, 7492, 748, 7486, 744, 7440, 7442, 7444, 7448, 743, 7430, 7431, 7432, 7433, 7434, 7435, 7436, 740, 742, 7425, 741, 7410, 7419
Cystic fibrosis	2770
Organic brain problem (dementia)	290, 2901, 2902, 2904, 294, 2942
Dental and mouth disorders	5231, 5254, 5234
Depression and depressive disorders	2962, 2963
Diabetes mellitus	249, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 250, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509

continued ...

... Table B.1 continued

Chronic Condition Category	Codes
Conduction disorder or cardiac dysrhythmia	426, 427, 4273, 4274, 4276, 4278, 4261, 4265, 4268
Epilepsy	345
Esophageal disorder and GI ulcers	4562, 5357, 5344, 5346, 5345, 5347, 5349, 5334, 5336, 5335, 5337, 5339, 5326, 5325, 5327, 5329, 5316, 5315, 5317, 5319
Degenerative eye problem (glaucoma/eye)	3792, 3793, 3794, 3795, 377, 3770, 3771, 3772, 3773, 3774, 3775, 3776, 3777, 3761, 3762, 3763, 3764, 3765, 3768, 3721, 3705, 3706, 369, 3690, 3691, 3692, 3696, 3697, 365, 366, 3660, 3661, 3662, 3663, 3664, 3665, 3650, 3651, 3652, 3653, 3654, 3655, 3656, 3657, 3658, 362, 363, 3630, 3631, 3632, 3633, 3634, 3635, 3641, 3636, 3637, 3620, 3621, 3622, 3623, 3624, 3625, 3626, 3627, 3628, 3611, 360, 3600, 3601, 3602, 3603, 3604, 3605, 3606, 3608, 076
Female infertility and GU anatomic disorders (e.g. prolapse, endometriosis)	6491, 6480, 6482, 6420, 6421, 6422, 6427, 6429, 6292, 626, 6257, 619, 618, 617
Diverticulosis, diverticulitis, enterocolitis, intestinal malabsorption	562, 5620, 5621, 5584, 555
Gout or other crystal arthropathy	712, 7121, 7122, 7123, 7128, 7129, 274, 2741, 2748
Chronic Hepatitis	5714
Hypertension	405, 4050, 4051, 4059, 404, 403, 402, 4020, 4021, 4029, 401
Immunity disorder	288, 2885, 2886, 2790
Kidney and Vesicoureteral Disorders (excl. renal failure)	596, 59681, 59682, 59683, 59689, 5900, 588, 583, 5838, 582, 5828, 581, 5818
Male GU excluding BPH	607, 6078

continued ...

... Table B.1 continued

Chronic Condition Category	Codes
Malignant neoplasm	141, 143, 145, 146, 147, 148, 149, 150, 154, 159, 151, 153, 160, 158, 161, 162, 157, 163, 164, 144, 170, 171, 174, 172, 175, 155, 195, 198, 200, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 201, 2010, 2011, 2012, 2014, 2015, 2016, 2017, 202, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2029, 2028, 2019, 2008, 208, 2090, 2091, 2092, 2093, 230, 231, 233, 234, 2333, 2097, 207, 206, 205, 204, 203, 199, 1988, 197, 196, 194, 192, 191, 176, 190, 187, 188, 189, 186, 180, 183, 184, 182, 165, 156, 152, 142, 140
Malnutrition and F/E cond (not obesity/overweight)-includes disorders of metabolism	275, 273, 272, 271, 270, 268, 263
Menopause and perimenopause	627
Acute myocardial infarction	410
Migraines	3463, 3464, 3465, 3467
Misc mental health	3078
Osteoarthritis	7193, 7160, 7162, 7163, 7164, 7165, 7166, 7168, 7169, 713, 715, 7150, 7151, 7152, 7153, 7158, 7159, 7181, 7185, 7187
Other endocrine	628, 258, 257, 256, 255, 253, 252, 251, 242, 2420, 2421, 2422, 2423, 2424, 2428, 2429, 244, 245, 241, 240
Other MSK including osteoporosis	7161, 717, 7174, 7178, 7180, 7184, 7371, 7372, 7373, 7374, 7330, 7334, 732, 730, 7300, 7301, 7302, 7303, 7307, 7308, 7309, 897, 887
Paralysis	343, 342, 3428
Personality disorder	301, 3011, 3012, 3015, 3018, 302, 3025, 3027, 3028
Pulmonary heart disease	416
Rheumatoid arthritis	714, 7143, 7148
Schizophrenia and Psychotic Disorders	295, 2950, 2951, 2952, 2953, 2954, 2955, 2956, 2957, 2958, 2959, 297
Sickle cell anemia	2826
Chronic skin ulcer	696, 707, 7072, 694, 6946
Sleep disorders	3274
STI	0932, 0541

continued ...

... Table B.1 continued

Chronic Condition Category	Codes
Cardiomyopathy and Structural Heart Disease	4297, 4298, 4141
Substance-use Disorders	291, 305, 3050, 3052, 3053, 3054, 3055, 3056, 3057, 3058, 3059, 303, 3030, 3039, 304, 3040, 3041, 3042, 3043, 3044, 3045, 3046, 3047, 3048, 6483, 3049
Tuberculosis	137
Thrombosis and Embolism	445, 4450, 4458, 444, 4442, 4535, 4537, 4448
Heart valve disorder	397, 396, 395, 394, 424, 4249
Non-thrombotic, non-atherosclerotic vascular disease	4438, 4593, 446, 457

Appendix C: Extended output from the chronic conditions study

In this appendix, we include the complete version of Table 3.4 appearing in the main text. The information is presented in Table C.1, which includes the average costs (and standard deviations) for all 69 conditions taken into account in the study. The costs are estimated based on individuals with each specific chronic condition but no other chronic condition (columns 3 and 4), and all individuals that have been diagnosed with each condition (columns 5 and 6). Furthermore, in this appendix we include Table C.2, which includes the complete regression output for the model used in the main text. The table also includes additional information about the number of observations with each specific variable equal to 1, and the average cost of patients with this variable equal to 1.

Table C.1: Ordering of conditions and corresponding costs.

Chronic Condition	Order	Average Cost (and Std Dev) members with only this cond.		Average Cost (and Std Dev) all members with this cond.	
allergy	55	2,068	(2,914)	7,962	(12,341)
anemia	16	4,112	(7,654)	25,353	(34,793)
aneurysm	62	1,948	(2,093)	15,961	(21,645)
anxiety	53	2,157	(2,897)	8,921	(14,358)
asthma	42	2,742	(3,930)	12,526	(18,963)
athero	40	2,763	(4,674)	15,081	(21,050)
back	25	3,572	(5,998)	13,379	(17,333)
behavio	50	2,240	(2,803)	5,589	(9,435)
benign	7	8,473	(16,587)	12,453	(14,776)

continued ...

... Table C.1 continued

Chronic Condition	Order	Average Cost (and Std Dev) members with only this cond.		Average Cost (and Std Dev) all members with this cond.	
bipol	32	3,206	(4,180)	10,104	(13,316)
bph	65	1,892	(2,891)	10,001	(15,045)
breast	48	2,333	(2,541)	6,451	(9,410)
cerebro	17	3,978	(6,321)	17,505	(22,390)
chf	60	1,958	(2,544)	25,987	(29,871)
chroninf	15	4,309	(13,239)	11,264	(15,657)
cnspps	28	3,508	(4,908)	16,404	(21,894)
concard	52	2,204	(3,673)	14,463	(21,893)
congen	36	2,991	(4,392)	12,795	(17,821)
cystic	1	18,245	(15,919)	32,056	(24,196)
dem	49	2,279	(2,803)	15,186	(20,356)
dental	69	706	(479)	14,033	(16,699)
depress	46	2,420	(3,056)	9,570	(15,115)
dm	33	3,180	(4,426)	11,252	(17,601)
dysrhy	30	3,401	(6,327)	17,082	(22,790)
epilepsy	29	3,446	(4,766)	12,513	(19,351)
esoph	43	2,738	(3,491)	10,660	(15,808)
eye	57	2,011	(3,316)	9,602	(14,456)
femalegu	26	3,554	(4,225)	7,154	(9,750)
gi	13	5,441	(8,697)	12,781	(17,469)
gout	67	1,387	(2,116)	13,641	(21,916)
hep	5	12,423	(29,036)	21,076	(36,295)
hiv	2	17,094	(10,167)	24,392	(17,381)
htn	63	1,925	(3,774)	9,070	(14,753)
hyprlip	66	1,669	(2,605)	8,351	(13,736)
immun	38	2,853	(4,019)	22,767	(32,132)
kidney	24	3,606	(4,312)	18,171	(25,258)
liver	27	3,530	(4,648)	15,559	(22,019)
lupus	44	2,553	(3,264)	11,831	(18,461)
malegu	54	2,079	(3,065)	8,548	(12,778)
malig	11	6,950	(13,331)	14,843	(20,473)
malnutr	56	2,044	(3,660)	9,867	(17,186)
menop	61	1,952	(2,132)	7,379	(10,708)
mi	6	12,136	(16,907)	30,792	(33,213)
migrain	22	3,691	(4,065)	8,399	(11,608)
miscmh	59	1,978	(3,820)	11,486	(15,093)
ms	4	15,599	(15,205)	23,994	(21,190)
obesity	47	2,352	(3,891)	10,128	(16,202)

continued ...

