ABSTRACT

Title of Dissertation:	ASSESSING THE IMPACT OF POLYPHARMACY ON THE ELDERLY USING NATIONALLY REPRESENTATIVE SURVEY DATA
	Adam Marcus Eschenlauer, Doctor of Philosophy, 2023
Dissertation directed by:	Dr. Luisa Franzini, Professor and Chair, Department of Health Policy and Management

Background: Polypharmacy is a growing issue that affects individuals of all ages yet is most prevalent among patients aged 65 and older with chronic comorbidities. Although integral to most treatment plans, pharmaceutical intervention may negatively impact one's health when five or more medications are taken daily. Given the concurrent rise in elderly population and polypharmacy prevalence, it is vital that we better understand the impact that concomitant medication use has on this vulnerable segment of population.

Purpose: This research examines the factors leading to polypharmacy among the elderly population and explores its various impacts on healthcare utilization.

Data and Methods: This study uses Medical Expenditure Panel Survey (MEPS) Data. Fixed-Effects regression analyses examine relationships between predictive factors and polypharmacy,

polypharmacy and expenditures, and polypharmacy and utilization. Classification models assess the ability of machine learning to correctly predict utilization within the sample population.

Key Results: Aside from clinical indicators, demographic and socio-economic factors play a role in determining polypharmacy status. Polypharmacy risk is higher for women (1.088, $p < 0.001$), high income individuals (1.107, $p < 0.01$), and those covered by Medicaid (1.110, $p < 0.001$). Conversely, married individuals (0.930, $p < 0.001$) and non-Hispanic Blacks (0.864, $p < 0.001$) have reduced risks of polypharmacy. We find polypharmacy to be associated with higher total ($p < 0.001$), inpatient ($p < 0.01$), outpatient ($p < 0.01$), and prescription medical expenditures ($p < 0.001$) when holding other predictors constant. We find the risk of hospitalization to be higher for polypharmacy patients (RR: 1.592, $p < 0.001$) than nonpolypharmacy patients after controlling for multimorbidity and medication class. Lastly, machine learning algorithms classify admissions with an overall accuracy of 84.9%; however, a low true positive rate (TPR) of 41.7% and high true negative rate (TNR) of 96.5% indicate best performance is achieved in predicting non-admissions.

Conclusion: Polypharmacy is associated with several non-clinical factors and has a statistically significant impact on medical expenditures and admissions. Though imperfect, predictive analysis methods improve our ability to identify patients at risk for admissions and present a potential opportunity for future applications aimed at reducing utilization and costs.

ASSESSING THE IMPACT OF POLYPHARMACY ON THE ELDERLY USING NATIONALLY REPRESENTATIVE SURVEY DATA

by

Adam Marcus Eschenlauer

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, College Park, in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2023

Advisory Committee:
Dr. Luisa Franzini, Chair
Dr. Jie Chen
Dr. Dahai Yue
Dr. Xuanzi Qin
Dr. Kerry M. Green, Dean's Representative

Dedication

In loving memory of my grandparents, Peter and Audrey Kehl, who filled my childhood with love, support, and lasting memories that I will cherish for eternity.

To my late father-in-law, Pablo Yataco, who always believed that I would one day become a doctor…although I am fairly certain he envisioned the white coat and stethoscope variety.

Acknowledgements

I would like to thank my amazing wife, Silvia, for her enduring love and support over the past 20 years. Your personal and professional sacrifices have directly enabled my career and allowed me to reach this very milestone. Your steadfast commitment to our children has shaped their character and enabled their personal and academic success. You are the love of my life and best friend. I love you so much! To our two children, Alec and Soleil, I want to thank you as well for the many sacrifices you have made over the years and for taking every move and change in stride. I am truly proud of your achievements and even more proud of the fine young adults you have become. I love you both very much and cannot wait to see what the future has in store for you!

I would also like to thank my parents, Ron and LouAnn, for raising me with a strong work ethic and exemplifying this trait in their daily lives. I am grateful for your continued love and support, and I know that you are proud of my accomplishments. I love you both very much! To my mother-in-law Rosa, I want to thank you for welcoming me to the family with open arms all those years ago. I especially want to thank you for remaining close with Alec and Soleil despite the many miles between us. Gracias por todo y te quiero mucho!

I would like to thank my academic advisor and dissertation chair, Luisa Franzini, for her mentorship, support, and willingness to work with my condensed timeline. I would also like to thank my dissertation committee, Jie Chen, Dahai Yue, Xuanzi Qin, and Kerry Green for their thoughtful feedback and support throughout the dissertation process. A special thanks to Xuanzi for sharing her expertise in

pharmaceutical research and agreeing to be part of this process while managing the move from Tennessee to Maryland.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Age-adjusted Charlson Comorbidity Index	ACCI
Adverse Drug Events	ADE
Adverse Drug Reactions	ADR
Agency for Healthcare Research and Quality	AHRQ
Akaike Information Criterion	AIC
Area Under the Curve	AUC
Bayesian Information Criterion	BIC
Centers for Medicare and Medicaid Services	CMS
Electronic Healthcare Records	HER
Food and Drug Administration	FDA
False Positive Rate	FPR
Generalized Linear Model	GLM
Healthcare Utilization Project	HCUP
Medicare Current Beneficiary Study	MCBS
Medical Expenditure Panel Survey	MEPS
National Drug Code	NDC
Over the Counter	OTC
Receiver Operating Characteristic	ROC
True Positive Rate	TPR
Variation Inflation Factor	VIF

Chapter 1: Introduction

Advancements in medicine over the past century have increased life expectancy as well as contributed to the population growth of individuals aged 65 and older. Individuals within this vulnerable group often experience worsening health and may present with comorbidities that require complex treatment. Pharmaceutical intervention, a vital component of these treatment plans, may negatively impact patient health and utilization when multiple medications are co-prescribed. Polypharmacy, the act of taking five or more chronic medications daily (Montero-Odasso et al., 2019), is a growing issue with ramifications for our healthcare system and the millions of elderly it impacts annually.

Each year, approximately 13.2 million adults aged 65 years and older are hospitalized in the United States (US) (*Changes in Hospitalizations, HCUP, 2021).* Hospitalizations alone account for one-third of total healthcare costs, with $1.19 trillion spent on hospital care in 2018 alone (Hartman et al., 2020). Aside from the financial impact, hospitalized elderly patients experience significant functional decline which results in their loss of independence, decreased quality of life, and an increased rate of readmissions (Courtney et al., 2011).

Over the past two decades, researchers have sought to better understand the relationships between polypharmacy and various health outcomes within the elderly population (Davies et al., 2020). While several studies have linked polypharmacy to falls, those attempting to examine the direct association between polypharmacy and hospitalizations have concluded with mixed results (Davies et al., 2020; Hammond & Wilson, 2013). Among studies that have suggested the existence of a positive

association between polypharmacy and hospitalization (Davies et al., 2020), however, few have adequately controlled for medication type or comorbidities in their study design (Chang et al., 2020).

Given the increasingly frequent use of polypharmacy to treat patients with comorbidities, there exists a critical need to better understand its impact on the elderly population. The overarching goal of this research is to better understand how polypharmacy affects the elderly and their use of healthcare services. The results will inform a growing body of research on the topic aimed at reducing the adverse effects of polypharmacy and improving health outcomes for our seniors. To further assess polypharmacy's impact on the elderly population, subsequent chapters will address three specific research aims:

1. Explore the predictors of polypharmacy among individuals aged 65 and older.
2. Estimate the association between polypharmacy and total medical expenditures among individuals aged 65 and older.
    a. Sub-aim: Estimate the marginal effects of polypharmacy across total, inpatient, outpatient, emergency room, and prescription expenditures.
3. Estimate the association between polypharmacy and hospital admissions among individuals aged 65 and older.
    a. Sub-aim: Explore the use of predictive analytics to classify patients at risk for hospitalization using polypharmacy status and other individual-level factors.
    b. Sub-aim: Estimate potential cost-savings associated with use of the best performing classification model.

Chapter 2: Literature Synthesis

Background

Polypharmacy, the concomitant use of multiple medications to treat one or more illnesses, is a growing concern among the elderly that has become more prevalent in recent years (Davies et al., 2020). As individuals age, they begin to experience an overall decline in health. This decline is often a direct result of chronic illnesses that impact an individual's normal physical or cognitive functioning. Identified as a primary risk factor for polypharmacy, the presence of comorbidities is shown to be positively correlated with age (Cantlay et al., 2016). As individuals progress beyond 65 years of age, the existence of multiple chronic illnesses complicates treatment. For these individuals, physicians must develop comprehensive medical management plans which incorporate various treatment modalities and therapeutics to include pharmacological intervention. Often, the complexities of these individual's conditions require the prescription of multiple simultaneous medications resulting in polypharmacy. Additionally, system-level factors including poorly updated medical records, automated prescription refills, and inappropriate prescribing practices further attribute to polypharmacy risk (Halli-Tierney et al., 2019).

The use of multiple drugs to treat complex chronic illnesses has led to a high prevalence of polypharmacy within the elderly population. Recent estimates indicate 25 to 40% of all adults over the age of 65 are prescribed at least 5 medications (Todd et al., 2018). With an elderly population of 54.1 million in the United States (US), between 13.5 to 21.6 million seniors are impacted by polypharmacy (*2020 Profile of Older Americans*, n.d.). As the population ages and the proportion comprised by those

65 and older continues to grow, it is expected that the number affected by polypharmacy could reach 32.3 million by 2040 (*2020 Profile of Older Americans*, n.d.). While medications have many proven benefits, polypharmacy has been associated with serious adverse events such as falls, frailty, disability and mortality within the elderly population (Montero-Odasso et al., 2019). With a growing elderly population and polypharmacy prevalence on the rise, research into polypharmacy's effect on the elderly continues to expand.

As research into polypharmacy grows, their remains a general lack of consensus surrounding how it is defined. A systematic review by Masnoon et al. (2017), found 138 definitions of polypharmacy and associated terms among existing literature (Masnoon et al., 2017). Among the available literature, polypharmacy was most commonly defined as the simultaneous use of five or more chronic medications daily (Montero-Odasso et al., 2019). Hyperpolypharmacy was consistently used to describe the concomitant use of 10 or more medications (Masnoon et al., 2017).

Like the variance in definition described above, the variable construct of polypharmacy also differed across studies. Polypharmacy was most frequently depicted in studies as a dichotomous exposure variable where the simultaneous prescription of less than five medications constituted the control arm (nonpolypharmacy) and the prescription of five or more medications represented the treatment arm (polypharmacy) (Davies et al., 2020; T. R. Fried et al., 2014). Others ascribed to similar methodologies using different thresholds to define polypharmacy. A review of international studies conducted in Australia indicated the threshold varied from two to five concomitant medications with four medications being the

most frequently used threshold for polypharmacy (Hammond & Wilson, 2013). A few studies recoded polypharmacy into a categorical exposure variable using similar thresholds (Young et al., 2021). The numerous definitions of polypharmacy and its varied use in studies add to the diverse and complex nature of polypharmacy research.

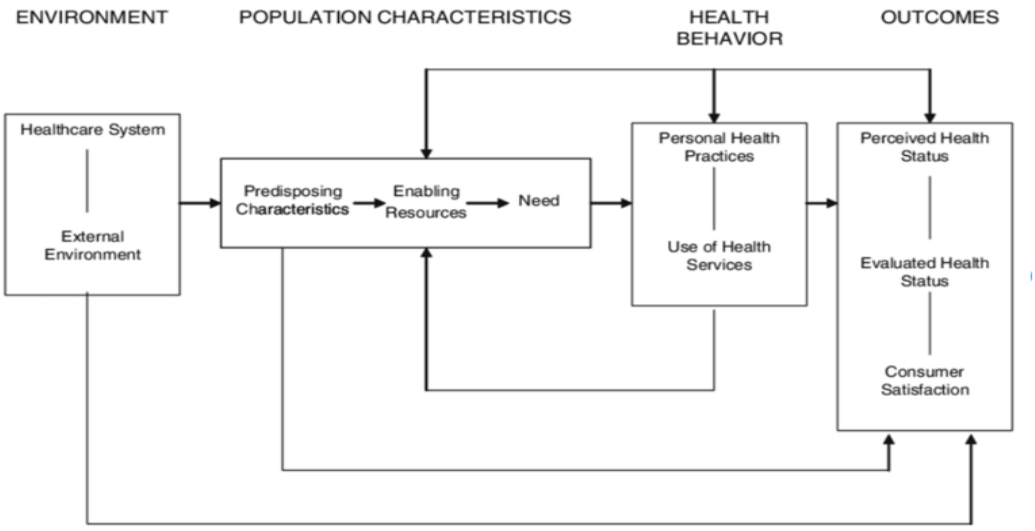
Identified as a potential contributing factor to poor health outcomes among the elderly, polypharmacy related research has grown steadily since the early 1990s (Davies et al., 2020). Studies on polypharmacy have largely sought to determine its association with a variety of adverse outcomes; these outcomes range from specific physical ailments to measures of healthcare utilization (Davies et al., 2020). Physical ailment-based studies have sought to examine polypharmacy's impact on Body Mass Index (BMI), circulatory disease, depression, functional decline, falls, fractures, frailty, malnutrition, and pain. Utilization based studies have primarily examined polypharmacy's association with hospital admissions; however, studies have also been conducted to determine its impact on emergency department visits and length of inpatient stays (Davies et al., 2020).

Conceptual Frameworks

A review of the existing literature on polypharmacy has not revealed an overarching conceptual model that is central to all studies. Additionally, studies evaluating the association between polypharmacy and hospitalization have not ascribed to a conceptual framework as the basis for their analyses (Chang et al., 2020; Davies et al., 2020). If a conceptual model were to be loosely applied to these types of studies, Anderson's Emerging Behavioral model (see Figure 2.1) would likely be

the best fit due to its focus on factors impacting utilization broadly (R. M. Andersen, 1995).

Figure 2.1: Andersen's Emerging Behavioral Model – Phase 4



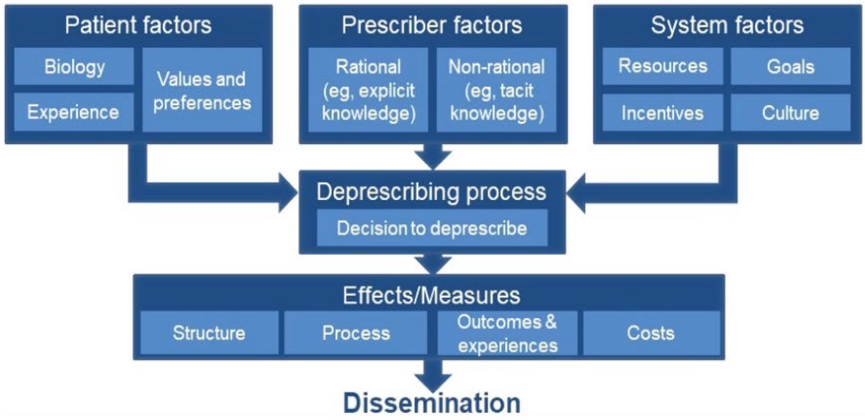
Source: "Revisiting the behavioral model and access to medical care: Does it matter?" R.M. Andersen, 1995, Journal of Health and Social Behavior, 36.

Frequently, polypharmacy researchers have developed their own conceptual model to explain any number of aspects affected by polypharmacy among the elderly. Most polypharmacy-related conceptual models mentioned in the literature combine a deprescribing framework with the predisposing, enabling, and need factors from Andersen's Behavioral Model (R. Andersen & Newman, 1973) to explain the general concepts related to prescribing and medication use (Linsky et al., 2019). These conceptual frameworks typically comprise patient, prescriber and system factors that interact to explain prescribing practices and medication use among polypharmacy patients (Ouellet et al., 2018; Thompson et al., 2019).

To better illustrate the complex factors impacting polypharmacy and deprescribing efforts, Linsky et al. developed a novel conceptual framework in 2019

(see Figure 2.2) that incorporated key components from existing models into one; organized into patient, prescriber and system factors, this model was designed to be more comprehensive than those developed previously (Linsky et al., 2019). The model illustrated below is unique due to its incorporation of concepts from both Andersen and Donabedian (Donabedian, 1988); the factors are loosely based on Andersen while the effects/measures section uses Donabedian to assess quality of deprescribing trials based upon the four categories (Linsky et al., 2019).

Figure 2.2: Advancing the Science of Deprescribing: A Novel Comprehensive Conceptual Framework



Source: Amy Linsky MD, Journal of the American Geriatrics Society, Volume: 67, Issue 10, Pages: 2018 - 2022

It is important to note, however, that deprescribing frameworks such as Linsky's are not specifically designed to explain the association between polypharmacy and changes in health services utilization. In a study by Barnason et al. (Barnason et al., 2010), social cognitive theory was used as opposed to a deprescribing framework due to its ability to better explain the intersectionality between personal, behavioral, and environmental factors (Heffernan, 1988). The use of social cognitive theory was primarily used in a small subset of studies that examined theory-based interventions designed to improve medication adherence

(Patton et al., 2017). It is important to note that while some studies involving polypharmacy did ascribe to a conceptual model, it was primarily studies that evaluated deprescribing efforts that did so.