... Table C.1 continued

Chronic Condition	Order	Average Cost (and Std Dev) members with only this cond.		Average Cost (and Std Dev) all members with this cond.	
osteo	23	3,626	(5,881)	12,327	(16,707)
othendo	39	2,822	(5,139)	9,320	(15,281)
othmsk	21	3,716	(4,727)	11,693	(17,301)
panc	9	7,323	(6,346)	19,722	(21,869)
para	20	3,741	(6,344)	20,970	(32,339)
parkin	14	4,453	(7,644)	15,202	(17,848)
periph	64	1,900	(2,646)	20,442	(26,943)
persnal	45	2,423	(3,708)	9,360	(14,110)
pulmhrt	34	3,086	(5,276)	28,448	(33,038)
renal	8	7,481	(17,098)	23,470	(31,909)
rheum	10	7,309	(9,896)	13,766	(17,321)
schiz	19	3,835	(5,730)	16,199	(21,398)
sickle	12	6,780	(7,344)	19,049	(21,786)
skin	18	3,923	(6,950)	14,029	(22,270)
sleep	51	2,237	(2,661)	11,644	(17,101)
sti	41	2,757	(3,330)	10,747	(21,627)
strctht	58	2,007	(4,110)	21,593	(27,815)
subst	35	2,994	(4,330)	8,951	(14,561)
tb	68	1,058	(0)	1,058	(0)
thrombemb	3	16,177	(24,393)	27,853	(34,436)
valve	37	2,982	(6,456)	15,361	(22,286)
vasc	31	3,316	(4,732)	17,812	(24,675)

Table C.2: Regression output, sample sizes, and average costs for each condition order.

Variable	Coefficient	Std Error	p-value	sample size	average cost
<i>(Intercept)</i>	7.7921	0.0511	0.000	(-)	(-)
<i>allergy</i> ₁	-0.1012	0.0528	0.055	9,837	2,326
<i>allergy</i> ₂	0.2488	0.0138	0.000	11,115	4,092
<i>allergy</i> ₃	0.0448	0.0085	0.000	29,788	11,268
<i>anemia</i> ₁	0.4910	0.0548	0.000	4,400	11,869
<i>anemia</i> ₂	0.8514	0.0250	0.000	3,898	32,959
<i>anemia</i> ₃	0.6357	0.0446	0.000	1,208	44,318
<i>anemia</i> ₄	0.4193	0.1119	0.000	203	58,741
<i>aneurysm</i> ₁	0.2142	0.1356	0.114	109	3,569
<i>aneurysm</i> ₂	0.3586	0.0795	0.000	276	4,644
<i>aneurysm</i> ₃	0.1863	0.0631	0.003	440	6,953
<i>aneurysm</i> ₄	0.2294	0.0561	0.000	556	9,350
<i>aneurysm</i> ₅	0.1172	0.0264	0.000	2,612	20,598

continued ...

... Table C.2 continued

Variable	Coefficient	Std Error	p-value	sample size	average cost
<i>anxiety</i> ₁	-0.0853	0.0532	0.109	7,672	2,376
<i>anxiety</i> ₂	0.2866	0.0138	0.000	11,169	4,037
<i>anxiety</i> ₃	0.1554	0.0152	0.000	9,320	6,163
<i>anxiety</i> ₄	0.1963	0.0185	0.000	6,263	9,204
<i>anxiety</i> ₅	0.1718	0.0142	0.000	11,490	20,121
<i>asthma</i> ₁	0.1866	0.0525	0.000	12,167	3,831
<i>asthma</i> ₂	0.4741	0.0148	0.000	10,763	7,106
<i>asthma</i> ₃	0.2965	0.0169	0.000	8,107	10,817
<i>asthma</i> ₄	0.2775	0.0203	0.000	5,457	14,849
<i>asthma</i> ₅	0.2067	0.0157	0.000	9,870	29,272
<i>athero</i> ₁	0.3240	0.0545	0.000	4,928	4,747
<i>athero</i> ₂	0.4888	0.0171	0.000	8,214	7,818
<i>athero</i> ₃	0.2437	0.0178	0.000	7,902	11,090
<i>athero</i> ₄	0.2136	0.0196	0.000	6,303	14,815
<i>athero</i> ₅	0.0961	0.0164	0.000	10,977	28,182
<i>back</i> ₁	0.4839	0.0526	0.000	11,272	7,547
<i>back</i> ₂	0.5116	0.0181	0.000	8,026	13,013
<i>back</i> ₃	0.2830	0.0246	0.000	4,489	17,539
<i>back</i> ₄	0.2494	0.0351	0.000	2,075	23,952
<i>back</i> ₅	0.1109	0.0433	0.010	1,213	36,514
<i>behavio</i> ₁	-0.0579	0.0556	0.298	3,567	2,485
<i>behavio</i> ₂	0.2548	0.0257	0.000	2,829	4,043
<i>behavio</i> ₃	0.1624	0.0354	0.000	1,480	6,510
<i>behavio</i> ₄	0.1424	0.0329	0.000	1,679	13,979
<i>benign</i> ₁	0.5307	0.0761	0.000	537	12,453
<i>bipol</i> ₁	0.3362	0.0552	0.000	4,033	5,754
<i>bipol</i> ₂	0.4406	0.0324	0.000	1,866	10,326
<i>bipol</i> ₃	0.2617	0.0484	0.000	808	15,574
<i>bipol</i> ₄	0.1935	0.0491	0.000	787	26,259
<i>bph</i> ₁	-0.2036	0.0667	0.002	939	1,962
<i>bph</i> ₂	0.2405	0.0314	0.000	1,859	3,225
<i>bph</i> ₃	0.1356	0.0265	0.000	2,668	4,670
<i>bph</i> ₄	0.1314	0.0251	0.000	2,881	5,958
<i>bph</i> ₅	0.0436	0.0133	0.001	11,239	14,095
<i>breast</i> ₁	0.0272	0.0805	0.735	443	2,672
<i>breast</i> ₂	0.2932	0.0703	0.000	350	4,851
<i>breast</i> ₃	0.1509	0.0894	0.092	216	6,883
<i>breast</i> ₄	0.2073	0.0792	0.009	275	14,238
<i>cerebro</i> ₁	0.4740	0.0533	0.000	8,876	12,709

continued ...

... Table C.2 continued

Variable	Coefficient	Std Error	p-value	sample size	average cost
<i>cerebro</i> ₂	0.2700	0.0217	0.000	5,288	25,556
<i>chf</i> ₁	0.0254	0.1923	0.895	50	2,836
<i>chf</i> ₂	0.4672	0.0900	0.000	217	5,021
<i>chf</i> ₃	0.3610	0.0597	0.000	519	8,079
<i>chf</i> ₄	0.3398	0.0469	0.000	849	10,390
<i>chf</i> ₅	0.2641	0.0164	0.000	9,800	28,869
<i>chroninf</i> ₁	0.3632	0.0680	0.000	856	8,904
<i>chroninf</i> ₂	0.2150	0.0814	0.008	264	18,916
<i>cnsdns</i> ₁	0.4044	0.0531	0.000	8,335	7,293
<i>cnsdns</i> ₂	0.4965	0.0173	0.000	8,753	12,802
<i>cnsdns</i> ₃	0.3103	0.0217	0.000	6,009	18,434
<i>cnsdns</i> ₄	0.3239	0.0286	0.000	3,536	24,523
<i>cnsdns</i> ₅	0.2248	0.0303	0.000	3,018	38,454
<i>concard</i> ₁	-0.0473	0.1060	0.656	199	2,584
<i>concard</i> ₂	0.4256	0.0685	0.000	375	5,553
<i>concard</i> ₃	0.2000	0.0663	0.003	399	7,389
<i>concard</i> ₄	0.2330	0.0709	0.001	347	10,874
<i>concard</i> ₅	0.2061	0.0444	0.000	893	25,407
<i>congen</i> ₁	0.2620	0.0615	0.000	1,462	4,578
<i>congen</i> ₂	0.4739	0.0335	0.000	1,631	8,430
<i>congen</i> ₃	0.2278	0.0363	0.000	1,398	11,777
<i>congen</i> ₄	0.2619	0.0447	0.000	923	16,137
<i>congen</i> ₅	0.1160	0.0382	0.002	1,254	26,727
<i>cystic</i> ₁	1.8343	0.1899	0.000	51	32,056
<i>dem</i> ₁	0.1560	0.0844	0.065	381	3,440
<i>dem</i> ₂	0.4230	0.0456	0.000	850	5,665
<i>dem</i> ₃	0.1934	0.0388	0.000	1,186	8,128
<i>dem</i> ₄	0.0701	0.0193	0.000	5,423	19,047
<i>dental</i> ₁	0.5280	0.3505	0.132	14	14,033
<i>depress</i> ₁	0.0495	0.0520	0.342	18,674	3,024
<i>depress</i> ₂	0.3927	0.0127	0.000	16,646	5,661
<i>depress</i> ₃	0.2277	0.0149	0.000	11,368	8,619
<i>depress</i> ₄	0.2453	0.0181	0.000	7,016	12,339
<i>depress</i> ₅	0.1903	0.0143	0.000	12,271	24,133
<i>dm</i> ₁	0.2698	0.0518	0.000	28,222	5,018
<i>dm</i> ₂	0.3956	0.0138	0.000	18,210	9,259
<i>dm</i> ₃	0.1950	0.0170	0.000	10,510	13,830
<i>dm</i> ₄	0.2207	0.0225	0.000	5,729	19,636
<i>dm</i> ₅	0.1158	0.0216	0.000	5,970	34,211

continued ...

... Table C.2 continued

Variable	Coefficient	Std Error	p-value	sample size	average cost
<i>dysrhy</i> ₁	0.4445	0.0528	0.000	11,196	8,042
<i>dysrhy</i> ₂	0.5525	0.0172	0.000	9,562	13,560
<i>dysrhy</i> ₃	0.3299	0.0207	0.000	6,604	18,937
<i>dysrhy</i> ₄	0.3440	0.0270	0.000	3,905	25,779
<i>dysrhy</i> ₅	0.1731	0.0263	0.000	3,941	39,585
<i>epilepsy</i> ₁	0.3540	0.0630	0.000	1,261	5,540
<i>epilepsy</i> ₂	0.4303	0.0504	0.000	702	9,597
<i>epilepsy</i> ₃	0.3479	0.0663	0.000	408	16,216
<i>epilepsy</i> ₄	0.2273	0.0590	0.000	520	30,454
<i>esoph</i> ₁	0.1201	0.0527	0.023	10,354	3,465
<i>esoph</i> ₂	0.3528	0.0139	0.000	12,445	5,935
<i>esoph</i> ₃	0.1932	0.0155	0.000	9,632	9,101
<i>esoph</i> ₄	0.1998	0.0184	0.000	6,724	12,498
<i>esoph</i> ₅	0.1144	0.0144	0.000	11,198	22,801
<i>eye</i> ₁	-0.0491	0.0527	0.351	10,688	2,458
<i>eye</i> ₂	0.2701	0.0134	0.000	13,758	4,339
<i>eye</i> ₃	0.0305	0.0069	0.000	63,387	11,948
<i>femalegu</i> ₁	0.4102	0.0521	0.000	15,173	5,251
<i>femalegu</i> ₂	0.3935	0.0233	0.000	3,822	9,373
<i>femalegu</i> ₃	0.1548	0.0382	0.000	1,350	13,133
<i>femalegu</i> ₄	0.1525	0.0469	0.001	866	21,387
<i>gi</i> ₁	0.5305	0.0522	0.000	16,630	10,121
<i>gi</i> ₂	0.3941	0.0252	0.000	3,745	21,649
<i>gi</i> ₃	0.2692	0.0734	0.000	463	36,597
<i>gout</i> ₂	0.0200	0.0637	0.754	427	2,479
<i>gout</i> ₃	0.1155	0.0501	0.021	696	3,441
<i>gout</i> ₄	0.1266	0.0424	0.003	975	4,753
<i>gout</i> ₅	0.0974	0.0176	0.000	5,914	17,601
<i>hep</i> ₁	1.0308	0.0586	0.000	1,749	21,076
<i>hiv</i> ₁	1.7206	0.0649	0.000	913	24,392
<i>htn</i> ₁	-0.2024	0.0523	0.000	17,507	1,987
<i>htn</i> ₂	0.1715	0.0108	0.000	30,227	3,423
<i>htn</i> ₃	0.0480	0.0101	0.000	33,998	4,963
<i>htn</i> ₄	0.1334	0.0097	0.000	29,656	6,904
<i>htn</i> ₅	0.1331	0.0088	0.000	77,225	15,527
<i>hyprlip</i> ₁	-0.3742	0.0533	0.000	7,600	1,666
<i>hyprlip</i> ₂	-0.0228	0.0110	0.039	19,477	2,463
<i>hyprlip</i> ₃	-0.0834	0.0103	0.000	28,801	3,561
<i>hyprlip</i> ₄	-0.0137	0.0065	0.034	123,944	10,799

continued ...

... Table C.2 continued

Variable	Coefficient	Std Error	p-value	sample size	average cost
<i>immun</i> ₁	0.1473	0.0775	0.057	504	4,109
<i>immun</i> ₂	0.5386	0.0531	0.000	626	10,034
<i>immun</i> ₃	0.4991	0.0546	0.000	595	18,180
<i>immun</i> ₄	0.4393	0.0622	0.000	459	23,492
<i>immun</i> ₅	0.3739	0.0465	0.000	835	46,447
<i>kidney</i> ₁	0.3423	0.0568	0.000	2,887	7,679
<i>kidney</i> ₂	0.3431	0.0241	0.000	3,801	12,716
<i>kidney</i> ₃	0.2387	0.0289	0.000	2,819	21,261
<i>kidney</i> ₄	0.2315	0.0402	0.000	1,470	29,884
<i>kidney</i> ₅	0.1157	0.0499	0.021	893	46,269
<i>liver</i> ₁	0.2540	0.0598	0.000	1,795	6,097
<i>liver</i> ₂	0.5557	0.0340	0.000	1,640	14,474
<i>liver</i> ₃	0.3096	0.0449	0.000	949	21,396
<i>liver</i> ₄	0.1505	0.0500	0.003	771	32,712
<i>lupus</i> ₁	0.0475	0.0238	0.046	3,416	11,831
<i>malegu</i> ₁	-0.0286	0.0666	0.668	948	2,764
<i>malegu</i> ₂	0.0608	0.0180	0.001	5,718	9,507
<i>malig</i> ₁	0.8265	0.0518	0.000	27,394	13,472
<i>malig</i> ₂	0.5110	0.0307	0.000	2,787	26,871
<i>malig</i> ₃	0.2413	0.1234	0.051	142	43,331
<i>malnutr</i> ₁	-0.2338	0.0544	0.000	5,070	2,121
<i>malnutr</i> ₂	0.0939	0.0152	0.000	9,444	3,614
<i>malnutr</i> ₃	-0.0219	0.0147	0.136	9,615	5,570
<i>malnutr</i> ₄	0.0335	0.0160	0.037	7,862	7,920
<i>malnutr</i> ₅	0.0765	0.0114	0.000	16,810	19,084
<i>menop</i> ₁	-0.1540	0.0637	0.016	1,185	2,132
<i>menop</i> ₂	0.1782	0.0322	0.000	1,709	3,513
<i>menop</i> ₃	0.0413	0.0166	0.013	6,562	9,333
<i>mi</i> ₁	0.7898	0.0634	0.000	1,313	30,792
<i>migrain</i> ₁	0.3656	0.0529	0.000	9,330	6,444
<i>migrain</i> ₂	0.4167	0.0309	0.000	2,079	12,861
<i>migrain</i> ₃	0.1674	0.0545	0.002	631	22,601
<i>miscmh</i> ₁	-0.2627	0.1459	0.072	92	1,909
<i>miscmh</i> ₂	0.1560	0.1097	0.155	143	3,405
<i>miscmh</i> ₃	0.0233	0.1054	0.825	155	4,996
<i>miscmh</i> ₄	0.1125	0.0508	0.027	674	16,000
<i>ms</i> ₁	1.6102	0.0579	0.000	2,208	23,994
<i>obesity</i> ₁	-0.1056	0.0543	0.052	5,086	2,598
<i>obesity</i> ₂	0.2701	0.0168	0.000	7,646	4,755

continued ...

... Table C.2 continued

Variable	Coefficient	Std Error	p-value	sample size	average cost
<i>obesity</i> ₃	0.1779	0.0183	0.000	6,354	7,680
<i>obesity</i> ₄	0.2364	0.0217	0.000	4,366	11,216
<i>obesity</i> ₅	0.2045	0.0174	0.000	6,777	23,436
<i>osteo</i> ₁	0.4383	0.0517	0.000	29,081	8,241
<i>osteo</i> ₂	0.3949	0.0148	0.000	18,938	12,615
<i>osteo</i> ₃	0.2169	0.0226	0.000	7,465	18,979
<i>osteo</i> ₄	0.1067	0.0346	0.002	3,142	32,600
<i>othendo</i> ₁	0.0582	0.0518	0.261	23,329	3,443
<i>othendo</i> ₂	0.2619	0.0122	0.000	20,236	6,418
<i>othendo</i> ₃	0.0849	0.0150	0.000	12,388	9,851
<i>othendo</i> ₄	0.1066	0.0184	0.000	7,546	13,893
<i>othendo</i> ₅	0.0555	0.0167	0.001	8,966	26,579
<i>othmsk</i> ₁	0.3514	0.0520	0.000	19,666	7,775
<i>othmsk</i> ₂	0.2894	0.0196	0.000	8,528	13,860
<i>othmsk</i> ₃	0.1542	0.0288	0.000	3,580	28,050
<i>panc</i> ₁	0.7735	0.0896	0.000	295	19,722
<i>para</i> ₁	0.5363	0.0841	0.000	391	9,274
<i>para</i> ₂	0.6710	0.0732	0.000	336	21,053
<i>para</i> ₃	0.5027	0.0921	0.000	214	42,209
<i>parkin</i> ₁	0.5420	0.0621	0.000	1,419	13,185
<i>parkin</i> ₂	0.1908	0.0619	0.002	472	21,265
<i>periph</i> ₁	-0.1031	0.1767	0.560	60	2,178
<i>periph</i> ₂	0.7286	0.0951	0.000	191	5,179
<i>periph</i> ₃	0.3841	0.0692	0.000	364	5,950
<i>periph</i> ₄	0.3566	0.0541	0.000	597	7,870
<i>periph</i> ₅	0.1572	0.0164	0.000	7,516	22,676
<i>persnal</i> ₁	-0.0564	0.0724	0.436	654	3,043
<i>persnal</i> ₂	0.2485	0.0501	0.000	704	5,471
<i>persnal</i> ₃	0.1209	0.0387	0.002	1,188	15,143
<i>pulmhrt</i> ₁	0.9215	0.1259	0.000	130	14,719
<i>pulmhrt</i> ₂	0.8678	0.0834	0.000	253	19,857
<i>pulmhrt</i> ₃	0.3522	0.0813	0.000	267	19,930
<i>pulmhrt</i> ₄	0.1389	0.0522	0.008	672	37,722
<i>renal</i> ₁	0.6163	0.0532	0.000	11,244	22,126
<i>renal</i> ₂	0.4216	0.0676	0.000	512	52,826
<i>rheum</i> ₁	0.6939	0.0533	0.000	6,855	12,834
<i>rheum</i> ₂	0.2665	0.0626	0.000	521	26,030
<i>schiz</i> ₁	0.4774	0.0589	0.000	2,077	10,274
<i>schiz</i> ₂	0.4685	0.0564	0.000	584	22,256

continued ...