Impacts on Health and Utilization

An often-necessary component in the management of chronic illnesses, Polypharmacy is thought to negatively impact one's health in several ways that lead to increased healthcare utilization. Three of the leading contributors to increased health services utilization among the elderly are Adverse Drug Events, cognitive and functional decline, and falls (Cantlay et al., 2016). Hospitalizations among the elderly are especially costly and have a deleterious effect on the health of the elderly population. When compared with the non-elderly, data from the Medicare Current Beneficiary Study (MCBS) shows medical expenditures more than double for individuals between the ages of 70 and 90; moreover, this 10 percent of the population is responsible for nearly 52 percent of the overall spending within a given year (Nardi et al., 2016).

Aside from the monetary impact of their inpatient stay, elderly patients undergo many life-altering changes as result of their hospitalization. While admitted, elderly patients experience significant functional decline resulting in their loss of independence, decreased quality of life, and an increased rate of readmissions (Courtney et al., 2011). In-hospital factors leading to functional decline include restricted mobility, under-nutrition, continence, and polypharmacy; adverse outcomes to medications occurred 2.5 times more frequently in patients over the age of 65 (Admi et al., 2015). For many of these patients, hospitalization marks the beginning

of a heightened reliance on medical services that becomes more profound with age. Given the rising number of elderly and exorbitant healthcare costs associated with the care of this population, examination of mechanisms leading to increased healthcare utilization among this group has become increasingly important.

Adverse Drug Events

Adverse Drug Events (ADEs) or Adverse Drug Reactions (ADRs) are a primary cause of hospitalizations among the elderly. Defined as unintended, harmful events attributed to the use of medications, ADRs are more common among individuals who take multiple medications daily (Coleman & Pontefract, 2016). From 2007 to 2009, ADEs were implicated in an estimated 265,802 emergency room visits resulting in 99,628 hospitalizations among US adults age 65 and older; 48% of these hospitalizations were among adults 80 years of age or older (Budnitz et al., 2011). The rate of ADE-induced hospitalizations was 3.5 times higher for adults 85 years of age and older (Budnitz et al., 2011). The high rate of hospitalization among the eldest indicates an increased susceptibility to adverse effects of polypharmacy as one progresses in age.

Elderly patients are at increased risk for Adverse Drug Events (ADE) caused by polypharmacy due to pharmacokinetics and pharmacodynamics, reduced physiological reserve, multimorbidity, geriatric syndromes and physician prescribing practices (Held et al., 2017). The risks associated with ADEs increase exponentially as the number of concomitant medications increase. Crouch and Chapelhow (2008) suggest that with two drugs there are two possible interactions; with five drugs the possible interactions increase to 20 and with ten drugs there are 90 possible

interactions (Kaufman, 2011). This amplification effect further compounds issues for the elderly, especially those above 80 years old who are the most frail and susceptible to adverse events from drug interactions.

Interactions and Non-Adherence

Adverse Drug Events often occur due to prescribing of potentially inappropriate medications (PIMs) that lead to drug-drug interactions (DDI), drug-disease interactions, and medication non-adherence (Young et al., 2021). Adverse Drug Reactions are further classified into six types: dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of Use), and failure of therapy (Failure) (Edwards & Aronson, 2000). The mean prevalence of ADR-induced hospitalizations within the elderly population is 10%, while the prevalence occurring during hospitalization is 11.5% (Alhawassi et al., 2014). Among the medications responsible, anticoagulants, antibiotics, and diabetes medications were implicated in nearly 47% of all admissions (Shehab et al., 2016). Benzodiazepines and Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) represented other classes of medication frequently implicated in previous studies (Abe et al., 2015). Despite being frequently implicated within research, the above medications are not listed as top causes of ADRs in all studies.

Efforts to limit the potentially harmful effects of polypharmacy within the elderly population led to the creation of the Beers Criteria by Dr. Mark Beers and colleagues in 1991 (Beers et al., 1991). This criteria contained a list of medications for which the potential risks of use outweighed the potential benefits (Beers et al., 1991). Updated on a continual basis, a partial list was adopted by the Center for

Medicaid and Medicare Services (CMS) as a quality indicator to be used for long-term care facilities (LTCF) (Marcum & Hanlon, 2012). In 2006, the National Committee for Quality Assurance (NCQA) selected some of the "do-not-use" and drug-disease interaction criteria to be used as ambulatory care quality indicators as one of their Healthcare Effectiveness Data and Information Set (HEDIS) measures (Marcum & Hanlon, 2012). In 2011, control of the list and the responsibility to update and maintain it, transferred to the American Geriatric Society (AGS) where it continues to serve as the primary set of criteria used today (American Geriatrics Society Beers Criteria® Update Expert Panel, 2019).

Identification of ADRs is often made difficult by the fact that some emulate 'traditional diseases' and manifest in all systems of the body (Coleman & Pontefract, 2016). Patients admitted for drug-related reasons exhibit a broad range of symptoms including weakness or drowsiness, biochemical or hematological derangements (such as acute kidney injury, electrolyte imbalance or anemia), bleeding, gastrointestinal disturbances, hypoglycemia or healthcare-associated infections (Coleman & Pontefract, 2016). In some instances, ADRs may be fatal; fatal cases involving ADRs are often attributed to hemorrhages caused by the co-administration of anticoagulants and NSAIDs (Wester et al., 2008).

Systematic reviews of the literature found both study designs and the size of the sample populations used across studies to vary greatly (Alhawassi et al., 2014; Davies et al., 2020). The range between the smallest and largest sample populations used across studies was 64,366, with 80 (De Paepe et al., 2013) and 64,446 (Sikdar et al., 2012) representing the smallest and largest samples respectively. Studies were

also found to have used various definitions of polypharmacy which led to different thresholds being used throughout the research (Davies et al., 2020). Despite the variance among studies, nearly all indicated a positive association between polypharmacy related adverse medication management outcomes such as drug-drug interactions and non-adherence which supports generalizability of the results (Davies et al., 2020).

Falls

An unfortunate consequence of drug-drug or drug-disease interactions, falls, constitute a substantial proportion of adverse drug events and function as a mediator between polypharmacy and hospitalization. Within the elderly population, falls can have a long-standing negative impact on an individual's health. Studies have indicated that polypharmacy may increase the risk of falls among the elderly by five times (Montero-Odasso et al., 2019). In 2009 alone, there were more than 2.2 million non-fatal fall injuries in the United States that resulted in 581,000 hospitalizations (Ambrose et al., 2013). Annually, 30-40% of patients over the age of 65 will fall at least once; many of these falls will result in emergency rooms visits and subsequent hospitalizations (Ambrose et al., 2013). Approximately 40% of annual falls, however, could be preventable (Zaninotto et al., 2020).

The risk of falls among the elderly have been linked to several factors including female sex, older age, multimorbidity, muscle weakness, poor balance and lower-limb functioning, visual impairment, history of stroke, dementia, epilepsy, hypotension, and history of previous falls (Deandrea et al., 2010). Additionally, specific drug classes including antihypertensives, analgesics, sedatives, anti-

depressants, and anticholinergics may increase the risk of falls and related injuries (Tinetti et al., 2014; Woolcott et al., 2009). Benzodiazepines and non-benzodiazepine hypnotics may also increase the risk of fall (Johnell et al., 2017). While "fall-risk inducing drugs" (FRIDs) carry secondary effects including dizziness, imbalance, and mobility impairment that alone lead to an increased risk of falls (Seppala et al., 2018), additional studies have shown that the number of simultaneously prescribed medications may also play a role in increasing fall risk among the elderly (Dhalwani et al., 2017; T. R. Fried et al., 2014).

Studies evaluating fall-risk in relation to polypharmacy have shown the risk of falls to be positively correlated with the number of medications taken. A case-control study by Laflamme et al estimated the fall risk associated with the concomitant use of $\geq$10 medications to 1.8 times greater than the risk associated with using only one medication (Laflamme et al., 2015). Five separate cohort studies conducted by Kojima, Bergland, Clough-Gorr, Pluijm, and Bennet all found similar results (Morin et al., 2019). The fact that these studies were conducted in the United States, Europe, and Asia are a testament to the generalizability of the results.

Functional Decline (Frailty)

Multimorbidity in patients over the age of 65 is a common occurrence that contributes to disability and functional decline. Medicare claims data indicates that 67% of all beneficiaries had two or more chronic conditions (T. R. Fried et al., 2014). The prevalence of multimorbidity increased to 81.5% among beneficiaries 85 years of age and older (Salive, 2013). The presence of multiple chronic conditions in the elderly often leads to an overall degradation of health. This decline in functional

ability can lead to frailty, making those patients more susceptible to poor health outcomes and further reliant on health services.

Frailty represents an additional mechanism leading to increased healthcare utilization that may be worsened by polypharmacy. A geriatric syndrome characterized by a reduction in physiological reserves and loss of resistance to stressors as a result of increasing age, frailty serves as a measure of disability and functional decline among the elderly (Midão et al., 2021). Frailty may also influence several factors that impact the therapeutic efficacy of drugs to include pharmacokinetics and pharmacodynamics, as well as toxicity (Gutiérrez-Valencia et al., 2018). Polypharmacy and frailty are imagined to interact across a number of pathways to include through physiological changes, multiple pathologies and chronic disease, life expectancy, or functional or cognitive status (Gutiérrez-Valencia et al., 2018). Synonymous with disability, comorbidity and other characteristics, frailty is considered by some to have a biological basis and be a distinct clinical condition (L. P. Fried et al., 2001). Frailty is most frequently assessed in both research and clinical practice using the Frailty Phenotype (L. P. Fried et al., 2001; Kojima et al., 2018).

Frailty and polypharmacy are both widely studied among the elderly population; however, little is known about the impact they have on one another (Palmer et al., 2016). A systematic review of the literature conducted by Gutierrez-Valencia et al. included 25 observational studies; 11 of the studies were conducted using cross-sectional analysis while the other 14 were prospective cohort studies (Gutiérrez-Valencia et al., 2018). Quality of the studies were assessed using the Newcastle-Ottawa Scale (NOS) (Stang, 2010) for longitudinal studies and a modified

NOS as described in two separate studies by Herzog and Alshabanat (Alshabanat et al., 2015; Herzog et al., 2013). The quality of studies when evaluated for risk of bias were good; longitudinal studies had a median score of 7.5 out of 9 while the cross-sectional studies had a median score of 8 out of 10. Results suggest adjustments made for confounding performed fairly well to reduce bias within the models (Gutiérrez-Valencia et al., 2018).

Differences in study design to include the definitions and categorizations of polypharmacy and frailty used across studies make generalization of the results difficult. Most studies defined polypharmacy as the concomitant use of five or more medications; however, some studies used thresholds of three and six while others decided to create a third category for medication use ≥10 labeled as either hyper or excessive polypharmacy (Herr et al., 2017; Poudel et al., 2016). Across the 25 studies, 5 different measurements for frailty were used; however, Fried's criteria was used as the primary basis for 14 of the studies (Gutiérrez-Valencia et al., 2018). The sample sized used in the studies varied greatly from 31 (Hilmer et al., 2011) to over 10,000 (Chhetri et al., 2017). Small sample sizes like the one used in Hilmer often reduces the statistical power of the study as well as increase the margin of error; it also tends to lead to cases of bias and thus carries little weight among the studies conducted.

Overall results from the 25 studies were mixed. Differences in outcomes among the studies can occur due to a variety of factors; however, the use of multiple study designs is likely a main contributor to the differences in findings among the 25 studies referenced in the systematic review. Despite the differences in outcomes,

many studies found polypharmacy to be positively correlated with frailty (odds ratio 1.77-2.55) (Gutiérrez-Valencia et al., 2018). The likelihood of being frail among hyperpolypharmacy (≥10) users was much higher with odds ratios of 4.47-5.8 (Gnjidic, Hilmer, Blyth, Naganathan, Cumming, et al., 2012; Herr et al., 2015). A few studies were able to show that the likelihood of frailty increased incrementally with each medication added (odds ratio 1.13-1.20) (Castell et al., 2013; Gnjidic et al., 2012). While results of the referenced studies indicate the presence of an obvious relationship between polypharmacy and frailty, no direct link has been established. Additionally, no expressed attempts to evaluate the joint impact of polypharmacy and frailty on health services utilization were found among the literature.

Cost

A review of the existing literature has revealed that cost-based research involving polypharmacy is less extensive than the outcomes-based research described above. Some cost-based research involving polypharmacy has attempted to assess the impact of medication review/reconciliation on cost reduction to patients (Malet-Larrea et al., 2017). Others have assessed polypharmacy-related medication costs attributed to patients with terminal illnesses such as cancer (McDermott et al., 2018). In their "Polypharmacy Outcomes Project", Kojima et al. conducted a study using long-term care residents at nursing home in Hawaii to determine the overall monthly costs of medications among those with polypharmacy (Kojima et al., 2012). During the study, the Beers Criteria was used to identify and reduce the use of drugs deemed potentially harmful when used in the elderly population. Average pre- and post-intervention monthly per-patient medication costs were calculated. Pre and post-

intervention monthly costs were $874 and $843 respectively; marking a $30 decrease attributed to the intervention (Kojima et al., 2012).

Much of the existing cost-based research examines the medical costs attributed to fatal falls and fall injuries using either data derived from the Web-based Injury Statistics Query and Reporting System (WISQARS) or the Medicare Current Beneficiary Survey (MCBS) (Florence et al., 2018; Haddad et al., 2019). Results from these studies indicated that total healthcare spending on elderly falls ranged from $48 million in Alaska to $4.4 billion in California (Haddad et al., 2019). When reviewed based upon Medicare being the primary payer, Florida had the highest fall-related expenditures at $3 billion (Haddad et al., 2019). Using an estimated fraction of total healthcare expenditures attributed to falls derived from the MCBS, Florence et al. applied that fraction to the total U.S. Healthcare Expenditures from the Centers for Medicare & Medicaid Services (CMS) National Health Expenditure Accounts (NHEA) to arrive at an estimated annual cost of $49.5 billion nationally (Florence et al., 2018). Although these studies focus on the cost attributed to falls, a common adverse drug event, no analysis was conducted to estimate the proportion attributable to polypharmacy.

Kwak et al. (2022), however, examined healthcare expenditures associated with polypharmacy among elderly patients with cardiovascular disease using 2017 Medical Expenditure Panel Survey (MEPS) Data. This study found polypharmacy to be positively associated with increased total healthcare expenditures (IRR 1.98, 95% CI 1.43-2.74); associations with total polypharmacy-related and total nonpolypharmacy-related expenditures were (IRR 2.87, 95% CI 1.51-5.45) and (IRR

1.78, 95% CI 1.26-2.52) respectively (Kwak et al., 2022). Following adjustment for covariates, average total healthcare expenditures among polypharmacy patients were 2.16 times greater than nonpolypharmacy patients ($19,068 : $8,815) (Kwak et al., 2022). Limited by its narrow sample population (elderly cardiovascular patients) and use of a single year of data, expanded research on the association between polypharmacy and total medical expenditures is needed to improve generalizability of the results.

Predictive Analyses

Advancements in computing technology has contributed to the growth of applied machine learning. A convergence between computer science and advanced statistics, machine learning has made it possible to automate the process of finding patterns within data. These methods are used quite frequently within the business community; however, they have only recently made their way into the medical/public health realm. As research into the use of applied machine learning within the medical field continues to grow, findings suggest these methods have many potential applications and deliver great value to the field (Kim & Park, 2019; Orchard et al., 2018; Peterson et al., 2021; Staffa & Zurakowski, 2021).

To date, applications for predictive analysis with the medical field range from the identification of chemotherapy patients at high risk for preventable emergency department visits and hospital admissions to predicting 1-year mortality rates for palliative care patients (Blanes-Selva et al., 2021; Peterson et al., 2021). A study by Peterson et al. (2021), found their primary model to have classified preventable acute care use (ACU) with an area under the curve (AUC) of 0.783 (Peterson et al., 2021).

This finding suggests that the model can correctly distinguish between the true positive rate (TPR) and false positive rate (FPR), positive class and negative class, 78% of the time. Another study by Li et al. (2021), attempted to predict 90 day hospital readmissions for dental patients; their best performing model was able to correctly distinguish between those who would be admitted and those who would not 74% (AUC = 0.743) of the time (Li et al., 2021).

Most predictive analysis studies examined utilized Electronic Health Record (EHR) data (Patel et al., 2020; Peterson et al., 2021); however, others used nationally representative data (Kim & Park, 2019; Li et al., 2021). Kim et al. (2019) utilized Korea's National Health Insurance Service (NHIS) data set to develop a model to predict high-cost health care users using medical check-up data (Kim & Park, 2019). Using this nationally representative data base, they were able to develop their optimal model (AUC = 0.838) using the full complement of variables derived from eligibility, diagnosis, medical check-up and cost and utilization data (Kim & Park, 2019).