... Table C.2 continued

Variable	Coefficient	Std Error	p-value	sample size	average cost
<i>schiz</i> ₃	0.1830	0.0703	0.009	378	39,402
<i>sickle</i> ₁	1.1121	0.1356	0.000	109	16,705
<i>sickle</i> ₂	0.7573	0.3188	0.018	17	34,080
<i>skin</i> ₁	0.4735	0.0527	0.000	10,077	8,817
<i>skin</i> ₂	0.4182	0.0268	0.000	3,220	18,432
<i>skin</i> ₃	0.3375	0.0458	0.000	945	37,202
<i>skin</i> ₄	0.0969	0.0750	0.196	354	60,463
<i>sleep</i> ₁	0.0781	0.0562	0.164	3,133	2,961
<i>sleep</i> ₂	0.4378	0.0222	0.000	3,888	5,143
<i>sleep</i> ₃	0.2447	0.0221	0.000	3,955	7,409
<i>sleep</i> ₄	0.2466	0.0250	0.000	3,135	10,623
<i>sleep</i> ₅	0.1386	0.0169	0.000	7,122	21,814
<i>sti</i> ₁	0.0179	0.1064	0.866	197	3,045
<i>sti</i> ₂	0.4920	0.1110	0.000	140	7,932
<i>sti</i> ₃	0.2162	0.1527	0.157	74	10,335
<i>sti</i> ₄	0.3799	0.2219	0.087	35	14,749
<i>sti</i> ₅	0.4230	0.1842	0.022	51	46,078
<i>strcght</i> ₁	-0.0441	0.1024	0.667	221	2,730
<i>strcght</i> ₂	0.2530	0.0578	0.000	552	5,031
<i>strcght</i> ₃	0.2236	0.0447	0.000	940	8,126
<i>strcght</i> ₄	0.2302	0.0379	0.000	1,267	10,392
<i>strcght</i> ₅	0.1393	0.0175	0.000	7,576	26,894
<i>subst</i> ₁	0.1974	0.0520	0.000	18,449	4,192
<i>subst</i> ₂	0.4639	0.0158	0.000	9,648	8,736
<i>subst</i> ₃	0.3136	0.0224	0.000	4,437	14,126
<i>subst</i> ₄	0.2960	0.0322	0.000	2,024	19,788
<i>subst</i> ₅	0.2042	0.0328	0.000	1,849	33,290
<i>tb</i> ₁	-0.8281	1.3114	0.528	1	1,058
<i>thrombemb</i> ₁	0.7685	0.0830	0.000	400	27,853
<i>valve</i> ₁	0.1872	0.0582	0.001	2,290	4,953
<i>valve</i> ₂	0.3141	0.0240	0.000	3,748	8,369
<i>valve</i> ₃	0.0775	0.0157	0.000	9,402	20,683
<i>vasc</i> ₁	0.2197	0.0686	0.001	806	5,361
<i>vasc</i> ₂	0.3694	0.0383	0.000	1,255	9,684
<i>vasc</i> ₃	0.1583	0.0413	0.000	1,099	14,658
<i>vasc</i> ₄	0.2256	0.0474	0.000	846	20,569
<i>vasc</i> ₅	0.0917	0.0404	0.023	1,161	36,218

Appendix D: Sensitivity analysis: Impact of inclusion criteria used in the chronic conditions study

In this appendix, we investigate the impact of changing the inclusion criteria (i.e., when a member is considered to have a chronic condition) on the cost contributions that were estimated in the main analysis. We study the effect of stricter (see Subsection D.1), and more flexible inclusion criteria (see Subsection D.2). In both cases, we use the same L_{max} as in the main analysis (i.e., $L_{max} = 5$), as well as the same number of centers for the clustering analysis (i.e., 2 centers).

D.1 Stricter inclusion criteria

We require a member to have at least one claim with a corresponding diagnoses code in 2012, and a second claim with a diagnoses code (for the same condition) at least twelve months apart. Thus, our inclusion criteria is stricter than it was in the main analysis. These inclusion criteria identify 375,157 members with at least one chronic condition in 2012. Figure D.1 shows a similar effect to that of Figure 3.1 in the main analysis, where the number of members with each number of conditions decreased exponentially as the number

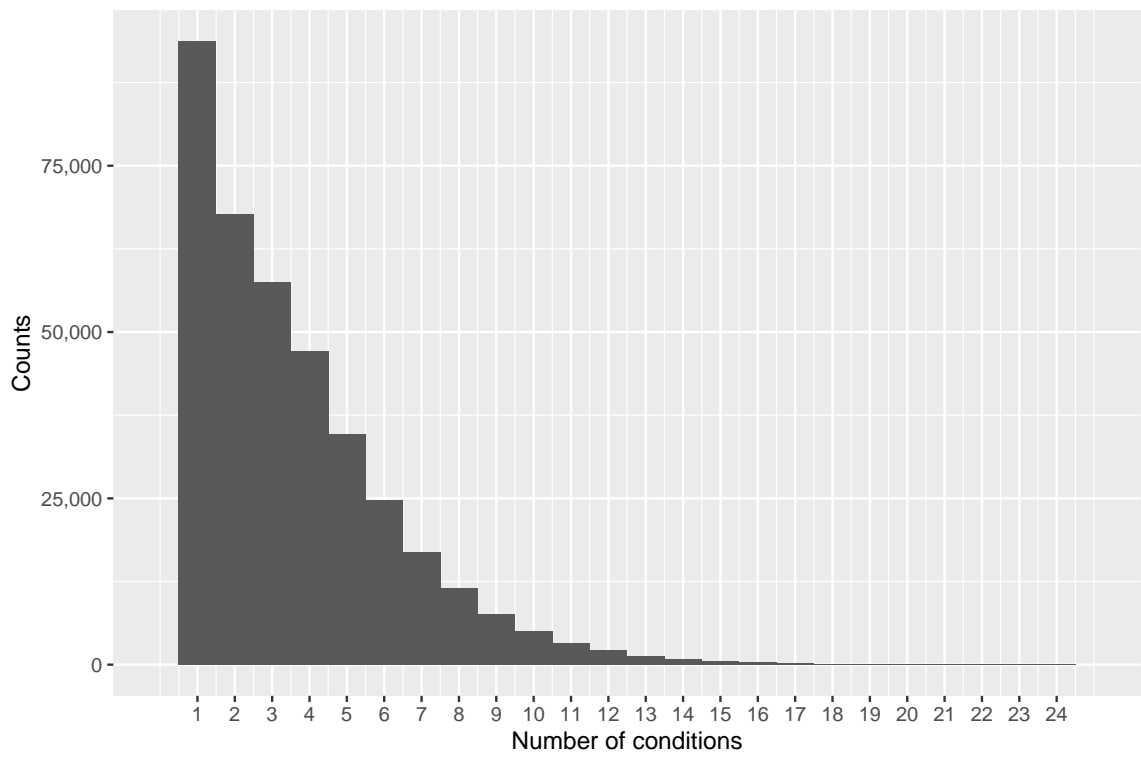


Figure D.1: Counts of members with each number of chronic conditions in the stricter inclusion criteria population.

of chronic condition increased. In this case, the average number of chronic conditions per member was 3.6 (with a standard deviation of 2.65), which are slightly lower numbers compared to the main analysis.

The resulting regression model (after applying Algorithm 1) consists of 11 fewer variables, which means that some conditions correspond to a smaller number of coefficients than they did in the main analysis. There are no members with tuberculosis in this data set, so this condition is not included in this model.

Figure D.2, shows the slopes of the coefficients for each chronic condition consisting of at least two coefficients. We see that there are no conditions with a negative slope. In the main analysis, there were three conditions with a negative slope. Two of the conditions only consist of one coefficient in this model, so we cannot draw any conclusions about their slope. However, Parkinson's disease still consists of two coefficients and has a small positive slope in this case, which gives us the opposite effect of what was estimated in the previous analysis. While all conditions have a positive slope, chronic hepatitis has a considerably higher slope than the rest. This condition only consisted of one coefficient in the main analysis, so we had no information about its slope.

The clusters resulting from the clustering analysis have a similar effect as the clusters resulting from the main analysis, since one cluster included conditions with a relatively constant increase as the order that they appear in a member increases, and the other cluster included conditions that did not have a clear increase in cost. In total, 46 conditions were taken into account in the clustering analysis. The majority of conditions continued to be-

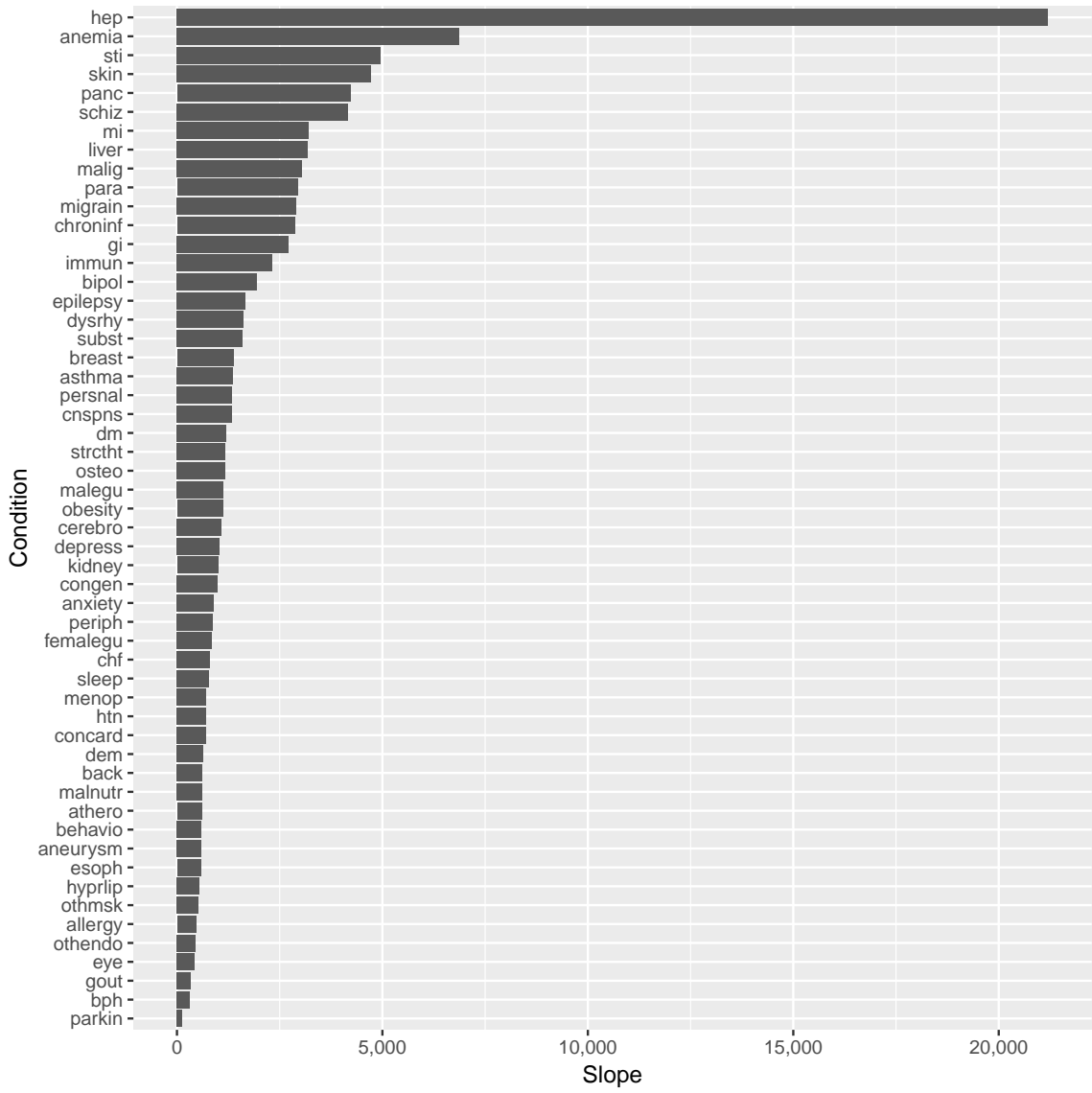


Figure D.2: Slopes for each chronic condition in the stricter inclusion criteria population.

Table D.1: Conditions that switched clusters compared to the main analysis (stricter criteria).

Change	Names of conditions
From 1st-type to 2nd-type cluster	Chronic skin ulcer Osteoarthritis Non-thrombotic, non-athlerosclerotic vascular disease
From 2nd-type to 1st-type cluster	Aneurysm Other MSK including osteoporosis Epilepsy Female infertility and GU anatomic disorders Hyperlipidemia Peripheral atherosclerosis Other central and peripheral nervous system disorders

long in the same type of cluster as they did in the main analysis. Note that if the number of cost coefficients corresponding to a condition changed, but the condition continued to belong to the same type of cluster, we assume that this condition did not change its cost behavior. Table D.1 includes the 10 conditions that switched the type of cluster that they were included in. Below we investigate in more detail what caused these changes.

In the main analysis, both hyperlipidemia, and peripheral atherosclerosis, had a contribution that was relatively stable after an increase from being ordered first to second. While in the main analysis they were both included in the type-2 cluster, they were an exception compared to how the other conditions of the cluster behaved. In the model of this section, both conditions had their coefficient decrease by 1, but their behavior remained consistent to the conditions of a type-1 cluster. In the case of female infertility and GU anatomic disorders, in the main analysis the cost contributions of this condition do not reveal any clear patterns, as they fluctuate from one order to the next. In this section, the cost contribution behaves more as a type-1 cluster.

In the case of aneurysm, the last coefficient affects the selected cluster (slight decrease, compared to an increase observed in the main analysis), but the cost magnitude is similar in both models. Similarly, in epilepsy, the last coefficient, which corresponded to 360 obser-

vations, indicated a small decrease compared to a previously constant increase (observed in the main analysis). This caused the condition to be included in a different cluster. Nevertheless, the cost magnitude remained about the same. The same is true for other central and peripheral nervous system disorders. For other MSK including osteoporosis, in this version of the model there were coefficients that were not statistically significant, and the condition consisted of five instead of three variables (as in the main analysis), with the cost contribution in the fifth order being slightly lower than the fourth. This led the condition to be included in a different cluster.

Regarding chronic skin ulcer, in the original analysis, the coefficient corresponding to the last order (ranked fourth or higher in a patient), was not statistically significant. This was the coefficient that affected the decision for entering the type-1 cluster, since it showed a decrease compared to previous contributions. However, in this version the coefficient is statistically significant and shows a continued increase.

For the remaining two conditions, there is a more clear difference compared to the main analysis. In particular, for osteoarthritis, there was a different effect observed, with an increase instead of a decrease in the contribution. Nevertheless, the magnitude of cost was similar. Finally, for non-thrombotic, non-atherosclerotic vascular disease, 488 patients cause a very large increase in the last coefficient, which corresponds to the condition being ranked third or higher in a patient. In the main analysis, the condition consisted of five coefficients, but the maximum cost contribution was lower than what we observed in this case.

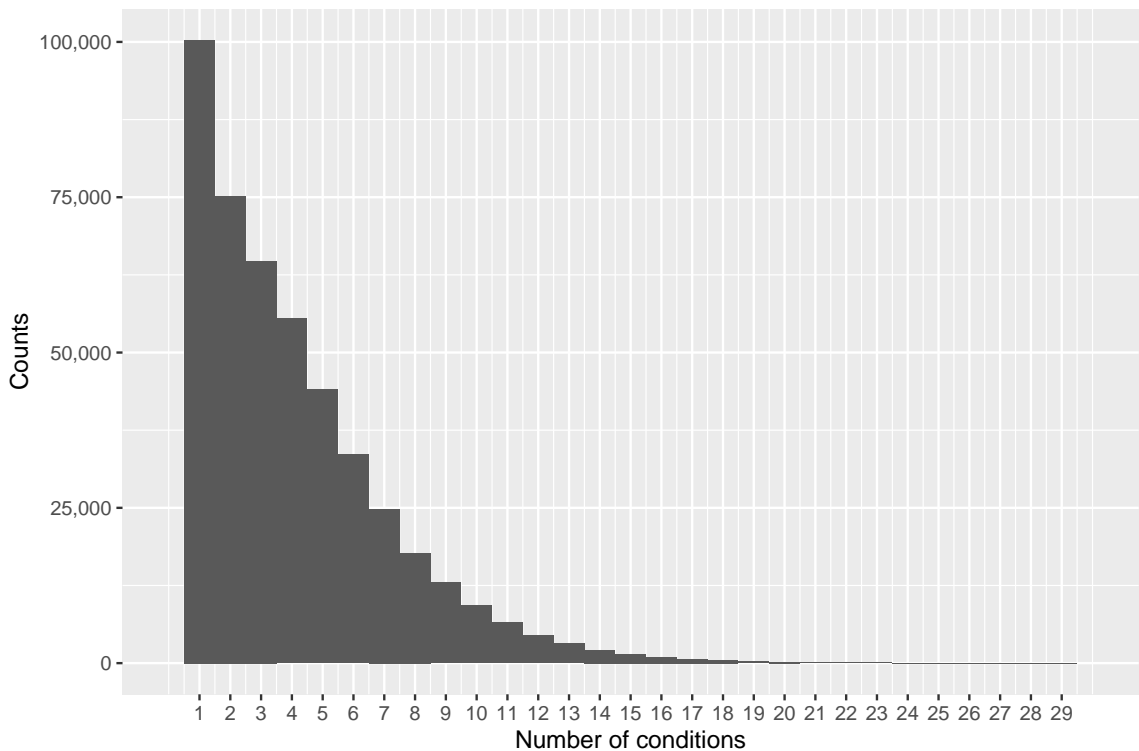


Figure D.3: Counts of members with each number of chronic conditions in the more flexible inclusion criteria population.

D.2 More flexible inclusion criteria

We require a member to have at least one claim with a corresponding diagnoses code in 2012, and at least two claims (for the same condition) in total during the 2007-2012 time period. Thus, our inclusion criteria is more flexible than it was in the main analysis. In total, we identify 458,835 members with at least one chronic condition diagnosis in 2012. Figure D.3 shows a similar exponential decrease to that of the main analysis and the stricter inclusion criteria version. In this case the average number of chronic conditions per member was 4.1 (with a standard deviation of 3.1), which shows that an increased number

of conditions were diagnosed compared to the other two versions.