These predictive models have the real potential to impact both patients and the healthcare industry. Li et al.'s (2021) study demonstrated that use of their predictive model to predict all-cause 90 day readmissions would result in a potential annual savings of over $500 million (Li et al., 2021). Existing research also points to the benefits of using machine learning over traditional risk scoring systems. Patel et al. (2020) demonstrated that machine learning approaches outperformed the traditional LACE and HOSPITAL indices which are commonly used to identify a patient's risk of readmission (Patel et al., 2020). The key advantages attributed to machine learning methods over traditional (questionnaire) scoring systems are their ability to be applied

to real data and detect underlying patterns in high-dimensional data sets (Patel et al. 2020). Within the above studies, no mention was made to polypharmacy or any attempt to evaluate the impact it has on any specific population.

Limitations and Gaps in Existing Research

Existing literature on polypharmacy indicates that several studies examining the association between polypharmacy and healthcare utilization have been conducted. Among those that examined the association with hospital admissions, the majority found polypharmacy to be positively correlated; however, many of the studies failed to sufficiently control for multimorbidity and medication class within their design (Davies et al., 2020). Given that many medications have secondary effects that mimic the symptoms of some chronic conditions, failure to control for the presence of comorbidities may lead to an overestimation of the effect attributed to polypharmacy. Additionally, many high-risk medications are often prescribed that carry an elevated risk of adverse drug events (Alhawassi et al., 2014; Johnell et al., 2017; Seppala et al., 2018). These medications must be controlled for as they have the potential to produce a drug-induced hospitalization in the absence of concomitant medications.

Among previous studies, several generalized limitations were noted that could have impacted their findings. While all the studies reviewed used the elderly as their sample population, some chose to use a subset of the population that was markedly older (> 80 years) than those selected in other studies (Abe et al., 2015; Hammami et al., 2020). Those who comprise the subset population would be more likely to be frail, have a higher number of comorbidities, and use a greater number of

medications. The discrepancies across sample populations would prohibit generalization of the results. Additionally, the high degree of specificity used to define sample populations often resulted in small (< 400) sample sizes (Abe et al., 2015; Hammami et al., 2020). Due to the age of the individuals that comprised the sample populations, all studies could have potentially been affected by threats to internal validity through maturation. As individuals age, their decreased physical reserve makes them more susceptible to adverse health outcomes (L. P. Fried et al., 2001; Herr et al., 2015); natural losses in physical strength and cognitive function may mimic symptoms of polypharmacy and lead one to believe that the impact of polypharmacy is larger than it is.

Despite the breadth of previous research on the topic, gaps still exist that demand further inquiry. While several studies have attempted to examine the association between polypharmacy and hospital admissions (Abe et al., 2015; Chang et al., 2020; T. R. Fried et al., 2014), they have largely failed to control for both comorbidities and medication class. Additionally, no studies were found that attempted to identify causality or association using US nationally representative survey data. The use of a large sample population in conjunction with nationally representative data that incorporates accurate sample weights and survey design would add to the robustness and generalizability of the study.

There exists a definitive gap in knowledge concerning the non-pharmaceutical cost impact of polypharmacy. Cost-based polypharmacy research should aggregate financial data at the individual and medical system levels. Prospective studies should include both prescription-related costs and direct costs related to medical care

received. Research in this area would provide a deeper understanding of polypharmacy's overall fiscal impact to our healthcare system and the burden it places on patients.

Lastly, it is imperative that new and innovative ways to identify at-risk polypharmacy patients are developed. The use of classification models applied to patient data is a potential way to achieve this goal. Over the past decade, a growing body of research has sought to apply predictive analytics models to Electronic Healthcare Records (EHR) to reduce potentially avoidable utilization and costs (Lee et al., 2020). Although 69% of the studies reported improvement after model implementation, they lacked generalizability (Lee et al., 2020). Building and testing of potential classification models using nationally representative data would improve generalizability of the results and add to the growing body of research on the use of predictive analytics in healthcare settings.

Chapter 3: Study Design

Data

This study utilizes ten years (2010-2019) of compiled Medical Expenditure Panel Survey (MEPS) data. MEPS is a large-scale, nationally representative panel survey of families, individuals, medical providers, and employers in the U.S. (*MEPS | Home*, n.d.). The panel design consists of several rounds of interviews with respondents over a period of two calendar years; the interviews collect data on demographics, individual health status, expenditures, and insurance coverage (*MEPS | Background, n.d.).* Overall survey response rates ranged from 39.5% to 56.3% with its lowest and highest rates seen in 2019 and 2012, respectively (*MEPS | Response Rates*, n.d.). Data files from 2020 were purposefully omitted from this study to avoid anomalies that may have resulted due to the COVID-19 pandemic. All data files used in this analysis are publicly available and downloadable from the Agency for Healthcare Research and Quality (AHRQ) website.

To build a comprehensive data set capable of answering the various questions posed in this study, Household Full Year Files were joined with their respective Prescribed Medicines and Hospital Inpatient Stay Component Event files. All three files were joined using the "DUPERSID" variable in the MEPS file. This variable combines the panel number ("PANEL"), dwelling unit identifier ("DUID"), and person identifier ("PID") into one variable that allows for accurate matching of each observation across all three data files (*IPUMS MEPS*, n.d.). However, prior to 2018, the "DUPERSID" variable only contained the "DUID" and "PID". Thus, the

"DUPERSID" variable had to be concatenated with the "PANEL" variables for years 2010-2017 prior to being joined.

Prior to final consolidation of years 2010-2019, each individual year was carefully examined against the others to ensure that variable names and constructs aligned. This approach prevented the inadvertent creation of additional variables, missing values, and allowed for successful matching in the final data set. The resulting annual combined files were then appended to create one large file containing 10 years of merged data. The full data set prior to cleaning and implementation of exclusion criteria totaled 304,580 respondents.

Exclusion Criteria and Missing Values

The target population for this study is individuals aged 65 and older. To ensure only our target population was used in the analysis, all observations for individuals under the age of 65 were removed from our data. Likewise, observations with missing values on one or more of our variables of interest were also omitted from the final data file. Following extensive data cleaning and preparation, the final data set contained 13,338 total observations and 166 variables. The total number of variables also incorporates variations and/or modifications of variables; not all variables represent independently unique measures.

Age-adjusted Charlson Comorbidity Index (ACCI)

Disease severity among patients was ascertained using the Age-adjusted Charlson Comorbidity Index (ACCI) (M. Charlson et al., 1994). This score was calculated by assigning severity-based weights to individual chronic illness and age

variables in the data (see Table 3.1); the weighted values were then grouped by patient and summed to generate respective ACCIs. To improve interpretation of results and allow for group-wise comparison, patients were further categorized into three groups based upon comorbidity severity using their ACCIs: mild (≤ 5), moderate (6-7), and severe (≥ 8). This categorical construct of ACCI was used as the primary measure of disease severity across all aims as it has been shown to be a robust proxy for the inclusion of individual chronic illness variables within regression models (M. E. Charlson et al., 2022; Ludvigsson et al., 2021). Additionally, the use of ACCI as our primary measure of disease severity reduces the potential for bias by eliminating prospective correlation that exists between individual chronic illnesses and medication class.

Table 3.1
Age and chronic illness associated Charlson weights

Variable	*Weight*	*N (%)*
Age (Years)		
65-69	3	4,335 (32.5%)
70-79	4	5,798 (43.5%)
80-89	5	3,205 (24.0%)
Arthritis	1	8,198 (61.5%)
Cancer	2	3,934 (29.5%)
Cognitive Limitations	2	1,639 (12.3%)
Diabetes	1	3,568 (26.8%)
Emphysema	1	840 (6.3%)
Heart Attack	1	1,562 (11.7%)
Stroke	1	1,704 (12.8%)

Note: Age-related weights are calculated by adding one point for each decade of age beginning at age 40 (M. Charlson et al., 1994). The minimum and maximum ages represented in the sample are 65 and 85; minimum and maximum ACCIs are 3 and 13, respectively.

Polypharmacy

Throughout the study, the term polypharmacy is used to define individuals who take five or more medications daily. The term hyperpolypharmacy defines individuals who take 10 or more medications daily and is only used in categorical constructs of the polypharmacy variable (Kennel et al., 2018). Lastly, nonpolypharmacy is the term used for patients who take four or less medications daily.

Polypharmacy status was ascertained using the prescription name variable "RXNAME" to identify uniquely prescribed medications for everyone in our sample. Uniquely prescribed medicines were summed for each respective individual; totals were assigned to a new variable "TOTMEDS" which was then used to divide the sample population into groups representative of their polypharmacy status. To ensure that no duplicate medications were included in our count, the prescription name was cross reference with two additional variables: prescription drug name "RXDRGNAM" and prescription national drug code "RXNDC." National Drug Codes (NDC) are a unique three-segment number used to identify all medications authorized for human use (*FDA*, 2019). Among the 13,338 individuals represented in our sample, 7,354 (55%) were polypharmacy and 5,984 (45%) were nonpolypharmacy. Additionally, 2,315 (31%) of the polypharmacy patients met the threshold for hyperpolypharmacy.

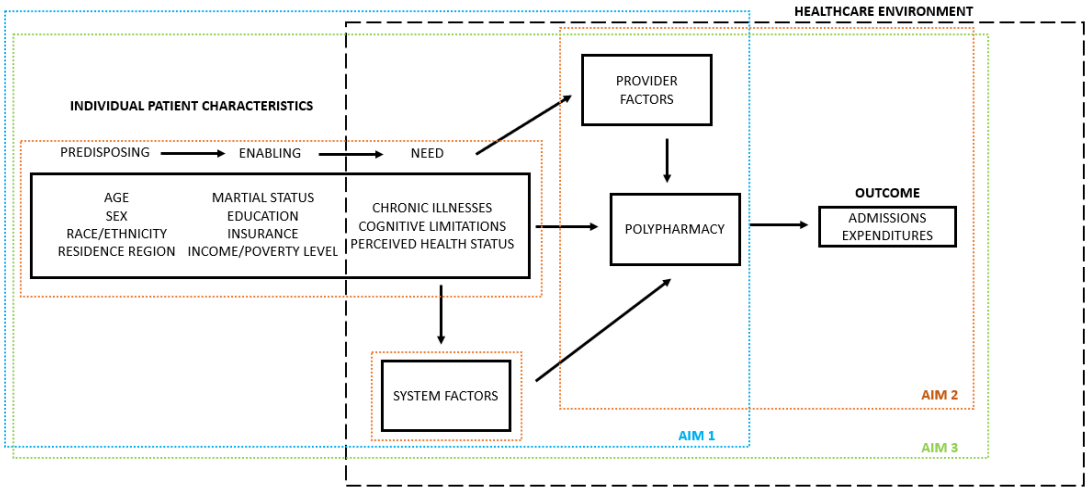
Overarching Conceptual Framework

The conceptual framework used in this study was adapted from three distinct conceptual models: Andersen's Model of Healthcare Utilization, Ryvicker's

Behavioral-Ecological Model, and Linsky's Novel Deprescribing Framework (R. M. Andersen, 1995; Linsky et al., 2019; Ryvicker, 2018). Depicted in Figure 3.1, the framework highlights polypharmacy's relationships with a myriad of individual and system-level factors (see Figure 3.1). Moving from left to right in the model, we note that Anderson's concepts of predisposing, enabling, and need-based factors are recognized as primary contributors to polypharmacy (R. M. Andersen, 1995). Comprised of demographic, socioeconomic, and clinical factors, these individual patient characteristics converge to create a synergistic effect on one's health that leads to a patient's interaction with the healthcare environment.

The relationship between individual patient characteristics and polypharmacy is further mediated by provider and system-level factors that operate within the healthcare environment. On the provider side, factors such as medical specialty and experience will affect their prescribing preferences and may impact polypharmacy. Likewise, system-level factors including pharmacy type and location may also represent a contributing factor. Collectively, individual, provider, and system-level factors all have a varying impact on polypharmacy status which in turn is thought to be independently associated with both healthcare utilization and expenditures. Elements of the conceptual framework that correspond with each research aim are outlined and demarked by color in Figure 3.1.

Figure 3.1: Polypharmacy's Role Within the Elderly Population: A Novel Conceptual Framework



Adapted from elements of Andersen's Emerging Model – Phase 4 (Andersen,1995), Ryvicker's Behavioral-Ecological Framework (Ryvicker, 2018), and Linsky's Novel Deprescribing Framework (Linsky et al., 2019).

Chapter 4: Exploring the Predictors of Polypharmacy Among Individuals Aged 65 and Older

Introduction

Polypharmacy's rise in prevalence has made it a major public health issue globally (Payne & Avery, 2011; Tang et al., 2022). Most commonly defined as the concomitant use of 5 or more medications daily (Masnoon et al., 2017), polypharmacy is most prevalent among elderly patients with chronic multimorbidity (Davies et al., 2020). Affecting upwards of 50% of all Medicare patients in the US (Tinetti et al., 2004), polypharmacy prevalence varies greatly by country (Khezrian et al., 2020). With polypharmacy rates as high as 90% across some populations (Khezrian et al., 2020), it is vital that the mechanisms leading to polypharmacy are better understood.

Background

Research into the predictive factors of polypharmacy among the elderly has grown in response to the rise of polypharmacy prevalence worldwide. While an equally important issue to the United States (US) population, the majority of studies designed to explore the predictors of polypharmacy directly were conducted in Europe and Asia (Jyrkkä et al., 2009; Rieckert et al., 2018; Wongpakaran et al., 2018). Existing studies have examined associations between polypharmacy and a variety of factors representing demographic, socioeconomic, and clinical characteristics (Khezrian et al., 2020). Several studies have found independent associations between polypharmacy and prominent chronic illnesses including diabetes, heart disease, HIV/AIDS, anxiety, and depression (Ellenbogen et al., 2020;

Jokanovic et al., 2015; Jyrkkä et al., 2009); these studies all indicated the presence of chronic illnesses to increase the odds of polypharmacy. Higher degrees of multimorbidity were also found to be positively associated with polypharmacy (Rieckert et al., 2018; Wongpakaran et al., 2018).

Although studies have consistently found positive associations between polypharmacy and chronic illnesses, research into associations between polypharmacy and demographic factors have delivered mixed results. While several studies have indicated increases in age to be positively associated with polypharmacy (Jyrkkä et al., 2009; Tang et al., 2022), others have found the association to be negative, particularly in patients aged 85 and older (Jokanovic et al., 2015; Rieckert et al., 2018). Likewise, being female was found to be positively associated with polypharmacy in some studies (Jyrkkä et al., 2009) and statistically insignificant in others (Rieckert et al., 2018). In other demographic areas such as race/ethnicity, little research into its association with polypharmacy has been conducted (Khezrian et al., 2020). In a 2015 study by Cashion et al., however, they did find non-Hispanic Whites to have an increased prevalence of polypharmacy when compared with non-Hispanic Blacks (Cashion et al., 2015).

Studies focused on polypharmacy's relationship with socioeconomic factors are underrepresented in the literature (Khezrian et al., 2020). Those that do exist, however, have indicated that geographic variation in residence may impact polypharmacy (Cashion et al., 2015; Guthrie et al., 2015). Additionally, residents of community living settings such as nursing homes may have higher risks of polypharmacy than those residing at home (Guthrie et al., 2015). Early results seen

across demographic and socioeconomic factors as well as the general lack of studies on these topics, suggest further research in these areas is warranted.

Innovation

This study seeks to expand upon existing research by further exploring predictors impacting polypharmacy. The study examines multiple demographic and socioeconomic factors while also including known influencers such as chronic illnesses. This study also seeks to improve generalizability of the results by utilizing nationally representative survey data over a period of ten years. Coupled with improvements in generalizability, increased knowledge of the predictive factors for polypharmacy has the potential to inform future policy and improve the lives of our elderly.

Conceptual Framework

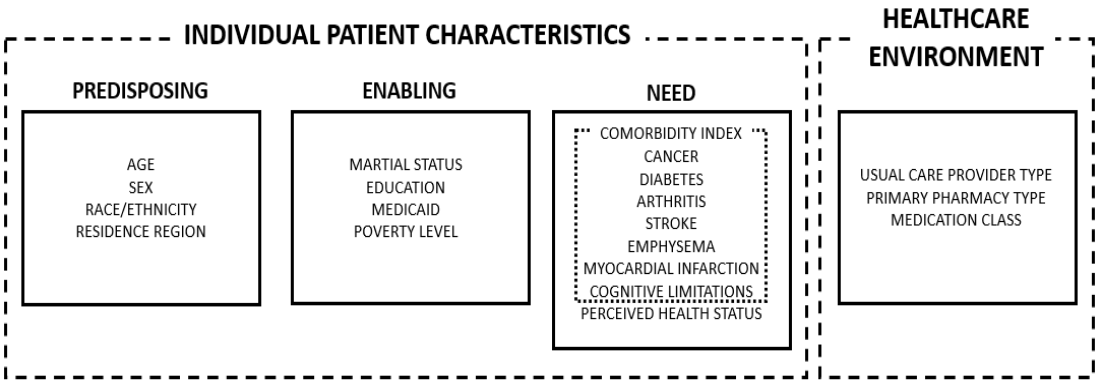
Nested within the overarching conceptual framework in Figure 3.1, theorized factors contributing to polypharmacy are depicted primarily within the constructs of Andersen's Emerging Behavioral Model (R. M. Andersen, 1995.) The interactions between independent factors and polypharmacy were used to inform development of the model used in this analysis. Lastly, independent variable selection utilizes the groupings in Figure 4.1 which is derived from the Aim 1 portion of the conceptual model outlined in blue.

Methods

Data and Measures

To explore the predictors of polypharmacy within the target population, our analysis utilized the combined MEPS file containing ten years (2010 – 2019) of aggregated data. The comprehensive nature of MEPS data allows for the exploration of relationships between polypharmacy and a myriad of demographic, socioeconomic, and clinical factors. To foster a complete analysis of possible contributing factors, prospective variables were selected using the proposed conceptual framework and divided into two overall groups: individual patient characteristics and healthcare environment factors. Individual patient characteristics were further broken down into three groups using Andersen's criteria of predisposing, enabling, and need factors (R. M. Andersen, 1995); the final breakdown of factors explored in this aim are depicted in Figure 4.1 below.

Figure 4.1: Perceived Factors Affecting Polypharmacy



Source: Andersen's Emerging Behavioral Model – Phase 4, (Andersen, 1995)

The binary construct of polypharmacy was used as the response variable in this aim as it is most applicable to our research question and allows for straightforward interpretation of the results. Nonpolypharmacy patients were assigned

the value of “0”, thus representing the control group for our sample. Conversely, polypharmacy patients were assigned the value of “1” and constitute the treatment group of our sample.

In total, 13 independent variables were evaluated for their associations with polypharmacy. While these factors were selected based upon their alignment with the conceptual model, they are described in this section using their variable class. Among the 13 independent variables utilized in this aim, three are binary and 10 are categorical. Binary variables included sex, marital status, and dual eligible beneficiary status. Across these variables, zero values were assigned to “male”, “unmarried”, and “non-dual eligible”; these values served as the reference categories for each variable.

Categorical constructs were used for ten variables representing age, race/ethnicity, residence region, education, poverty level, perceived health status, provider type, pharmacy type, comorbidity index severity level, and medication class. Age was categorized into four groups spanning the spectrum of ages represented in our sample: less than 70, 70 to 74, 75 to 79, and 80 or older. A categorical variable was used for age as it allowed for a more meaningful interpretation of age’s association with polypharmacy. The race/ethnicity variable contains five categories: non-Hispanic White (reference), non-Hispanic Black, Hispanic, non-Hispanic Asian, non-Hispanic other/mixed race. Region of residence was divided in Northeast (reference), Midwest, South, and West. Education comprises five levels: less than high school (reference), high school, Associate’s or other degree, Bachelor’s Degree, Master’s or Doctoral degree. Poverty level was composed of poor (reference), near

poor, low income, middle income, and high income; categorization represents family income as a percentage of Federal Poverty Line. Provider type consists of General Practice (reference), Medical Specialist, and Alternative Care. Five categories were used to represent the primary type of pharmacy used by patients: clinic/hospital (reference), drug store, other store, mail-order, and online. Comorbidity index severity level was categorized into three groups using each patient's ACCI score: mild (≤ 5), moderate (6-7), and severe (≥ 8). Finally, the primary medication class variable depicts the Multum Therapeutic Class #1 and is divided into 15 distinct drug classes; anti-infectives constitute the reference group for this variable.

Analyses

First, descriptive analysis was used to assess baseline characteristics across polypharmacy status. Univariate tests for differences in each variable across strata were conducted using chi-squared tests. Second, Time Fixed Effects Modified Poisson regression was used to estimate the associations between polypharmacy and the hypothesized contributing factors from Figure 4.1. Calendar years corresponding to each respective year of MEPS data constituted the Fixed Effects estimator and were used to account for potential observable and unobservable systematic differences between the appended years of data. Re-weighting was performed by dividing person-level weights by ten to account for the compiled years of data. The newly derived weights replaced the standard MEPS person-level weights included in the data set and were used in the survey design. The full MEPS survey design was applied and used throughout the analysis.

Modified Poisson regression was selected for our analyses as exponentiation of its coefficients delivers relative risk ratios when used with a binary outcome variable. Relative risk ratios are deemed more meaningful to epidemiologists and medical studies as most clinical research is used to assess risk (Zou, 2004). Modified Poisson also delivers several benefits over traditional logistic regression despite its common use in studies with a binary response variable. Unlike odds ratios which are highly dependent upon the data and model specification, risk ratios derived using Modified Poisson regression are generally considered robust (Norton & Dowd, 2018a; Zou, 2004). Results derived using Modified Poisson can be compared across studies, whereas the model specification issues that arise when using logistic regression preclude odds ratios from having any meaningful comparison across different models (Norton & Dowd, 2018a). Lastly, relative risk ratios allow for the discussion of results in terms of the probability of an event occurring (risk); comparison of results in terms of percentage increases and decreases of the probability of an event occurring is more useful to research and clinical community alike.

Prospective models were compared using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC); the model with the lowest AIC and BIC values represented the best fit and was used in the analyses. Coefficients and significance levels were also compared across models as an additional measure used to assess model fit. Potential correlation was assessed pre-analyses using correlation matrices; Variance Inflation Factors (VIF) were used as a post-estimation check to

rule out multicollinearity. With a high VIF of 2.3 (threshold < 10) on age, multicollinearity was ruled out for this study.

Sensitivity analyses used model variation and the exclusion/inclusion of MEPS survey design to assess the robustness of findings. Model variation was conducted by adding and subtracting independent variables from our model as well as altering variable constructs. Once the optimal model was designated, it was run with and without the MEPS survey design. This comparison served as a final model assessment and allowed us to view the findings within the context of sample and population-level parameters. Lastly, our model was run using logistic regression to determine how the two types of regression differ in terms of the results; this method also was used to assess the rationale for using Modified Poisson which stated that odds ratios are highly dependent upon model specification and often exaggerate the magnitude of the results. All analyses were performed using R version 4.1.3. The full model used in the analysis is depicted below.

$$Y_i = \beta_0 + \beta_1 X_a + \beta_2 X_b + \beta_3 X_c + \beta_4 X_d + \beta_5 X_e + \beta_6 X_f + \beta_7 X_g + \beta_8 X_h + \beta_9 X_i + \beta_{10} X_j + \beta_{11} X_k + \beta_{12} X_l + \beta_{13} X_m + \delta_{2\text{-}10} T_{11\text{-}19} + \mu_i$$

Y_i: Polypharmacy

X_a: Age

X_b: Gender

X_c: Marital Status

X_d: Race/Ethnicity

X_e: Education

X_h: Dual Eligibility Status

X_i: Comorbidity Index Severity Level

X_j: Perceived Health Status

X_k: Usual Provider Type

X_l: Primary Pharmacy Type

X_m: Medication Class

X_f: Poverty Level

X_g: Region of Residence

$T_{11\text{-}19}$: Year Fixed Effects Estimator

Results

Descriptive Statistics

Among the 13,338 individuals who compose the sample, 7,354 (55%) were found to be polypharmacy. Of the 7,354 polypharmacy patients, 2,315 (31%) meet the threshold for hyperpolypharmacy ($\geq$ 10 medications). Additionally, the mean number of unique medications taken per patient was 5.96 (range 1-35: SD 4.22). Age was relatively balanced across the four categories; however, highest proportions of polypharmacy patients were observed in individuals between the ages of 70 and 80. Females made up 58% of the sample and a larger proportion of polypharmacy patients (59.5%). Nearly fifty-two percent of our sample was married and over two-thirds identified as being non-Hispanic White. Thirteen percent of respondents had household incomes at or below the federal poverty line while 35% were designate as "High Income"; 39% of all respondents resided in the southern region of the US. Lastly, 15% of patients were also insured under Medicaid, making them dual-eligible beneficiaries (see Table 4.1a).

Table 4.1a
Socio-demographic characteristics across polypharmacy

	Total (N=13338)	Polypharmacy NO (N=5984)	Polypharmacy YES (N=7354)	P-value
Age (years)				
65-69	4335 (32.5%)	1985 (33.2%)	2350 (32.0%)	0.064
70-74	3309 (24.8%)	1448 (24.2%)	1861 (25.3%)	
75-79	2489 (18.7%)	1060 (17.7%)	1429 (19.4%)	
> 80	3205 (24.0%)	1491 (24.9%)	1714 (23.3%)	
Gender				
MALE	5620 (42.1%)	2639 (44.1%)	2981 (40.5%)	<0.001
FEMALE	7718 (57.9%)	3345 (55.9%)	4373 (59.5%)	
Marital Status				
NOT MARRIED	6439 (48.3%)	2695 (45.0%)	3744 (50.9%)	<0.001
MARRIED	6899 (51.7%)	3289 (55.0%)	3610 (49.1%)	
Race/Ethnicity				
NH WHITE	8981 (67.3%)	3973 (66.4%)	5008 (68.1%)	0.022
NH BLACK	1952 (14.6%)	902 (15.1%)	1050 (14.3%)	
HISPANIC	1416 (10.6%)	623 (10.4%)	793 (10.8%)	
NH ASIAN	725 (5.4%)	375 (6.3%)	350 (4.8%)	
NH OTHER/MULTI-RACE	264 (2.0%)	111 (1.9%)	153 (2.1%)	
Education				
LESS THAN HIGH SCHOOL	2739 (20.5%)	1151 (19.2%)	1588 (21.6%)	<0.001
HIGH SCHOOL	6084 (45.6%)	2669 (44.6%)	3415 (46.4%)	
AA OR OTHER DEGREE	1009 (7.6%)	464 (7.8%)	545 (7.4%)	
BACHELORS	1935 (14.5%)	944 (15.8%)	991 (13.5%)	
MASTERS OR DOCTORAL	1571 (11.8%)	756 (12.6%)	815 (11.1%)	
Poverty Level				
POOR	1769 (13.3%)	767 (12.8%)	1002 (13.6%)	0.015
NEAR POOR	829 (6.2%)	341 (5.7%)	488 (6.6%)	
LOW INCOME	2245 (16.8%)	987 (16.5%)	1258 (17.1%)	
MIDDLE INCOME	3846 (28.8%)	1692 (28.3%)	2154 (29.3%)	
HIGH INCOME	4649 (34.9%)	2197 (36.7%)	2452 (33.3%)	
Residence Region				
NORTHEAST	2427 (18.2%)	1130 (18.9%)	1297 (17.6%)	0.002
MIDWEST	2840 (21.3%)	1246 (20.8%)	1594 (21.7%)	
SOUTH	5159 (38.7%)	2219 (37.1%)	2940 (40.0%)	
WEST	2912 (21.8%)	1389 (23.2%)	1523 (20.7%)	
Dual Eligible				
NO	11340 (85.0%)	5264 (88.0%)	6076 (82.6%)	<0.001
YES	1998 (15.0%)	720 (12.0%)	1278 (17.4%)	

Note: Univariate tests for differences in each variable across strata were conducted using a chi-square test for categorical variables. P-values associated with these tests are shown in the last column.

Examination of individual health characteristics across polypharmacy status suggested the existence of a strong relationship between comorbidity and polypharmacy. Individuals with moderate and severe levels of comorbidity have the

greatest within group proportions of polypharmacy at 61% and 69%, respectively. In terms of perceived health status, proportions of individuals represented in the polypharmacy group increased as perceived health worsened. Polypharmacy patients composed 52% of those who responded to be in "excellent" health and 78% of those in "poor" health.

Table 4.1b
Individual health and health environment characteristics across polypharmacy

		Polypharmacy		
	Total (N=13338)	NO (N=5984)	YES (N=7354)	P-value
Comorbidity Index Level				
MILD	6944 (52.1%)	3639 (60.8%)	3305 (44.9%)	<0.001
MODERATE	4555 (34.2%)	1782 (29.8%)	2773 (37.7%)	
SEVERE	1839 (13.8%)	563 (9.4%)	1276 (17.4%)	
Perceived Health Status				
EXCELLENT	2165 (16.2%)	1328 (22.2%)	837 (11.4%)	<0.001
VERY GOOD	3874 (29.0%)	1952 (32.6%)	1922 (26.1%)	
GOOD	4239 (31.8%)	1724 (28.8%)	2515 (34.2%)	
FAIR	2351 (17.6%)	790 (13.2%)	1561 (21.2%)	
POOR	709 (5.3%)	190 (3.2%)	519 (7.1%)	
Usual Source of Care Provider				
GENERAL PRACTICE	12726 (95.4%)	5677 (94.9%)	7049 (95.9%)	0.0911
MEDICAL SPECIALIST	577 (4.3%)	287 (4.8%)	290 (3.9%)	
ALTERNATIVE CARE	35 (0.3%)	20 (0.3%)	15 (0.2%)	
Primary Pharmacy Type				
CLINIC/HOSPITAL	887 (6.7%)	383 (6.4%)	504 (6.9%)	0.368
DRUG STORE	6676 (50.1%)	3018 (50.4%)	3658 (49.7%)	
OTHER STORE	3672 (27.5%)	1690 (28.2%)	1982 (27.0%)	
MAIL-ORDER	1998 (15.0%)	845 (14.1%)	1153 (15.7%)	
ONLINE	105 (0.8%)	48 (0.8%)	57 (0.8%)	
Multum Therapeutic Class #1				
ANTI-INFECTIVES	434 (3.3%)	330 (5.5%)	104 (1.4%)	<0.001
ANTINEOPLASTICS	68 (0.5%)	44 (0.7%)	24 (0.3%)	
CARDIOVASCULAR AGENTS	4728 (35.4%)	1694 (28.3%)	3034 (41.3%)	
CNS AGENTS	1644 (12.3%)	667 (11.1%)	977 (13.3%)	
COAGULATION MODIFIERS	292 (2.2%)	177 (3.0%)	115 (1.6%)	
GI AGENTS	428 (3.2%)	236 (3.9%)	192 (2.6%)	
HORMONE MODIFIERS	802 (6.0%)	486 (8.1%)	316 (4.3%)	
MISCELLANEOUS AGENTS	42 (0.3%)	18 (0.3%)	24 (0.3%)	
GENITOURINARY AGENTS	72 (0.5%)	40 (0.7%)	32 (0.4%)	
NUTRITIONAL PRODUCTS	178 (1.3%)	94 (1.6%)	84 (1.1%)	
RESPIRATORY AGENTS	397 (3.0%)	152 (2.5%)	245 (3.3%)	
TOPICAL AGENTS	728 (5.5%)	392 (6.6%)	336 (4.6%)	
PSYCHOTHERAPEUTIC AGENTS	400 (3.0%)	200 (3.3%)	200 (2.7%)	
IMMUNOLOGICAL AGENTS	8 (0.1%)	7 (0.1%)	1 (0.0%)	
METABOLIC AGENTS	3117 (23.4%)	1447 (24.2%)	1670 (22.7%)	

Note: Univariate tests for differences in each variable across strata were conducted using a chi-square test for categorical variables. P-values associated with these tests are shown in the last column.

Within the context of the healthcare environment, over 95% of patients are seen by primary care providers for their routine care. Those treated regularly within the primary care setting experience higher intra-group rates of polypharmacy (55%), when compared with those followed by medical specialists (50%) or alternative care providers (43%). Additionally, cardiovascular agents (41.3%), metabolic agents (22.7%), and central nervous system agents (13.3%) were the most prevalent medication classes taken among polypharmacy patients. Lastly, examination of differences across polypharmacy status by data year revealed that 2012 (42%) and 2013 (71%) were associated with the lowest and highest within year polypharmacy rates, respectively.

Table 4.1c
Year Fixed Effects estimator across polypharmacy

		Polypharmacy		
	Total (N=13338)	NO (N=5984)	YES (N=7354)	P-value
Year Fixed Effects Estimator				
10	1502 (11.3%)	643 (10.7%)	859 (11.7%)	<0.001
11	1210 (9.1%)	511 (8.5%)	699 (9.5%)	
12	557 (4.2%)	325 (5.4%)	232 (3.2%)	
13	760 (5.7%)	219 (3.7%)	541 (7.4%)	
14	1443 (10.8%)	734 (12.3%)	709 (9.6%)	
15	797 (6.0%)	257 (4.3%)	540 (7.3%)	
16	1379 (10.3%)	622 (10.4%)	757 (10.3%)	
17	1341 (10.1%)	556 (9.3%)	785 (10.7%)	
18	2255 (16.9%)	969 (16.2%)	1286 (17.5%)	
19	2094 (15.7%)	1148 (19.2%)	946 (12.9%)	

Note: Univariate tests for differences in each variable across strata were conducted using a chi-square test for categorical variables. P-values associated with these tests are shown in the last column.

Multivariate Regression

Results showed polypharmacy to have statistically significant associations with several socio-demographic, individual health, and healthcare environment

factors. Among socio-demographic factors (Table 4.2a), individuals over the age of eighty (RR: 0.875, $p < 0.001$), married individuals (RR: 0.930, $p < 0.001$), non-Hispanic Blacks (RR: 0.864, $p < 0.001$), and non-Hispanic Asians (RR: 0.880, $p < 0.05$) were associated with lower relative risks of polypharmacy. Conversely, being female (RR: 1.088, $p < 0.001$), a high school graduate (RR: 1.061, $p < 0.01$), middle income (RR:1.077, $p < 0.05$), and high income (RR: 1.107, $p < 0.01$) were associated with greater polypharmacy risk. Dual eligible beneficiaries (RR: 1.110, $p < 0.001$) and patients residing in the South (RR: 1.060, $p < 0.05$) were also found to have higher relative risks of polypharmacy.