The resulting regression model (after applying Algorithm 1) consists of 21 more variables than it did in the main analysis, which means that some conditions correspond to an increased number of coefficients compared to the main analysis.

Figure D.4, shows the slopes of the coefficients for each chronic condition. The only condition with a negative slope is Parkinson's disease. This condition also had a negative slope in the main analysis, but in this case the absolute value of the slope is smaller. Of the other two conditions that had a negative slope in the main analysis, rheumatoid arthritis now consists of only one coefficient (so a slope cannot be estimated), and pulmonary heart disease was included in a 1st-type cluster in the clustering analysis that follows below, which shows that even though its slope was not negative, a decrease in the cost contribution was observed.

The two clusters had again similar characteristics to those included in the main analysis, and the analysis of Subsection D.1. In total, 55 chronic conditions were taken into account in the clustering analysis. While the majority of conditions were included in same type of cluster as in the main analysis, 13 conditions were included in a different cluster. Table D.2 includes those conditions. Most conditions that switched a cluster were different than the analysis of Subsection D.1. The only exceptions were aneurysm, hyperlipidemia, and other central and peripheral nervous system disorders. Below we describe the changes observed in the cost behavior of the conditions included in Table D.2.

Hyperlipidemia had a contribution that was relatively stable after an increase from the

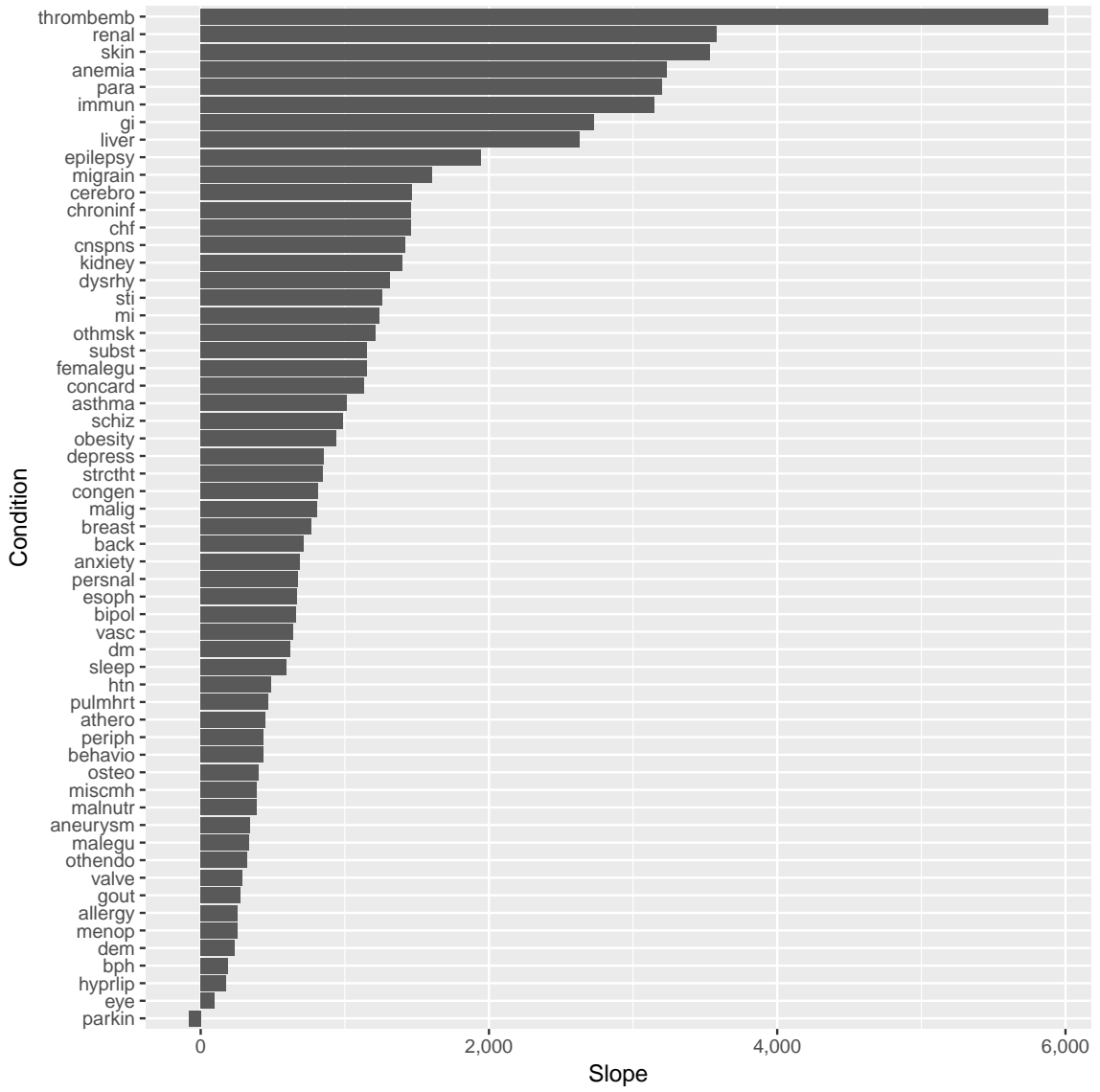


Figure D.4: Slopes for each chronic condition in the stricter inclusion criteria population.

Table D.2: Conditions that switched clusters compared to the main analysis (more flexible criteria).

Change	Names of conditions
From 1st-type to 2nd-type cluster	Non-cardiac congenital disorder Conduction disorder or cardiac dysrhythmia Esophageal disorder and GI ulcers Kidney and Vesicoureteral Disorders (excl. renal failure) Chronic Liver Disease (excl. chronic hepatitis) Chronic skin ulcer Migraines
From 2nd-type to 1st-type cluster	Aneurysm Behavior disorders Bipolar disorder Other central and peripheral nervous system disorders Immunity disorder Hyperlipidemia

first to the second order. While in the main analysis it was included in the type-2 cluster, it was an exception compared to the other conditions of the cluster. In the case of chronic skin ulcer, the last coefficient was not statistically significant in the main analysis, which led to a different result (the same that this condition was in a different cluster in the stricter version of Subsection D.1).

Non-cardiac congenital disorder has a similar cost magnitude as in the main analysis, but in the main analysis there is a slight decrease observed in the last coefficient which is not present here. Similarly, for conduction disorder or cardiac dysrhythmia, in the main analysis there is a decrease observed in the last coefficient which is not present here (the cost contribution is similar). In the main analysis, for kidney and vesicoureteral disorders (excl. renal failure), only the last coefficient shows a small decrease, which is not present here (the cost contribution continues to increase). The result was based on 893 observations in the main analysis. Bipolar disorder has a similar cost magnitude to the results of the main analysis, but one additional coefficient, which corresponds to a slight decrease. This moved the condition to a different cluster. For esophageal disorder and GI ulcers, the magnitude is the same, but the increase is more gradual compared to the main analysis. For other central

and peripheral nervous system disorder, the last coefficient changes to a slight decrease, but other than that the effect is very similar.

Behavior disorders have similar cost magnitude to the main analysis, but one additional coefficient, which corresponds to a slight decrease Immunity disorder have a similar cost magnitude, but the highest cost is reached in the fourth order and then remains stable. in the main analysis the cost cost contribution had a more gradual increase. In the case of migraines, the cost magnitude is very similar to the main analysis, but the second and third order contributions are reversed in this analysis.

Aneurysm has similar cost contributions, but in this case there is a large increase from the first to the second order and then the cost remains relatively stable. Finally, for chronic liver disease (excl. chronic hepatitis), in this model there is a constant increase, while in the main analysis there is a decrease after the second condition.

From this sensitivity analysis we see that in the majority of cases, the conditions continue to behave in a similar manner. While small changes may affect the type of cluster that some conditions are included in, with only very few exceptions the cost magnitude continues to be the same. Thus, we see that the proposed methodology can be used to obtain good estimates of the cost contributions of conditions, in patients with multiple chronic conditions.

Appendix E: Conversational agent scripts used in the technology adoption study

Tables E.1 and E.2 include the script followed by the conversational agents. In particular, Table E.1 includes the questions asked of the patient, and the corresponding action of the conversational agent based on the patient's answer (i.e., what to comment, and which question to ask next). Table E.2 includes the comments that the conversational agent makes to the patient after the questionnaire is completed.

Table E.1: Script followed by both conversational agent technologies. Part 1: Questions asked

QID	Question	Patient's Answer	Comment [& Action]
1	Did you weigh yourself today?	Yes	<ul style="list-style-type: none"> * Great, then. [Ask Q 2a] * Excellent. And [Ask Q 2a] * Okay! [Ask Q 2a] * Good. And [Ask Q 2a] * Wonderful. Now, [Ask Q 2a]
		No	<ul style="list-style-type: none"> * Ok - Please weigh yourself after you complete this survey [Ask Q 2a] * Got it. Please weigh yourself every after you finish this survey. [Ask Q 2a] * Ok, remember to weigh yourself after you finish this survey. And [Ask Q 2a] * It's important to weigh yourself every day. Please weigh yourself after you complete this survey. Now, [Ask Q 2a]
2a	Did you take all your heart failure medications as prescribed since the last survey?	Yes	<ul style="list-style-type: none"> * Wonderful, [Ask Q 3] * Good to hear. [Ask Q 3] * Great. [Ask Q 3] * Good! [Ask Q 3] * Okay, [Ask Q 3]
		No	[Ask Q 2b]
2b	Did you take most of your heart failure medications as prescribed since the last survey?	Yes	<ul style="list-style-type: none"> * Okay. Please be sure to always take all your medications as prescribed. [Ask Q 3] * Okay, but it's important to take all your medications as prescribed every day. [Ask Q 3] * Good to hear but please be sure to take all your medications exactly as prescribed every day. [Ask Q 3]
		No	[Ask Q 2c]

continued ...