Among clinical factors (Table 4.2b), patients with moderate (RR: 1.217, $p < 0.001$) and severe (RR: 1.306, $p < 0.001$) comorbidities were found to have increased polypharmacy risks when compared with patients with mild levels of comorbidity. Perceived health status was shown to have an inverse relationship with polypharmacy risk; the greatest relative polypharmacy risk (RR: 1.561, $p < 0.001$) was seen among patients with poor perceived health, the lowest category of health represented in the variable. Patients routinely seen by a medical specialist had a lower relative risk of polypharmacy (RR: 0.893, $p < 0.05$) than those treated by general practice providers. Lastly, while nearly all medication classes are associated with increased risks of polypharmacy, the greatest risks are seen among individuals prescribed cardiovascular agents (RR: 2.235, $p < 0.001$), respiratory agents (RR: 2.081, $p < 0.001$), and central nervous system agents (RR: 1.939, $p < 0.001$).

Table 4.2a
Associations between socio-demographic factors and polypharmacy

	Modified Poisson			
	RR	***95% CI***	***Robust SE***	***p-value***
Age [ref: 65-69 years]				
70-74	0.986	(0.939,1.036)	0.025	0.576
75-79	0.963	(0.915,1.013)	0.026	0.146
> 80	0.875	(0.830,0.922)	0.027	0.000
Gender [ref: male]				
Female	1.088	(1.047,1.131)	0.020	0.000
Marital Status [ref: not married]				
Married	0.930	(0.894,0.968)	0.020	0.000
Race/Ethnicity [ref: Non-Hispanic White]				
Non-Hispanic Black	0.864	(0.818,0.914)	0.028	0.000
Hispanic	0.957	(0.897,1.020)	0.035	0.173
Non-Hispanic Asian	0.880	(0.788,0.982)	0.056	0.023
Non-Hispanic Other	1.007	(0.895,1.133)	0.060	0.905
Education [ref: Less than HS]				
High School	1.061	(1.015,1.108)	0.022	0.008
Associate's/Other Degree	0.975	(0.904,1.052)	0.039	0.515
Bachelor's Degree	1.040	(0.979,1.105)	0.031	0.202
Master's or Doctoral Degree	1.069	(0.955,1.148)	0.036	0.067
Poverty Level [ref: Poor]				
Near Poor	1.006	(0.926,1.092)	0.042	0.892
Low Income	1.028	(0.961,1.099)	0.034	0.428
Middle Income	1.077	(1.008,1.115)	0.034	0.029
High Income	1.107	(1.030,1.190)	0.037	0.006
Region [ref: Northeast]				
Midwest	1.035	(0.979,1.094)	0.028	0.222
South	1.060	(1.007,1.115)	0.026	0.026
West	1.021	(0.959,1.088)	0.032	0.509
Dual Eligible [ref: No]				
Yes	1.110	(1.051,1.173)	0.028	0.000

Note: Table displays relative risk ratios, 95% confidence intervals, robust standard errors, and p-values for Time Fixed Effects Modified Poisson Regression utilizing MEPS full survey design. Person-level MEPS weights were re-scaled by dividing the weights by ten (PW/10) to account for ten years of pooled data. Calendar years corresponding to each year of MEPS data were used to account for potential observable and unobservable systematic differances between the appended years of data included in the study.

Table 4.2b
Associations between clinical factors and polypharmacy

	Modified Poisson			
	RR	***95% CI***	***Robust SE***	***p-value***
Comorbidity Index Severity Level [ref: Mild]				
Moderate	1.217	(1.163,1.274)	0.023	0.000
Severe	1.306	(1.238,1.377)	0.027	0.000
Perceived Health Status [ref: Excellent]				
Very Good	1.209	(1.119,1.305)	0.039	0.000
Good	1.426	(1.327,1.531)	0.036	0.000
Fair	1.524	(1.418,1.638)	0.037	0.000
Poor	1.561	(1.437,1.696)	0.042	0.000
Usual Source of Care Provider Type [ref: General Practice]				
Medical Specialist	0.893	(0.810,0.985)	0.050	0.024
Alternative Care	0.683	(0.433,1.079)	0.232	0.102
Primary Pharmacy Type Used [ref: Clinic/Hospital]				
Drug Store	0.967	(0.0.899,1.041)	0.037	0.375
Other Store	0.966	(0.888,1.052)	0.043	0.431
Mail-Order	1.041	(0.956,1.132)	0.043	0.354
Online	0.989	(0.799,1.224)	0.108	0.918
Multum Therapeutic Class #1 [ref: Anti-Infectives]				
Antineoplastics	1.136	(0.746,1.730)	0.214	0.552
Cardiovascular Agents	2.235	(1.885,2.651)	0.087	0.000
Central Nervous System Agents	1.939	(1.626,2.313)	0.090	0.000
Coagulation Modifiers	1.371	(1.073,1.751)	0.124	0.012
Gastro-Intestinal Agents	1.555	(1.257,1.923)	0.108	0.000
Hormone Modifiers	1.533	(1.260,1.865)	0.010	0.000
Miscellaneous Agents	1.807	(1.214,2.690)	0.202	0.004
Genitourinary Agents	1.452	(1.010,2.089)	0.185	0.044
Nutritional Products	1.650	(1.290,2.109)	0.125	0.000
Respiratory Agents	2.081	(1.705,2.540)	0.101	0.000
Topical Agents	1.742	(1.446,2.099)	0.095	0.000
Psychotherapeutic Agents	1.598	(1.296,1.970)	0.106	0.000
Immunological Agents	0.519	(0.085,3.177)	0.921	0.477
Metabolic Agents	1.845	(1.544,2.205)	0.091	0.000

Note: Table displays relative risk ratios, 95% confidence intervals, robust standard errors, and p-values for Time Fixed Effects Modified Poisson Regression utilizing MEPS full survey design. Person-level MEPS weights were re-scaled by dividing the weights by ten (PW/10) to account for ten years of pooled data. Calendar years corresponding to each year of MEPS data were used to account for potential observable and unobservable systematic differances between the appended years of data included in the study.

Examination of the results across our Fixed Effects estimator indicate that associations with polypharmacy varied considerably across the ten years of data included in our study. Statistically significant associations were found in years 2012-2015 as well as in 2019 ($p < 0.001$). The greatest increase in polypharmacy risk when

compared with our 2010 reference occurred in 2013 (RR: 1.194) and the greatest decrease occurred in 2019 (RR: 0.782).

Table 4.2c
Associations between data year and polypharmacy

	Modified Poisson			
	RR	***95% CI***	***Robust SE***	***p-value***
Year Fixed Effects Estimator [ref: 2010]				
2011	1.043	(0.957,1.138)	0.044	0.337
2012	0.755	(0.667,0.854)	0.063	0.000
2013	1.194	(1.109,1.285)	0.038	0.000
2014	0.854	(0.784,0.930)	0.043	0.000
2015	1.168	(1.092,1.249)	0.034	0.000
2016	0.944	(0.878,1.014)	0.037	0.115
2017	0.988	(0.917,1.063)	0.038	0.740
2018	0.985	(0.928,1.046)	0.030	0.618
2019	0.782	(0.730,0.838)	0.035	0.000

Note: Table displays relative risk ratios, 95% confidence intervals, robust standard errors, and p-values for Time Fixed Effects Modified Poisson Regression utilizing MEPS full survey design. Person-level MEPS weights were re-scaled by dividing the weights by ten (PW/10) to account for ten years of pooled data. Calendar years corresponding to each year of MEPS data were used to account for potential observable and unobservable systematic differances between the appended years of data included in the study.

Sensitivity analysis performed using model and variable construct variation found changes to the equation to exhibit negligible effect on the practical and statistical significance of the results. However, comparison between the continuous and categorical constructs of age helped explain the negative association between age and polypharmacy when used as a continuous variable. When the categorical construct was applied, we noted that all age groups carried statistically insignificant negative associations with polypharmacy except for individuals aged 80 and older (RR: 0.875, $p < 0.001$).

Survey design-based comparisons found minor variation in terms of practical significance across both models. Additionally, statistical significance was maintained across both models except for high school education level, middle income level,

South region of residence, and medical specialist provider type; all four of these variable categories were statistically insignificant at the $p < 0.05$ level in our non-survey weighted model. Lastly, comparison between our Modified Poisson regression model and the logistic regression model yielded comparable results in terms of statistical significance and the direction of association (see Table A.2); however, the odds ratios associated with logistic regression appeared to be overestimated across several factors.

Discussion

While many of the existing studies on our topic used logistic regression to derive odds ratios, a methodology that has been shown to make cross study comparisons difficult, it was still possible for us to compare previous findings with our results based on statistical significance and the direction of association. Across socio-demographic factors, our findings show female gender to be associated with increased polypharmacy risk (RR: 1.088, $p < 0.001$). This finding is consistent with a study by Jyrkka et al. 2009; however, Rieckert et al. 2018 found no association between sex and polypharmacy (Jyrkkä et al., 2009; Rieckert et al., 2018). Like Cashion et al. 2015, our study found non-Hispanic Blacks to have a decreased risk of polypharmacy (RR: 0.864, $p < 0.001$) when compared with non-Hispanic Whites (Cashion et al., 2015). In our study, we also found the risk of polypharmacy to be lower for non-Hispanic Asians (RR: 0.880, $p < 0.05$). While this may be attributed to healthier lifestyles or a propensity towards the use of alternative medicines, further research is needed to determine what other factors may impact this finding.

Increased polypharmacy risk seen among middle (RR:1.077, $p < 0.05$) and high income (RR: 1.107, $p < 0.01$) groups may indicate that poverty level serves as a predictor of healthcare access (McMaughan et al., 2020). This hypothesis is further supported by our finding for dual eligible beneficiaries. With a relative risk ratio of 1.110 ($p < 0.01$), our results suggest that the addition of Medicaid coverage increases a patient's risk of polypharmacy by 11%; the additional coverage is thought to increase the risk of polypharmacy through improved access to care for low-income populations. Increased polypharmacy risk among those with higher educational attainment is also indicative of improved access to care. College-educated individuals are more likely to work in industries where employer-based health insurance is more prevalent. Additionally, higher educational attainment is often associated with improved socio-economic status making insurance coverage more affordable and obtainable for this subset of the population.

In terms of clinical factors, our findings across comorbidity severity level comport with previous studies showing the presence of multiple chronic illnesses to be associated with significant increases in the odds of polypharmacy (Rieckert et al., 2018; Wongpakaran et al., 2018). Given that medications are typically prescribed to treat or assuage an ailment, we would expect individuals with multiple chronic illnesses to be impacted the most by concomitant medication use. Analysis of usual provider type found patients seen by medical specialists for their routine care to be associated with lower risks of polypharmacy (RR: 0.893, $p < 0.05$) when compared with those treated by general practitioners. This finding is likely impacted by several factors that are tied to increased polypharmacy risk in a general practice setting as

opposed to specific measures taken by medical specialist to lower the risk of polypharmacy among the patients they care for. Namely, most prescribing occurs in primary care settings as medications are often used as an early form of treatment prior to a patient's referral to a specialty clinic; most patients also received reauthorizations for refills through their primary care physicians. Additionally, most general practitioners are empaneled a greater number of patients and often have to choose between competing clinical priorities; most providers feel they lack the necessary time to truly address issues arising from polypharmacy (Payne & Avery, 2011). Lastly, despite our Fixed Effects estimator indicating several years of statistically significant associations with polypharmacy, the alternating (increase, decrease) relative risk ratios seen between 2012 and 2015 and the statistically insignificant associations from 2016 to 2018, reveal there to be no discernable trend in polypharmacy risk across the decade.

Overall, this study finds polypharmacy risk to be associated with socio-demographic, individual health, and healthcare environment factors. This study both confirms existing findings in the field and adds new insights that improve our understanding of why certain patients carry a higher risk of polypharmacy than others. The use of nationally representative survey data improves generalizability of the results by eliminating bias that may have occurred due to geographic variation and allows us to make inferences about the entire US population using the findings from our sample. In lieu of these findings, additional research into the factors affecting socio-demographic disparities within the context of polypharmacy is suggested.

Limitations

Primary limitations within this study can be attributed to the type of data used. MEPS data is cross-sectional and thus cannot be used for longitudinal studies; despite appending ten years of data, each year must be viewed as being independent of the preceding or following years. The prescribed medication files indicate prescribing patterns but do not necessarily infer usage. This study equates prescribing to usage; however, verification of usage is not possible. Additionally, only prescription medications are captured in the data precluding the inclusion of over-the-counter medications in our analyses. Despite our best attempts to capture all contributors to polypharmacy within the model, the list of factors included is not exhaustive; omitted variables have the potential to impact our findings and may lead to biased results. Lastly, while nationally representative survey data leads to improved generalizability of results, the self-reported nature of responses make them unverifiable and susceptible to response bias.

Chapter 5: Estimating the Association Between Polypharmacy and Total Medical Expenditures Among Individuals Aged 65 and older

Introduction

Totaling 56.1 million, adults aged 65 and older currently account for 16.9% of the US population (Bureau, n.d.). Coupled with a rapidly ageing population, this number is expected to reach an estimated 73 million by 2030 and 85.7 million by 2050 (Bureau, n.d.). This demographic shift is likely to have severe cost-related implications for our healthcare system whose National Health Expenditures (NHE) already account for 18.3% ($4.3 trillion) of the US Gross Domestic Product (GDP) (*NHE Fact Sheet | CMS*, n.d.). With Medicare spending alone growing by 8.4% in 2021 to $900.8 billion, the forecasted population expansion has the potential to catapult healthcare expenditures to new heights over the next two decades (*NHE Fact Sheet | CMS*, n.d.).

According to the Medicare Current Beneficiary Study (MCBS), individuals between the ages of 70 and 90 make up a mere 10% of the US population yet account for nearly 52% of annual healthcare spending (Nardi et al., 2016). A primary reason for the excessive cost of treating the elderly is the prevalence of chronic health conditions among the population. According to the Centers for Disease Control and Prevention (CDC), over 85% of individuals over the age of 65 have at least one chronic illness; this percentage is even higher at 87% for females (*Health Policy Data Requests - Percent of U.S. Adults 55 and Over with Chronic Conditions*, 2019). Additionally, more than 23% of elderly patients were found to have three or more

chronic conditions (*Health Policy Data Requests - Percent of U.S. Adults 55 and Over with Chronic Conditions*, 2019).

Caring for patients with high degrees of comorbidity often requires complex and costly treatment regimens. Pharmaceutical intervention, a vital component of most treatment plans, can lead to polypharmacy when multiple medications are prescribed for separate medical conditions. Although a necessary outcome in many instances, polypharmacy has the potential to negatively impact the utilization of medical services and associated healthcare costs (Davies et al., 2020). While polypharmacy's impact on several measures of utilization is well described in existing literature, its association with medical expenditures has garnered less attention from the research community.

Existing studies have largely sought to explore polypharmacy's association with prescription costs and estimate the cost-saving potential of deprescribing measures on medication expenditures (Kojima et al., 2012; Richardson et al., 2012). Over the past two years, however, attempts have been made to estimate polypharmacy's association with non-prescription expenditures (Kwak et al., 2022). Using a single year of MEPS data (2017) and a sample consisting of 1,610 elderly patients with cardiovascular disease, Kwak et al. found polypharmacy to have a practical and statistically significant association with total medical expenditures (IRR: 1.98, $p < 0.001$). These findings suggest that polypharmacy's impact on healthcare costs may extend beyond medication-related expenditures and further research on the topic is warranted. To improve generalizability of prospective findings, however,

future research should be conducted using multiple years of data and a broader sample that includes all patients aged 65 or older.

Innovation

This study goes beyond existing literature by estimating the association between polypharmacy and total medical expenditures. While adjusting for potential confounders across demographic, socioeconomic, and health-related factors, our analysis seeks to determine if polypharmacy's cost-related impact extends beyond prescription-related expenditures. Additionally, the study seeks to quantify this impact by estimating the marginal effects associated with polypharmacy across total, inpatient, outpatient, emergency room, and prescription expenditures. Carried out using nationally representative survey data, the marginal expenditures derived from our analyses provide generalized estimations that can be used to inform prospective policies at the local, state, and national levels.

Conceptual Framework

Utilizing the conceptual framework in Figure 3.1, we hypothesize polypharmacy to be a contributing factor to utilization-related outcomes including medical expenditures. Adjusting for the potential confounders included in Figure 4.1, we seek to estimate the independent association between polypharmacy and our variable of interest. Theorized relationships between polypharmacy and total medical expenditures as well as among potential confounders across socio-demographic and health-related factors were used to inform the regression model used in this study.

Methods

Data and Measures

To estimate the association between polypharmacy and total medical expenditures, our analysis utilized ten years of aggregated MEPS data (2010-2019). Using the conceptual framework outlined in Figure 3.1, polypharmacy was selected as the primary exposure variable. Confounders were composed of individual health and socio-demographic factors selected using Andersen's predisposing, enabling and need factors and healthcare environment factors derived from Linsky's deprescribing model (R. M. Andersen, 1995b; Linsky et al., 2019).