... Table E.1 continued

QID	Question	Patient's Answer	Comment [& Action]
2c	Did you take some of your heart failure medications as prescribed since the last survey?	Yes	<ul style="list-style-type: none"> * Okay. Please be sure to always take all your medications as prescribed. [Ask Q 3] * Okay, but it's important to take all your medications as prescribed every day. [Ask Q 3] * Fine but please be sure to take all your medications exactly as prescribed every day. [Ask Q 3]
		No	<ul style="list-style-type: none"> * Please be sure to take your medications right after we finish this survey. [Ask Q 3] * Please be sure to take your medications after you complete the rest of the survey. It's important to take your medications every day. [Ask Q 3] * It is very important you take your medications exactly as prescribed. Please do it after we are done with your heart health survey [Ask Q 3] * Following your medication prescription is very important - please take your medications after you finish your heart health survey. [Ask Q 3]
3	Did you eat any high salt foods since the last survey?	No	<ul style="list-style-type: none"> * Keep it up, now [Ask Q 4] * Good. And [Ask Q 4] * Okay, [Ask Q 4] * Great to hear! [Ask Q 4] * Perfect. [Ask Q 4]

continued ...

... Table E.1 continued

QID	Question	Patient's Answer	Comment [& Action]
		Yes	<ul style="list-style-type: none"> * Remember to keep your salt under 3 grams a day, and don't add additional salt to your food. [Ask Q 4] * Please keep your salt intake under 3 grams a day, it's important for your health. [Ask Q 4] * Remember, no more than 3 grams of salt a day, and don't add extra to your food. [Ask Q 4] * Your doctor recommends that you keep your salt under 3 grams a day, and refrain from adding extra salt at the table. [Ask Q 4]
4	Do you feel tired or short of breath with regular daily activities such as eating or taking a shower?	No	* Positive Interjection, [Ask Q 5]
		Yes	* Negative Interjection, [Ask Q 5]
5	Do you have cough or wheezing?	No	* Positive Interjection, [Ask Q 6]
		Yes	* Negative Interjection, [Ask Q 6]
6	Are your ankles swollen?	No	* Positive Interjection, [Ask Q 7]
		Yes	* Negative Interjection, [Ask Q 7]
7	Did your weight increase by 3 pounds or more in 1 day?	No	* Positive Interjection, [Ask Q 8]
		Yes	* Negative Interjection, [Ask Q 8]
8	Do you feel tired or short of breath at rest (for example when sitting)?	No	* Positive Interjection, [Ask Q 9]
		Yes	* Negative Interjection, [Ask Q 9]
9	Do you feel short of breath when you lie flat in bed?	No	* Positive Interjection, [Ask Q 10]
		Yes	* Negative Interjection, [Ask Q 10]

continued ...

... Table E.1 continued

QID	Question	Patient's Answer	Comment [& Action]
10	Do you need to be propped up with pillows in order to be able to sleep without shortness of breath?	Yes / No	<ul style="list-style-type: none"> * Okay, we're almost done. [Ask Q 11] * Almost there. [Ask Q 11] * Final question. [Ask Q 11] * Right. Last question, [Ask Q 11] * And lastly, [Ask Q 11]
11	Do you wake up from sleep in the middle of the night with shortness of breath and need to sit up to feel less short of breath?	Yes / No	<ul style="list-style-type: none"> * Thank you for completing your heart health survey. * You are all done with your heart health survey. * You have completed your heart health survey for today.

Table E.2: Script followed by both conversational agent technologies. Part 2: Advice given

Any Red Flags?	Conditions	Comment
No	If “WEIGHED SELF” & “TOOK MEDS” & “NOT MUCH SALT”	<ul style="list-style-type: none"> * You did well, today, weighing yourself, taking your medications, and complying with heart failure diet * Well done, today, you weighed yourself, took your medications, and complied with the heart failure diet * Way to go, weighing yourself, taking your medications, and keeping your salt intake under 3gms, today. * Good job, today. You just need to keep your salt intake under 3gms * You did well today. You just need to comply with the heart failure diet. * Good job, today. You just need to take your medications as prescribed * You did well, today. You just need to take your medications as prescribed to make it perfect * Good job, today. You just need to weigh yourself after we are done. * You did well, today. You just need to weigh yourself after we are done to make it perfect
	Else If “WEIGHED SELF” & “TOOK MEDS”	<ul style="list-style-type: none"> * Please remember to take your medications when we are done, as prescribed, and to keep your salt intake under 3gms.
	Else If “TOOK MEDS”	<ul style="list-style-type: none"> * Please remember to weigh yourself and record your weight when we are done, and to comply with the heart failure diet.
	Else	<ul style="list-style-type: none"> * Please remember to weigh yourself and record your weight when we are done, and to take your medications as prescribed.
Yes	If “WEIGHED SELF” & “TOOK MEDS” & “NOT MUCH SALT”	<ul style="list-style-type: none"> // Do nothing
	Else If “WEIGHED SELF” & “TOOK MEDS”	<ul style="list-style-type: none"> * Please make sure to keep your salt intake under 3gms * Remember it is very important to comply with the heart failure diet.

continued ...

... Table E.2 continued

Any Red Flags?	Conditions	Comment
	Else If “WEIGHED SELF” & “NOT MUCH SALT”	* Please remember to take your medications as prescribed after the survey. * It is very important that you take your medications as prescribed after we are done.
	Else If “TOOK MEDS” & “NOT MUCH SALT”	* Please remember to weigh yourself after we are done.
	Else If “WEIGHED SELF”	* It is important you weigh yourself after you finish the survey. * Please remember to take your medications when we are done as prescribed, and to keep your salt intake under 3gms.
	Else If “TOOK MEDS”	* Please remember to weigh yourself and record your weight when we are done, and to comply with the heart failure diet.
	Else	* Please remember to weigh yourself when we are done, and to take your medications as prescribed.
Yes	To all: If “WEIGHT INCREASED” If “TIRED REST” If “SHORT FLAT” If “PILLOW” If “SITUP”	* “X”, from what you told me, you are experiencing the following symptoms: * Your weight has increased more than 3 pounds in the last day. * you feel tired or short of breath when you rest. * you feel short of breath when you lie flat in bed. * you need to be propped up with pillows in order to be able to sleep without shortness of breath. * you wake up from sleep in the middle of the night with shortness of breath and need to sit up to feel less short of breath. This could be a sign of worsening heart failure. Please notify your heart failure nurse. If this is a medical emergency, please call 911.
	To all:	continued ...

... Table E.2 continued

Any Red Flags? Yes / No	Conditions To all:	Comment
		<p>Finally, please remember that I am a virtual assistant and not a health care professional. Please use your judgment and seek medical attention if you are not feeling well or have concerns about your health.</p> <ul style="list-style-type: none">* Have a good day and talk tomorrow!* Good bye, "X"!* Take care, "X"!* See you tomorrow. Good bye "X"!* Hope you have a good day. Bye!

Appendix F: Regression output from the technology adoption study

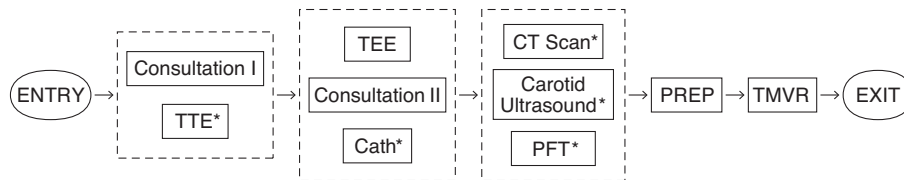
Table F.1 includes the linear regression model for predicting the number of times that the patient used the conversational agent technology, after excluding all race variables from the options of the best subsets method.

Table F.1: Regression output, adjusted $R^2 = 15\%$.

Variable	Coefficient	95% CI		P-value
(intercept)	20.3136	-13.7409	54.3680	0.2338
Age	0.6798	-0.0032	1.3628	0.051
Household income higher than \$100,000	3.2320	-14.2304	20.6944	0.7092
Some high school/ High school graduate	-17.9758	-34.6146	-1.3371	0.035
Number of medications to manage HF	-2.3482	-5.7876	1.0912	0.1743
Avatar study participant	-19.3634	-38.3248	-0.4019	0.0456

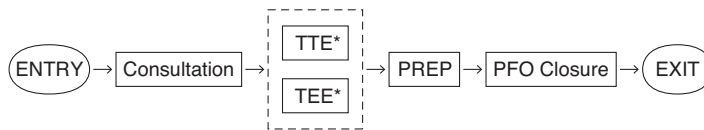
Appendix G: Procedure diagrams used in the multi-appointment scheduling study

In this appendix, we include the procedure diagrams (Figures G.1 through G.5), a short description of the procedures that the patients go through in each step, and the resources required.



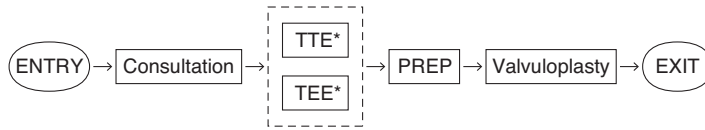
* Not all patients are required to go through this step.

Figure G.1: Procedure diagram for TMVR patients.



* Not all patients are required to go through this step.

Figure G.2: Procedure diagram for PFO patients.



* Not all patients are required to go through this step.

Figure G.3: Procedure diagram for Valvuloplasty patients.

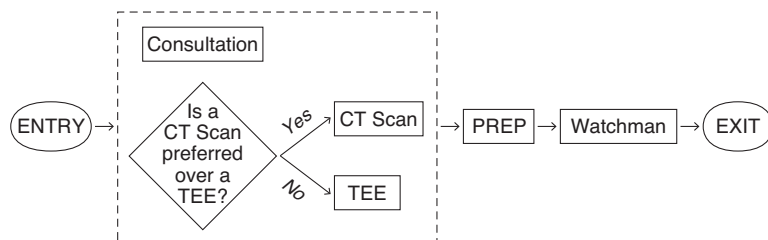
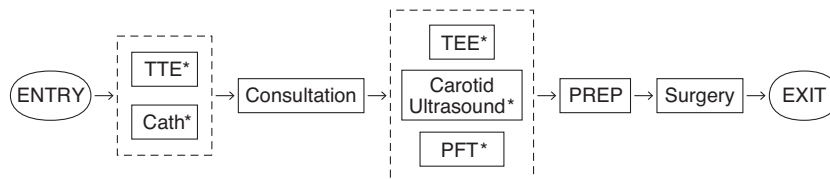


Figure G.4: Procedure diagram for Watchman patients.



* Not all patients are required to go through this step.

Figure G.5: Procedure diagram for elective surgery patients.

A transthoracic echocardiogram (TTE) uses sound waves to generate moving images of the heart. Another type of echocardiogram is the transesophageal echocardiogram (TEE), which generates clearer images than the TTE. However, the procedure takes a longer time, requires more resources and can be more difficult for the patient to go through. Some patients are not allowed to go through a TEE due to their history. In a computed tomography

(CT) scan, multiple X-ray images are combined to create tomographic images of the heart. A carotid ultrasound uses sound waves to create images of the inside of the carotid arteries. Pulmonary function tests (PFT) are a group of tests that determine how well the lungs of the patient are functioning. During the procedure readiness evaluation and preparation (PREP), the patients go through a number of tests to ensure that they are ready to go through the final interventional procedure or surgery. All of the aforementioned diagnostic tests take place in labs and use personnel and equipment resources specifically dedicated to the corresponding test. These resources are shared among many departments in the hospital.

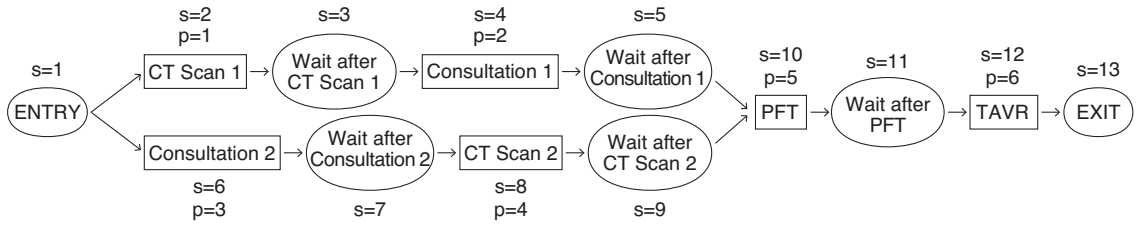
In the consultations the patients usually get examined by the physician that will perform the final procedure. Two surgeons, an interventional cardiologist, and a nurse practitioner participate in the consultation of the TAVR patients. A surgeon, an interventional cardiologist, and a nurse practitioner participate in the first consultation of a TMVR patient. The second consultation of a TMVR patient is with a heart failure cardiologist. In the case of the PFO closure and the valvuloplasty, the consultation is with an interventional cardiologist, and in the case of the elective surgery patients, the consultation is with the surgeon. Finally, the consultation of the Watchman patients is with an electrophysiologist and a surgeon. It is important to point out that the physicians specialize in a particular program, and therefore an interventional cardiologist who performs a TAVR procedure, for example, will not do a TMVR procedure. The only exception is in the case of the PFO closure and the valvuloplasty procedures, which can be performed by the same interventional cardiologist.

During the cardiac catheterization (Cath) a catheter is inserted to a blood vessel leading

to the heart, where it is possible to evaluate the function of the heart and open any blocked arteries. The procedure is performed by an interventional cardiologist and takes place in a cardiac catheterization lab. The TAVR and the TMVR procedures take place in a hybrid operating room (OR) by a team that includes a surgeon and an interventional cardiologist, the PFO closure is performed in a hybrid OR by an interventional cardiologist, and the valvuloplasty is performed in a cardiac catheterization lab by an interventional cardiologist. The Watchman takes place in a electrophysiology (EP) lab, with a team including an electrophysiologist and an echocardiogram doctor. Finally, surgeries take place in a OR.

Appendix H: Example of decision variable values used in the multi-appointment scheduling study

In this appendix, we use the example presented in Figure H.1 and Table H.1 in order to better illustrate the differences between the various decision variables of the IP. Figure H.1 provides an example of the appointments scheduled for a TAVR patient i . The top part of the figure shows the procedure diagram for this patient, who has to follow one of the two paths. The procedure diagram also shows the indexing for the positions (parameter s) and the procedures (parameter p) that this patient may have to go through. The bottom part of the figure includes part of the patient's schedule. In particular, the appointment for the TAVR procedure has been excluded. The schedule also shows the values for some of the parameters of the problem. It includes the corresponding p and s values, which are generated based on the possible paths that the patient can follow. Also, each day includes the corresponding d value. For illustrative purposes, we assume that Monday is the first day of the planning horizon, and therefore $d = 1$. The h values are also included in the figure. Not all times included in each day can be seen in the schedule. Nevertheless, by the values of h it can be understood that in a complete schedule each day would include 48 different h values, since in this case we are assuming that the time unit equals to 30 minutes.



	Monday (d=1)		Tuesday (d=2)		Wednesday (d=3)		Thursday (d=4)	
Time	h		h		h		h	
...	
9:30	19		67		115		163	
10:00	20	CT Scan (s=2, p=1)	68		116		164	
10:30	21		69		117		165	
11:00	22		70		118		166	PFT (s=10, p=5)
11:30	23		71		119		167	
12:00	24		72		120		168	
12:30	25		73		121		169	
13:00	26		74		122		170	
13:30	27		75		123		171	
14:00	28		76		124		172	
14:30	29	Consult (s=4, p=2)	77		125		173	
15:00	30		78		126		174	
15:30	31		79		127		175	
...	

Figure H.1: Part of appointments scheduled for TAVR patient i .

Table H.1 provides the values that some of the variables would take in the example presented in Figure H.1. It can be observed that variable $w_{i,s}^h$ takes the value 1, once the time that a specific procedure is scheduled for comes, and for all future times after that. On the other hand, variable $y_{i,s}^h$ only takes the value 1 during the times that the patient is scheduled to go through a specific procedure s . Variable $x_{i,p}^d$ takes the value 1 only for the day that a patient is scheduled to go through a procedure p , while variable x_i^d takes the value 1 only for the days that the patient has an appointment scheduled. Finally, variables u_i^d and v_i^d give the earliest and the latest time that a patient is scheduled to be in a procedure on day d . Note that time in this case counts from the beginning of each day, and not from the beginning of the planning horizon.

Table H.1: Values that the variables take in the example illustrated in Figure H.1.

Variable	Value	Position	Time/Day
$w_{i,s}^h$	0	$s = 2$	$h \leq 19$
	1		$h \geq 20$
	0	$s = 4$	$h \leq 27$
	1		$h \geq 28$
	0	$s = 10$	$h \leq 165$
	1		$h \geq 166$
$y_{i,s}^h$	0	$s = 2$	$h \leq 19, h \geq 21$
	1		$h = 20$
	0	$s = 4$	$h \leq 27, h \geq 31$
	1		$h = 28, h = 29, h = 30$
	0	$s = 10$	$h \leq 165, h \geq 167$
	1		$h = 166$
$x_{i,p}^d$	0	$p = 1$	$d \neq 1$
	1		$d = 1$
	0	$p = 2$	$d \neq 1$
	1		$d = 1$
	0	$p = 5$	$d \neq 4$
	1		$d = 4$
x_i^d	0		$d = 2, d = 3$
	1		$d = 1, d = 4$
u_i^d	0		$d = 2, d = 3$
	20		$d = 1$
	22		$d = 4$
v_i^d	0		$d = 2, d = 3$
	30		$d = 1$
	22		$d = 4$

Appendix I: Simulation parameters used in the multi-appointment scheduling study

In this appendix, we include the parameters used in the simulations. In particular, Table I.1 includes the number of resources of each type that are present in the hospital. Based on these numbers, we generate the initial availability of resources.

Table I.1: Number of each type of resource present in the hospital.

Lab	#	Personnel	#
TTE	1	Electrophysiologist	1
Carotid ultrasound	1	Heart failure cardiologist	1
PFT	1	Cardiothoracic surgeon (x 6 types)	2
Cardiac catheterization	3	Interventional cardiologist (x 3 types)	1
CT scan	1	Nurse practitioner (x 3 types)	1
TEE	2	Echocardiogram doctor	1
PREP	6		
EP lab	2		
OR	7		
Hybrid OR	2		

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