Total medical expenditures were used as the outcome variable in this study. This continuous variable represents the total annual amount spent on healthcare by each patient. The amount aggregates expenditures from across a variety of services and settings to include inpatient, outpatient, emergency room, and prescribed medication costs. Across our sample, all 13,338 patients had some form of healthcare expenditure throughout the year. The minimum and maximum total medical expenditure were $5 and $324,413, respectively. The standard deviation of total medical expenditures across our sample was $19,437.20. Continuous variables representing inpatient, outpatient, emergency room, and prescription expenditures were used as outcome variables in the sub-aim analyses.

Polypharmacy's binary construct was used as the exposure variable in the primary and sub-aim analyses as it allows for the direct comparison of associations with total medical expenditures between the two groups: polypharmacy ($\geq$ 5 medications) and nonpolypharmacy (< 5 medications). Effectively, polypharmacy

("1") patients constitute the treatment group within our study and nonpolypharmacy patients ("0") represent the control group. A categorical construct of polypharmacy consisting of nonpolypharmacy (< 5 medications), polypharmacy (≥ 5 & < 10 medications), and hyperpolypharmacy (≥ 10 medications) was used in the sensitivity analysis for the primary aim to assess the impact of polypharmacy severity on total medical expenditures.

Aside from polypharmacy, 12 independent variables were used in our study to adjust for potential confounding. Selected for their alignment with the conceptual model, they are described below using their variable class. Of the 12 variables used to adjust for potential confounding, one is continuous, three are binary, and eight are categorical. As the only continuous variable included in the model, age denotes patient age at the time of the survey. Binary variables consist of patient gender (male "0", female "1"), marital status (single "0", married "1"), and dual eligibility status (no "0", yes "1").

Categorical variables were used to adjust for race/ethnicity, residence region, education, family income level, perceived health status, provider type, comorbidity index severity level, and primary medication class. Race/ethnicity was divided across five categories: non-Hispanic White (reference), non-Hispanic Black, Hispanic, non-Hispanic Asian, non-Hispanic other/mixed race. Region of residence was divided in Northeast (reference), Midwest, South, and West. Education was composed of five levels: less than high school (reference), high school, Associate's or other degree, Bachelor's Degree, Master's or Doctoral degree. Family income level was divided into four categories: < $50k (reference), $50k-$99k, $100k-$149k, and ≥ $150k.

Perceived health status consists of five categories: excellent (reference), very good, good, fair, and poor. Provider type is composed of General Practice (reference), Medical Specialist, and Alternative Care. The comorbidity index severity level variable depicts patient comorbidity severity/disease burden and is divided into three categories using each patient's ACCI: mild ($\leq$ 5, reference), moderate (6-7), and severe ($\geq$ 8). Lastly, the medication class variable depicts the primary Multum Therapeutic Class #1 prescribed to patients and is divided into 15 distinct drug classes; anti-infectives constitute the reference group for this variable.

Primary Analyses

Time Fixed Effects Generalized Linear Model regression with Gamma distribution and log link was used in this study. Model selection was made after visual tests showed the dependent variable to have a positive/right skewed distribution and the Tweedie power parameter score of 2.28 verified Gamma to be the correct GLM family for our model (Deb et al., 2014; Dunn & Smyth, 2001). Hurdle models with a Logit first part and GLM w/Gamma second part were used in the sub-analyses for outcome variables that had a substantial point mass at zero; existing literature suggests hurdle models to be best suited to address the nuances of this data (Deb & Norton, 2018; Mihaylova et al., 2011). Lastly, model specification was further examined using AIC and BIC; the model with the lowest values across both measures was determined to be the best fit.

Calendar years corresponding to each respective year of MEPS data were used as the fixed effects estimator in our regression. This approach was used to specifically account for potential observable and unobservable systematic differences between our

data years. Existing MEPS person-level weights were re-weighted by dividing them by ten to account for the multiple years of appended data. The new weights were used in place of the standard MEPS weights in our survey design. The full MEPS survey design was applied to all models used in our analyses. Potential issues related to correlation were assessed pre-analyses using correlation matrices; Variance Inflation Factors (VIF) were used as a post-estimation check to rule out multicollinearity.

Sub-aim Analyses

Sub-aim analyses used the same model and methods as the primary aim to assess polypharmacy's impact on inpatient, outpatient, emergency room, and prescription expenditures. Polypharmacy's associations with these expenditures were assessed using the practical and statistical significance of the regression results. Additional analyses were conducted using marginal effects to estimate the cost differential between polypharmacy and nonpolypharmacy patients across the forms of expenditures. Marginal effects were calculated using group averages and were presented with their respective 95% confidence intervals.

Sensitivity analyses using model variation was conducted to validate the model. Through the addition and subtraction of variables, we evaluated for model robustness to ensure the correct model specification was being used. The model was also run using the categorical construct of polypharmacy to assess the impact of polypharmacy severity on our findings. This approach delivered a secondary validation of polypharmacy's association with total medical expenditures. All analyses were performed using R version 4.1.3. The full model used during the analyses is shown below.

$$Y_i = \beta_0 + \beta_1 X_a + \beta_2 X_b + \beta_3 X_c + \beta_4 X_d + \beta_5 X_e + \beta_6 X_f + \beta_7 X_g + \beta_8 X_h + \beta_9 X_i + \beta_{10} X_j + \beta_{11} X_k + \beta_{12} X_l + \delta_{2\text{-}10} T_{11\text{-}19} + \mu_i$$

Y_i: Medical Expenditures

X_a: Polypharmacy

X_b: Age

X_c: Gender

X_d: Race/Ethnicity

X_e: Education

X_f: Family Income Level

X_g: Region of Residence

X_h: Dual Eligibility Status

X_i: Usual Provider Type

X_j: Comorbidity Index Severity Level

X_k: Perceived Health Status

X_l: Medication Class

$T_{11\text{-}19}$: Year Fixed Effects Estimator

Results

Primary Aim

Findings from our primary analyses indicate polypharmacy to have a statistically significant association with total medical expenditures (Coef: 0.570, $p < 0.001$). The positive sign on the coefficient indicates that the amount of spending is higher for polypharmacy patients when compared with nonpolypharmacy patients. The impact of hyperpolypharmacy on total medical expenditures carries an even greater practical significance (Coef: 0.865) while remaining statistically significant at the $p < 0.001$ level. In addition to polypharmacy, we find statistically significant associations across several socio-demographic and health-related factors.

Table 5.1
Association between polypharmacy and total medical expenditures

	Gamma w/Binary Exposure				*Gamma w/Categorical Exposure*			
	Coeff.	*95% CI*	*Robust SE*	*p-value*	*Coeff.*	*95% CI*	*Robust SE*	*p-value*
Polypharmacy [ref: non-polypharmacy]								
Polypharmacy	0.570	(0.504,0.635)	0.033	0.000	0.432	(0.361,0.502)	0.036	0.000
Hyperpolypharmacy					0.865	(0.789,0.941)	0.039	0.000
Age [continuous]	0.001	(-0.004,0.007)	0.003	0.619	0.003	(-0.002,0.008)	0.003	0.276
Gender [ref: male]								
Female	-0.069	(-0.139,0.001)	0.036	0.055	-0.081	(-0.153,-0.009)	0.037	0.028
Marital Status [ref: not married]								
Married	-0.057	(-0.132,0.018)	0.038	0.135	-0.059	(-0.136,0.018)	0.039	0.133
Race/Ethnicity [ref: Non-Hispanic White]								
Non-Hispanic Black	-0.107	(-0.194,-0.020)	0.044	0.016	-0.082	(-0.171,0.007)	0.045	0.072
Hispanic	-0.124	(-0.238,-0.010)	0.058	0.033	-0.114	(-0.227,-0.001)	0.057	0.049
Non-Hispanic Asian	-0.333	(-0.489,-0.177)	0.079	0.000	-0.308	(-0.464,-0.152)	0.079	0.000
Non-Hispanic Other	-0.136	(-0.291,0.019)	0.079	0.086	-0.142	(-0.310,0.027)	0.086	0.100
Education [ref: Less than HS]								
High School	0.158	(0.071,0.283)	0.044	0.000	0.128	(0.041,0.216)	0.044	0.004
Associate's/Other Degree	0.143	(0.026,0.260)	0.059	0.016	0.109	(-0.009,0.227)	0.06	0.071
Bachelor's Degree	0.177	(0.071,0.283)	0.054	0.001	0.142	(0.035,0.248)	0.054	0.010
Master's or Doctoral Degree	0.246	(0.138,0.354)	0.055	0.000	0.203	(0.093,0.312)	0.056	0.000
Family Income [ref: < $50k]								
$50k-$99k	0.007	(-0.069,0.082)	0.039	0.861	0.014	(-0.065,0.092)	0.04	0.734
$100k-$149k	0.100	(0.001,0.199)	0.050	0.048	0.112	(0.013,0.211)	0.05	0.027
> $150k	0.098	(-0.022,0.218)	0.061	0.108	0.103	(-0.016,0.222)	0.060	0.090
Region [ref: Northeast]								
Midwest	-0.006	(-0.102,0.091)	0.049	0.904	-0.017	(-0.114,0.080)	0.049	0.730
South	-0.156	(-0.226,-0.085)	0.036	0.000	-0.176	(-0.247,-0.105)	0.036	0.000
West	-0.094	(-0.195,0.007)	0.051	0.068	-0.100	(-0.203,0.004)	0.052	0.058
Dual Eligible [ref: No]								
Yes	0.331	(0.237,0.426)	0.048	0.000	0.305	(0.209,0.401)	0.049	0.000
Usual Source of Care Provider Type [ref:General Practice]								
Medical Specialist	0.171	(0.031,0.311)	0.071	0.017	0.201	(0.056,0.345)	0.074	0.007
Alternative Care	-0.318	(-0.687,0.050)	0.187	0.090	-0.329	(-0.700,0.041)	0.188	0.081

Note: Table displays coeffecients, 95% confidence intervals, robust standard errors, and p-values for two regression models: 1) w/binary polypharmacy variable 2) w/categorical polypharmacy variable. Both regression models utilize MEPS Survey Design and Time Fixed Effects GLM Regression w/Gamma distribution and log link. Person-level MEPS weights were re-scaled by dividing the weights by ten (PW/10) to account for ten years of pooled data. Calendar years corresponding to each year of MEPS data were used to account for potential observable and unobservable systematic differences between the appended years of data included in the study.

Across measures of race/ethnicity, we find non-Hispanic Blacks (Coef: -0.107, $p < 0.05$), Hispanics (Coef: -0.124, $p < 0.05$), and non-Hispanic Asians (Coef: -0.333, $p < 0.001$) to be associated with lower total medical expenditures when compared with non-Hispanic Whites. We also find increased educational attainment to be associated with higher total medical expenditures; high school graduates (Coef: 0.158, $p < 0.001$), associate's degree holders (Coef: 0.143, $p < 0.05$), bachelor's degree holders (Coef: 0.177, $p < 0.001$), and master's or doctoral degree holders (Coef: 0.246, $p < 0.001$) are all associated with higher total medical expenditures

when compared with individuals who have less than a high school education. In terms of earnings, only individuals with gross family incomes between $100k and $150k are associated with increased total medical expenditures (Coef: 0.100, $p < 0.05$) when compared with those earning less than $50k per year. Patients residing in the South are shown to be associated with lower total medical expenditures (Coef: -0.156, $p < 0.001$) when compared with those who live in the Northeast. Dual eligible Medicare and Medicaid patients have higher total medical expenditures (Coef: 0.331, $p < 0.001$) than those who are Medicare beneficiaries only.

Across individual health and healthcare environment factors, patients who are regularly treated by medical specialists are associated with higher total medical expenditures (Coef: 0.171, $p < 0.05$) than those routinely seen by a general practitioner. Moderate (Coef: 0.331, $p < 0.001$) and severe (Coef: 0.533, $p < 0.001$) comorbidity levels are both associated with increased total medical expenditures. Worsening perceived health status was also shown to be associated with higher medical expenditures; very good (Coef: 0.160), good (Coef: 0.346), fair (Coef: 0.615), and poor (Coef: 0.970) statuses were all statistically significant at the $p < 0.001$ level. Among medication classes, only cardiovascular agents (Coef: -0.222, $p < 0.05$), miscellaneous agents (Coef: 0.869, $P < 0.001$), nutritional products (Coef: -0.308, $p < 0.05$), and immunological agents (Coef: 1.603, $p < 0.001$) were shown to have a statistically significant association with total medical expenditures when compared with the reference group. Lastly, examination of the coefficients and p-values on the fixed effects estimators indicate a steady increase in total expenditures

over 2010 values occurred in 2015 (Coef: 0.191, $p < 0.05$), 2017 (Coef: 0.175, $p < 0.01$), 2018 (Coef: 0.322, $p < 0.001$), and 2019 (Coef: 0.362, $p < 0.001$).

Table 5.1ctd
Association between polypharmacy and total medical expenditures

	Gamma w/Binary Exposure				*Gamma w/Categorical Exposure*			
	Coeff.	*95% CI*	*Robust SE*	*p-value*	*Coeff.*	*95% CI*	*Robust SE*	*p-value*
Comorbidity Index Severity Level [ref:Mild]								
Moderate	0.331	(0.262,0.400)	0.035	0.000	0.313	(0.245,0.382)	0.035	0.000
Severe	0.533	(0.443,0.623)	0.046	0.000	0.487	(0.398,0.576)	0.045	0.000
Perceived Health Status [ref: Excellent]								
Very Good	0.160	(0.069,0.251)	0.046	0.000	0.159	(0.069,0.249)	0.046	0.000
Good	0.346	(0.247,0.446)	0.051	0.000	0.325	(0.225,0.424)	0.051	0.000
Fair	0.615	(0.509,0.721)	0.054	0.000	0.567	(0.461,0.673)	0.054	0.000
Poor	0.970	(0.826,1.113)	0.073	0.000	0.920	(0.776,1.064)	0.073	0.000
Multum Therapeutic Class #1 [ref: Anti-Infectives]								
Antineoplastics	0.027	(-0.475,0.530)	0.255	0.915	0.040	(-0.464,0.544)	0.256	0.877
Cardiovascular Agents	-0.222	(-0.443,0.000)	0.113	0.050	-0.252	(-0.489,-0.014)	0.121	0.038
Central Nervous System Agents	0.114	(-0.115,0.343)	0.116	0.328	0.080	(-0.165,0.325)	0.124	0.522
Coagulation Modifiers	0.143	(-0.129,0.414)	0.138	0.302	0.132	(-0.149,0.413)	0.143	0.356
Gastro-Intestinal Agents	-0.103	(-0.367,0.161)	0.134	0.445	-0.114	(-0.393,0.164)	0.142	0.420
Hormone Modifiers	-0.171	(-0.428,0.086)	0.131	0.191	-0.168	(-0.444,0.108)	0.14	0.232
Miscellaneous Agents	0.869	(0.454,1.284)	0.211	0.000	0.867	(0.453,1.282)	0.211	0.000
Genitourinary Agents	0.373	(-0.321,1.066)	0.353	0.292	0.373	(-0.326,1.072)	0.355	0.295
Nutritional Products	-0.308	(-0.560,-0.057)	0.128	0.017	-0.328	(-0.593,-0.063)	0.135	0.015
Respiratory Agents	-0.167	(-0.413,0.080)	0.125	0.185	-0.178	(-0.439,0.083)	0.133	0.181
Topical Agents	-0.150	(-0.384,0.083)	0.119	0.206	-0.185	(-0.431,0.063)	0.125	0.139
Psychotherapeutic Agents	-0.070	(-0.344,0.206)	0.140	0.620	-0.058	(-0.341,0.225)	0.144	0.688
Immunological Agents	1.603	(0.646,2.559)	0.486	0.001	1.591	(0.639,2.544)	0.484	0.001
Metabolic Agents	-0.189	(-0.413,0.080)	0.114	0.099	-0.217	(-0.455,0.022)	0.121	0.075
Year Fixed Effects Estimator [ref: 2010]								
2011	-0.023	(-0.152,0.107)	0.066	0.726	-0.032	(-0.168,0.104)	0.069	0.641
2012	-0.054	(-0.227,0.118)	0.088	0.537	-0.043	(-0.210,0.124)	0.085	0.612
2013	0.052	(-0.087,0.191)	0.071	0.463	0.024	(-0.117,0.165)	0.072	0.740
2014	0.132	(-0.002,0.266)	0.068	0.053	0.147	(0.009,0.285)	0.070	0.037
2015	0.191	(0.044,0.338)	0.075	0.011	0.160	(0.008,0.313)	0.077	0.039
2016	0.102	(-0.040,0.244)	0.072	0.159	0.102	(-0.046,0.250)	0.075	0.175
2017	0.175	(0.042,0.308)	0.068	0.010	0.189	(0.050,0.327)	0.07	0.008
2018	0.322	(0.189,0.455)	0.068	0.000	0.331	(0.192,0.470)	0.071	0.000
2019	0.362	(0.240,0.484)	0.062	0.000	0.389	(0.262,0.516)	0.065	0.000

Note: Table displays coeffecients, 95% confidence intervals, robust standard errors, and p-values for two regression models: 1) w/binary polypharmacy variable 2) w/categorical polypharmacy variable. Both regression models utilize MEPS Survey Design and Time Fixed Effects GLM Regression w/Gamma distribution and log link. Person-level MEPS weights were re-scaled by dividing the weights by ten (PW/10) to account for ten years of pooled data. Calendar years corresponding to each year of MEPS data were used to account for potential observable and unobservable systematic differences between the appended years of data included in the study.

Sub-aim

Findings from our sub-aim further support the notion that polypharmacy status has an independent association with several forms of medical expenditures. Polypharmacy patients are shown to have greater odds of having inpatient (OR:1.814, $p < 0.001$), outpatient (OR: 1.596, $p < 0.001$), and emergency room (OR: 1.786, $p <$

0.001) related expenditures that nonpolypharmacy patients. Additionally, the amount of expenditures conditional upon any spending is higher for polypharmacy patients across inpatient (Coef: 0.190, $p < 0.01$), outpatient (Coef: 0.224, $p < 0.01$), and prescription (Coef: 0.682, $p < 0.001$) related costs. Although polypharmacy patients possess higher odds of having emergency room expenditures during the year, the amount spent on their care in this setting does not differ significantly from nonpolypharmacy patients.

Table 5.2
Marginal effects of polypharmacy on medical expenditures

	Logit				*GLM w/Gamma*			
	OR	*95% CI*	*Robust SE*	*p-value*	*Coeff.*	*95% CI*	*Robust SE*	*p-value*
Polypharmacy [ref: non-polypharmacy]								
Polypharmacy (Total $)					0.570	(0.504,0.635)	0.033	0.000
Polypharmacy (Inpatient $)	1.814	(1.591,2.068)	0.067	0.000	0.190	(0.073,0.307)	0.060	0.002
Polypharmacy (Outpatient $)	1.596	(1.454,1.753)	0.048	0.000	0.224	(0.067,0.382)	0.080	0.005
Polypharmacy (Emergency Room $)	1.786	(1.582,2.016)	0.062	0.000	0.100	(-0.034,0.233)	0.068	0.142
Polypharmacy (Prescription $)					0.682	(0.582,0.781)	0.051	0.000

Average Individual Expenditures [$]			
Total			***95 % CI ($)***
Non-Polypharmacy	$	4,566.48	(3417.01,6102.62)
Polypharmacy	$	8,071.40	(5963.90,10923.62)
Marginal Effect	$	3,504.92	(2546.89,4821.00)
Inpatient			
Non-Polypharmacy	$	19,361.01	(11668.12,32125.89)
Polypharmacy	$	23,413.20	(13891.04,39462.69)
Marginal Effect	$	4,052.19	(2222.92,7336.80)
Outpatient			
Non-Polypharmacy	$	1,486.23	(987.03,2237.89)
Polypharmacy	$	1,859.59	(1164.74,2968.97)
Marginal Effect	$	373.36	(177.71,731.08)
Emergency Room			
Non-Polypharmacy	$	955.36	(618.98,1474.53)
Polypharmacy	$	1,055.56	(662.02,1683.04)
Marginal Effect	$	100.20	(43.04,208.51)
Prescription			
Non-Polypharmacy	$	807.08	(509.35,1278.86)
Polypharmacy	$	1,595.49	(999.46,2546.96)
Marginal Effect	$	788.41	(490.11,1268.10)

Note: Table displays odds ratios (1st part),coeffecients (2nd part), 95% confidence intervals, robust standard errors, p-values, and marginal effects for four regression models that use the binary form of polypharmacy as the primary exposure variable : 1) w/inpatient expenditures, 2) w/outpatient expenditures, 3) w/emergency room expenditures, and 4) w/prescription expenditures. All regression models utilize MEPS Survey Design and Time Fixed Effects GLM Regression w/Gamma distribution and log link. Person-level MEPS weights were re-scaled by dividing the weights by ten (PW/10) to account for ten years of pooled data. Calendar years corresponding to each year of MEPS data were used to account for potential observable and unobservable systematic differences between the appended years of data included in the study. ** Only metrics pertaining to our primary exposure variable are shown in this table. All four regressions were adjusted for the same confounders used in the primary analysis and have the same regression model with the exception of the outcome variable of interest.

Further examination using marginal effects verifies that polypharmacy patients are associated with higher (mean) total ($8,071.40), inpatient ($23,413.20), outpatient ($1,859.59), and prescription ($1,595.49) expenditures. The highest average cost differential between the two groups is seen for inpatient expenditures ($4,052.19). Significant differences also exist across total medical expenditures and prescription expenditures with average marginal effects of $3,504.92 and $788.41, respectively. The use of marginal effects for emergency room expenditures shows the difference between our two groups to be small ($100.20); this result supports our previous analyses that found the association between polypharmacy status and emergency room expenditures conditional upon having any expenditure to be statistically insignificant. Lastly, sensitivity analyses performed using the categorical construct of polypharmacy validated the associations found when using the binary form of polypharmacy. After comparison, only minor changes to practical and statistical significance were observed across some variables; results can be viewed in Table 5.1.

Discussion

Our findings suggest polypharmacy to be associated with several forms of medical expenditures to include our main outcome of interest, total medical expenditures. More specifically, our primary analysis indicates that while controlling for potential confounders in our model, polypharmacy is shown to be associated with an increase in total medical expenditures (Coef: 0.570, $p < 0.001$). Given that our total medical expenditures variable aggregates costs from across different services and settings, one would expect there to be a cost differential across our polypharmacy

groups resulting from disparities in prescription-related costs alone. However, the magnitude of the association suggests total medical expenditures is not solely impacted by medication costs. As medical expenditures are primarily a byproduct of health services utilization, previous studies alluding to polypharmacy's positive associations with several negative outcomes deliver explanations for the mechanisms responsible for the increase in total expenditures among polypharmacy patients (Abe et al., 2015; Chang et al., 2020; Davies et al., 2020).

Despite the paucity of existing research on the topic, our study bolster's the findings by Kwak et al., 2020. While differences in methodology across sample population, scope, and analyses methods preclude direct comparison, the results both confirm polypharmacy to have a practically and statistically significant association with total medical expenditures. With respect to group means, we estimated polypharmacy patients to have a mean expected annual expenditure of $8,071; this estimation was 136% below the $19,068 mean expected expenditure found by Kwak et al. (Kwak et al., 2022). This difference may partially be attributed to the analysis methods used (GLM w/Gamma vs. Poisson); however, it most likely reflects the differences in disease severity across our sample populations. While our study was partially composed of polypharmacy patients with mild levels of comorbidity, the sample population use by Kwak et al. was composed entirely of patients with cardiovascular disease; many of these patients also presented with a severe degree of comorbidity.

Findings from our sub-analyses provided additional clarification regarding which health services contributed to the disparity in total medical expenditures across

polypharmacy status. With an odds ratio of 1.814 and Gamma coefficient of 0.190, polypharmacy status is associated with greater odds of having an inpatient medical expenditure and an increased amount of spending for those who have any inpatient expenditure during the year ($p < 0.001$). Polypharmacy's positive association with inpatient medical expenditures likely results from group differences in mean number of admissions per patient (NP: 0.15, P: 0.33). Examination of the average length of stay for patients with an admission showed nonpolypharmacy patients to average a higher number of nights (5.2) per admission when compared with polypharmacy patients (4.7). These findings from within our sample align with previous utilization-based studies that found positive associations between polypharmacy and admissions, but no statistically significant association with length of stay (Davies et al., 2020).

Polypharmacy patients were likewise associated with greater odds of having outpatient (OR: 1.596) and emergency room (OR: 1.786) expenditures when compared with nonpolypharmacy patients ($p < 0.001$). However, polypharmacy did not have a statistically significant association with the amount of emergency room expenditures. The lack of statistical significance between polypharmacy and the amount of emergency room expenditures as well as the small marginal effect ($100.20) between the two groups, may indicate a high degree of standardization exists across protocols and services rendered in the emergency room setting. Additionally, the transient nature of emergency departments limits the touch points between providers and patients; patients requiring higher levels of care are often admitted and those who do not are directly discharged leaving less room for cost-related variance. The positive association found between polypharmacy status and the

amount of spending on outpatient services likely stems from a 69% (NP: 1.026, P: 1.743) increase in the mean number of outpatient visits per year experienced by polypharmacy patients.

Our findings across prescription costs indicate a significant disparity exists between our two groups in terms of the amount of spending on prescription medications (Coef: 0.682, $p < 0.001$). Odds ratios for polypharmacy's association with having a prescription expenditure were not displayed in the table due to their irrational magnitude; the low threshold of individuals without a prescription-related expense (7) combined with the high degree of correlation between the two precluded any additional value from being obtained through their inclusion in the table. While it seems obvious that the number of medications will impact spending, the individual cost of each medication is likely to impact overall spending at an equal or even greater degree (Kojima et al., 2012; Vincent Rajkumar, 2020). Lastly, our estimated marginal effect across prescription costs ($788.41) mirrors the marginal effects found by Kwak et al. ($798). The fact that these estimations both use MEPS data and are nearly identical despite different sample populations, is a testament to the robustness of the findings.

The overall findings from this study show polypharmacy to be independently associated with both prescription and non-prescription related expenditures. The similarities found between our results and existing studies instills confidence in the accuracy of our findings. While the general lack of expenditure-based studies prevented robust cross-study comparisons, we were able to use our results to loosely emulate utilization-based studies focused on measuring polypharmacy's associations

with admissions and length of stay. The results from this study bolster existing findings in the field and add new insights were gaps in the research previously existed. The use of nationally representative survey data over multiple years improves generalizability of the results by eliminating bias that may have occurred due to geographic variation and allows us to make inferences about the entire US population using the findings from our sample. In lieu of these findings, future research should attempt to identify the specific mechanisms tied to polypharmacy that are responsible for increasing utilization and cost. Lastly, given the consistency with which studies have shown polypharmacy to have a negative impact on the elderly population, a renewed effort on the policy and clinical fronts is needed to reduce prescribing and implement alternative means of care for this vulnerable population.

Limitations

MEPS data provides access to a wide variety of expenditures; however, it does not provide an itemization of the cost components that compose each expenditure. While it is assumed that prescription related costs have been removed from other forms of expenditures and aggregated into its own variable, this cannot be confirmed. MEPS data is also cross-sectional and thus cannot be used for longitudinal studies; despite appending ten years of data, each year must be viewed as being independent of the preceding or following years. The prescribed medication files indicate prescribing patterns but do not necessarily infer usage. This study equates prescribing to usage; however, verification of usage is not possible. Additionally, only prescription medications are captured in the data precluding the inclusion of over-the-counter medications in our analyses. The chronic conditions available within

the data set are non-exhaustive which could potentially lead to an underestimation of the ACCI and impact our assessment of individual disease burden across the sample. Lastly, while nationally representative survey data leads to improved generalizability of results, the self-reported nature of responses make them unverifiable and susceptible to response bias.

Chapter 6: Estimating the Association Between Polypharmacy and Hospital Admissions Among Individuals Aged 65 and older

Introduction

Hospitalizations among the elderly are common occurrences that have broad implications for population health and rising national healthcare expenditures. Across the US annually, more than 13.2 million adults aged 65 and older are hospitalized (Fang et al., 2021). In 2017 alone, inpatient-related Medicare costs accounted for $99.8 billion worth of medical expenditures (Moore et al., 2020). Despite the high costs of inpatient care associated with this population, however, the negative impacts of hospitalizations on the overall health of the elderly are even more burdensome.

Among the elderly, hospitalization is often followed by irreversible functional decline that negatively impacts their independence and overall quality of life (Admi et al., 2015). Although some patients are hospitalized for acute issues unrelated to a mental or physical disability, they often exhibit signs and symptoms of functional decline following their hospital stay (Gill et al., 2004; Mudge et al., 2010). The propensity for admissions to worsen the health of elderly patients underlines the importance of identifying and mitigating potential factors associated with increased hospitalizations within this population. Of increasing importance to researchers and clinicians alike, is the impact that concomitant medication use has on admissions among those age 65 and older.

Polypharmacy, the simultaneous use of five or more medications (Varghese et al., 2023), has become increasingly common among the elderly population. While the use of concomitant medications is a central therapeutic component of treating patients

with multiple comorbidities, this approach is frequently associated with adverse outcomes (Davies et al., 2020; Dhalwani et al., 2017; Hammond & Wilson, 2013). Polypharmacy's association with hospital admissions has been well researched; however, the omission of disease severity and medication class from many existing studies have elicited calls for additional research on the topic to fully adjust for these factors within their models (Davies et al., 2020). A 2020 study by Chang et al., used Korean National Health Insurance Survey (KNHIS) data to estimate the risk of hospitalization associated with polypharmacy. In this study, polypharmacy patients were associated with an increased hazard risk (1.18) of hospitalization when compared with nonpolypharmacy patients; however, while the study adjusted for disease severity using the Charlson Comorbidity Index (CCI), it failed to adjust for medication class (Chang et al., 2020).

The identification of polypharmacy as a potential contributing factor to hospitalizations is an important first step towards reducing admissions and mitigating their negative effects. To do so, however, polypharmacy status must be incorporated within mechanisms capable of classifying patients according to their risk/probability of encountering the outcome of interest. Likely the most critical component in the fight to reduce admissions, proper identification of at-risk patients is a precursor to targeted intervention. Known for their ability to utilize pre-programmed algorithms to distinguish between groups based upon their propensity towards a given outcome, classification models represent a special form of machine learning that have gained popularity within the medical field due to their ability to identify at-risk patients.

Machine learning methods are being used across the globe to predict a variety of outcomes from readmissions to mortality (Blanes-Selva et al., 2021; Li et al., 2021). Classification models often use a combination of individual-level factors as training inputs that allow the model to identify patterns related to a specific outcome; these trained models can then be further used to make out-of-sample predictions (Malik & Munjal, 2021). For best model performance, a comprehensive set of training inputs is often needed. The addition of inputs associated with our outcome of interest improves the predictive capacity of the algorithm. In terms of predicting hospital admissions, the inclusion of polypharmacy status alongside other individual-level factors has the potential to strengthen our model and improve the accuracy of our predictions.

Innovation

First, this study looks to estimate the association between polypharmacy and hospital admissions while controlling for chronic comorbidity and medication class; despite the existence of studies on this topic, many fail to address potential confounding attributed to chronic illnesses and the class of medications prescribed (Davies et al., 2020). Additionally, this study utilizes Modified Poisson regression to elicit relative-risk ratios as opposed to odds ratios derived from logistic regression. Relative risk ratios are more meaningful to epidemiologists and medical studies as most clinical research is designed to assess risk (Zou, 2004). Unlike logistic regression, Modified Poisson regression is not dependent on model specification; its risk ratios are considered robust and allow for cross-study comparisons to be made (Norton & Dowd, 2018a; Zou, 2004).

This study also seeks to explore the use of machine learning methods to classify patients at risk for hospitalization. Novel approaches to the use of predictive analytics have been employed by using nationally representative survey data and polypharmacy status to train our model. The use of nationally representative survey data improves the generalizability of our results by allowing us to make assumptions at the population level. Also, the inclusion of polypharmacy status alongside other individual-level predictors in our training model improves the capability of algorithms to identify specific patterns related to our outcome of interest, thus allowing for the identification of patients at risk for hospitalization. Lastly, this study seeks to quantify the cost-reduction potential associated with large scale employment of these methods. The collective findings from this study can be used to inform and motivate policy makers at all levels to enact changes that improve healthcare delivery and accountability within geriatrics.

Conceptual Framework

In the primary aim, we theorize hospital admissions to be impacted by polypharmacy status as well as individual patient characteristics across socio-demographic and clinical factors. Using the conceptual framework in Figure 3.1, our model is adjusted for potential confounders that arise from Andersen's predisposing, enabling and need categories of population characteristics (R. M. Andersen, 1995.) Specifically, by adjusting for chronic comorbidities and medication class in addition to typical population-based characteristics, we are able to elucidate the independent association between polypharmacy and hospital admissions.

The sub-aim adds all predictive factors for hospitalization depicted in our conceptual framework to the training model to ensure maximum predictive power is achieved. Going beyond the model used in the primary aim, the sub-aim includes individual binary chronic illness variables to ensure disease specificity as well as measures of chronic illness severity (ACCI) are included in our analyses. Additionally, individual measures of health services utilization have been added to provide a greater degree of specification and depth to our training model. The theorized interactions between independent variables and the outcome variable used in this aim are encompassed within the green line in Figure 3.1.

Methods

Data and Measures

Our analyses utilized ten years of aggregated MEPS data (2010-2019) to estimate the association between polypharmacy and hospital admissions. The dependent and independent variables included in the model were selected using the conceptual framework in Figure 3.1; polypharmacy constitutes the primary exposure variable for this study. The model was adjusted for potential confounding by including several variables representing socio-demographic and clinical factors.

Hospitalization was used as the outcome variable in this study. This binary variable indicates a patient's hospital admission status during the year. Patients without a hospital admission during the year were designated as the reference category "0"; patients with at least one admission represented the non-reference category "1". Among our sample, 2,327 (17.4%) patients indicate having been

hospitalized during the year. This binary construct of hospitalization was used in both the primary and sub-aim analyses.

Polypharmacy's binary and categorical constructs were used as exposure variables in the primary aim to assess the impact of polypharmacy severity on its association with hospital admissions. The binary construct of polypharmacy consists of two groups: polypharmacy (≥ 5 medications) and nonpolypharmacy (< 5 medications). Polypharmacy ("1") patients constitute the treatment group within our study and nonpolypharmacy patients ("0") represent the control group. The categorical construct of polypharmacy consists of nonpolypharmacy (< 5 medications), polypharmacy (≥ 5 & < 10 medications), and hyperpolypharmacy (≥ 10 medications). Among the sample population, 7,354 (55%) patients were prescribed at least five concurrent medications; 2,315 (31%) of these polypharmacy patients met the threshold for hyperpolypharmacy (≥ 10 medications).

Nine independent variables were included in our primary analysis model to adjust for potential confounding. Among the variables selected, six represent socio-demographic factors and three represent clinical factors. Across socio-demographic factors, a continuous age variable was used to indicate patient age at the time of the survey. Binary variables consisting of patient gender (male "0", female "1"), marital status (single "0", married "1"), and dual eligibility status (no "0", yes "1") were also added to the model. Race/ethnicity was divided across five categories: non-Hispanic White (reference), non-Hispanic Black, Hispanic, non-Hispanic Asian, non-Hispanic other/mixed race. Lastly, region of residence was divided into four geographical locations: Northeast (reference), Midwest, South, and West.

Clinical factors used in our analyses measured disease severity, prescribed medication class, and perceived health status. To assess disease burden, a categorical representation of the ACCI was used. This comorbidity index severity level variable divides our sample population into three categories using each patient's ACCI: mild ($\leq$ 5, reference), moderate (6-7), and severe ($\geq$ 8). The Multum Therapeutic Class #1 variable depicts the primary class of medication prescribed to patients and is divided into 15 distinct drug types; anti-infectives constitute the reference group for this variable. Lastly, perceived health status was divided into five categories: excellent (reference), very good, good, fair, and poor.

Sub-aim analyses used the categorical construct of polypharmacy as our exposure variable and the same hospitalization variable as our outcome variable of interest. Our training model utilized all independent variables above as well as the individual chronic illness variables used to generate the ACCI and additional utilization and socio-demographic factors. In addition to the variables included in the primary analysis, 16 more variables were included to maximize the training effect of our model; in total, 26 independent variables were included in our model.

Across the 16 additional variables, two measured socio-economic status, 10 indicated the presence of chronic illnesses, and four depicted health services utilization. Family income and education variables were added as measures of socio-economic status. Family income is a continuous variable represented in dollars (US $) and education is a categorical variable consisting of five levels: less than high school (reference), high school, Associate's or other degree, Bachelor's Degree, Master's or Doctoral degree. Binary chronic illness variables added to our model include arthritis,

asthma, cancer, cognitive limitations, coronary heart disease, diabetes, emphysema, high blood pressure, high cholesterol, and stroke. Lastly, four measures of utilization using the number of visits were included: # of emergency room visits, # of outpatient visits, # of office-based visits, and # of dental visits.

Primary Analyses

Our primary analyses utilized Time Fixed Effects Modified Poisson regression to estimate the association between polypharmacy and hospital admissions. The Fixed Effects estimator comprises calendar years corresponding to each respective year of MEPS data; year fixed effects was used to account for potential observable and unobservable systematic differences between the appended years of data. Person-level weights were divided by ten to account for the compiled years of data. The adjusted weights replaced the standard MEPS weights in the survey design. The full MEPS survey design was applied and used throughout the analysis.

Modified Poisson regression was selected for our primary analysis as it has been shown to deliver robust relative risk ratios; this measure of association is considered to be more meaningful by epidemiologists whose primary focus within most clinical research is to assess risk (Norton & Dowd, 2018b; Zou, 2004). Additionally, results derived using Modified Poisson can be compared across studies, whereas model specification issues that arise when using logistic regression preclude odds ratios from having any meaningful comparison across different models (Norton & Dowd, 2018a). Lastly, relative risk ratios allow for the discussion of results in terms of the probability of an event occurring (risk); comparison of results in terms of

percentage increases and decreases of the probability of an event occurring is more useful to research and clinical community alike.

Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were collectively used to compare prospective models; the model with the lowest AIC and BIC values was deemed optimal and used in our study. Potential correlation was assessed both pre- and post-analysis. Pre-analysis checks using correlation matrices found no significant correlation between any of our independent variables; a maximum post-estimation VIF of 4.63 ruled out the presence of multicollinearity within our model.

Sensitivity analyses for our primary aim used model variation to assess the robustness of findings. Model variation was conducted in two ways: 1) adding and subtracting independent variables from our model, 2) altering the variable construct of our primary exposure variable (polypharmacy). The first method was primarily used to determine if changes to our model impacted the statistical and practical significance of associations between the dependent and independent variables. Comparisons using the binary and categorical constructs of polypharmacy assessed the impact of polypharmacy severity on associations with hospital admissions. This method also allowed for cross-model comparisons between all independent variables to be conducted. All analyses were performed using R version 4.1.3. The full model used in the primary analysis is depicted below.

$$Y_i = \beta_0 + \beta_1 X_a + \beta_2 X_b + \beta_3 X_c + \beta_4 X_d + \beta_5 X_e + \beta_6 X_f + \beta_7 X_g + \beta_8 X_h + \beta_9 X_i + \beta_{10} X_j + \delta_{2\text{-}10} T_{11\text{-}19} + \mu_i$$

Y_i: Hospital Admission	X_f: Region of Residence
X_a: Polypharmacy	X_g: Dual Eligibility Status
X_b: Age	X_h: Comorbidity Index Severity Level
X_c: Gender	X_i: Perceived Health Status
X_d: Marital Status	X_j: Medication Class
X_e: Race/Ethnicity	$T_{11\text{-}19}$: Year Fixed Effects Estimator

Sub-aim One

Sub-aim one analyses use traditional logistic regression and ensemble methods to classify patients at-risk for hospitalization. Logistic regression is often seen as the staple method for training data used in classification models due to the binary nature of most outcomes of interest (Jones et al., 2018; Li et al., 2021). Additionally, logistic regression models have been shown to deliver some of the best and most consistent results when used in health care related applications (Malik & Munjal, 2021). In addition to logistic regression, two Boosting, and two Bagging ensemble methods were used in our predictive analyses; in total, five classification methods were employed and compared in this sub-aim.

Bagging techniques used in this study include traditional and Random Forest methods. Also known as Bootstrap aggregating, this method divides the finite training data into multiple samples with replacement and generates independent decision trees on each sample. Known as base learners, the results from these independent training models are then aggregated using a voting method unique to classification to improve the predictive capacity of our model (Zhou, 2012). The primary difference between

Traditional Bagging and Random Forest methods involves the features used to split nodes in the decision trees; Random Forest uses a random subset of features and then selects the best split feature only. Traditional Bagging, however, considers all features when splitting the nodes (Zhou, 2012). In our analyses, the maximum number of features to consider at each split point was coded into our algorithm. Traditional Bagging set the maximum number of features equal to the number of independent variables (IV) in our model; optimal performance with Random Forest was achieved using $(\sqrt{\#\, IV}\ * 2)$ number of features.

Boosting and Extreme Gradient Boosting (XGB) ensemble methods were also used and compared in our analyses. Unlike Bagging algorithms which combine weak learners trained independently on parallel samples of data, boosting techniques combine weak learners trained in sequential manners using iterative adaptations of the sample data (Zhou, 2012). Like Bagging, however, Boosting relies on the use of averaging techniques following the combination of weak learners (Zhou, 2012). Bagging and Boosting methods are both used to improve model stability; however, Bagging does so through variance reduction while Boosting is mainly used to reduce bias (Hofner et al., 2011; Zhou, 2012).

Classification models used in our analyses were trained and validated using a 70/30 partition of the data set. Prior to partitioning the data and running each respective model, the "set.seed(12345)" command was used in R to ensure that all models were trained and validated on identical subsets of the data. The cutoff score was initially set to 0.5 as it represents the threshold most commonly used in classification model studies and serves as the default threshold for most ensemble

method algorithms (Patel et al., 2022; Zhou, 2012). Lastly, while variable class requirements differed across the machine learning methods used in the analyses, the regression model used to train the data remained the same throughout the study; the regression model used is depicted below.

$$Y_i = \beta_0 + \beta_1 X_a + \beta_2 X_b + \beta_3 X_c + \beta_4 X_d + \beta_5 X_e + \beta_6 X_f + \beta_7 X_g + \beta_8 X_h + \beta_9 X_i + \beta_{10} X_j + \beta_{11} X_j + \beta_{12} X_j + \beta_{13\text{-}22} X_{m\text{-}v} + \beta_{23\text{-}26} X_{w\text{-}z} + \mu_i.$$

Y_i: Hospital Admission

X_a: Polypharmacy

X_b: Age

X_c: Gender

X_d: Marital Status

X_e: Race/Ethnicity

X_f: Region of Residence

X_g: Education

X_h: Family Income

X_i: Dual Eligibility Status

X_j: Comorbidity Index Severity Level

X_k: Perceived Health Status

X_l: Medication Class

$X_{m\text{-}v}$: Individual Chronic Illnesses

$X_{w\text{-}z}$: Measures of Utilization

Model performance was evaluated using standard classification metrics. Standard metrics of performance include accuracy, True Positive Rates (TPR or Sensitivity), True Negative Rates (TNR or Specificity), and the Receiver Operating Characteristic (ROC) area under the curve (AUC). Accuracy, sensitivity, and specificity metrics were derived using confusion matrices. Class predictions made by our machine learning algorithms were compared with the actual classes to determine

their respective performance; measured in percentages, higher values were indicative of better performance. To compare models using their AUCs, a ROC curve comparison plot was generated using the "ROCR" package in R to depict the performance of all models included in the analysis. A commonly used method for quantifying model-induced performance improvement over random selection, the AUC is an estimation of the tradeoff between true and false positive rates (Hanley & McNeil, 1982).

Sensitivity analysis for sub-aim 1 primarily involved the use of cutoff score variation. Indicating the probability threshold at which predictions are classified as likely to occur "1", cutoff scores were varied from 0.5 to 0.8 in increments of 0.05 to determine which value delivered optimal results. Cutoff score optimization was likewise evaluated using the standard classification metrics of TPR, TNR, and accuracy. Lastly, predictive algorithms were retrained after excluding polypharmacy from the model. The exclusion of polypharmacy allowed for cross-model comparison of results using the standard classification metrics. The differences in performance observed between the two models were then attributed to the impact of including polypharmacy among our predictors.

Sub-aim Two

The purpose of this sub-aim was to estimate the potential cost savings associated with use of the best performing classification method to identify elderly patients at risk for hospitalization. This analysis evaluated cost-based model performance at the sample population and national levels. Using the confusion matrices derived from our respective models, sample-based cost performance was

estimated by applying the national average cost per Medicare admission ($14,700) to false negatives and a 15% reduction (0.85 × # admissions × $14,700) to true positives. The 15% reduction estimate represents the percentage of elderly hospitalizations thought to be preventable (Mahmoudi et al., 2020).

Potential cost savings were estimated by subtracting the lowest expected cost among the classification models from the unmitigated cost (# total admissions × $14,700). The potential cost averted was then divided by the unmitigated cost to determine the percentage of reduction. To estimate potential savings at the national level, the reduction percentage was multiplied by total inpatient Medicare expenditures ($99.8 billion) in 2017 (Statistical Brief #262 | HCUP, 2020).

Results

Primary Aim

Findings from our primary analyses show polypharmacy to have a statistically and practically significant association with hospital admissions (RR: 1.592, $p < 0.001$) while fully controlling for both comorbidity severity and medication class (see Table 6.1). Furthermore, the practical significance of the association is even greater among hyperpolypharmacy patients (RR: 2.106, $p < 0.001$). In addition to polypharmacy, statistically significant associations with hospital admissions were found across socio-demographic and clinical factors.

Among socio-demographic factors, only age (RR: 1.015, $p < 0.001$) was found to have a positive association with hospital admissions. Factors found to be negatively associated with admissions include Non-Hispanic Asian race (RR: 0.502, $p < 0.001$) and South region of residence (RR: 0.896, $p < 0.05$). Gender, marital status,

and dual eligibility status were not shown to have statistically significant associations with hospital admissions within our sample population.

Among clinical factors, comorbidity index severity level and perceived health status were positively associated with hospital admissions. Moderate (RR: 1.456) and severe (RR: 1.6876) levels of comorbidity were both found to have statistically significant associations at the $p < 0.001$ level. Perceived health status was shown to be inversely related with hospitalizations; as perceived health worsened, practical significance of the associations (good = RR: 1.429, fair = RR: 1.863, poor = RR: 2.573) increased ($p < 0.001$). Across medication class, only topical agents (RR: 0.657, $p < 0.05$) were shown to have a statistically significant association with hospital admissions. Examination of the risk ratios and p-values on the fixed effects estimators indicate the absence of any discernable trend across the decade of data utilized in the study. Lastly, sensitivity analysis performed using the categorical construct of polypharmacy delivered similar findings. Statistical significance remained unchanged across all variables; while minor changes were noted to practical significance among some factors, the direction of association remained the same.

Table 6.1
Association between polypharmacy and hospital admissions

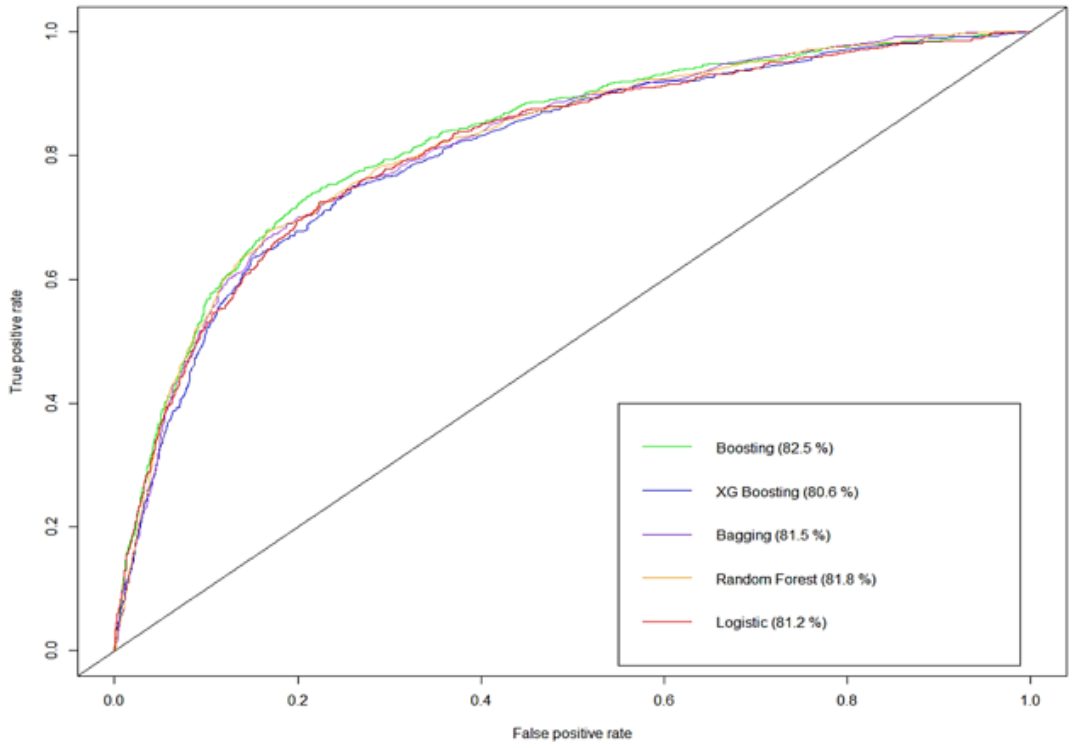
	Modified Poisson w/Binary Exposure				*Modified Poisson w/Categorical Exposure*			
	RR	*95% CI*	*Robust SE*	*p-value*	*RR*	*95% CI*	*Robust SE*	*p-value*
Polypharmacy [ref: non-polypharmacy]								
Polypharmacy	1.592	(1.433,1.768)	0.053	0.000	1.388	(1.242,1.551)	0.057	0.000
Hyperpolypharmacy					2.106	(1.855,2.392)	0.065	0.000
Age [continuous]	1.015	(1.008,1.022)	0.003	0.000	1.018	(1.011,1.025)	0.003	0.000
Gender [ref: male]								
Female	0.976	(0.890,1.071)	0.047	0.610	0.970	(0.885,1.064)	0.047	0.521
Marital Status [ref: not married]								
Married	0.932	(0.858,1.012)	0.042	0.092	0.936	(0.863,1.015)	0.041	0.111
Race/Ethnicity [ref: Non-Hispanic White]								
Non-Hispanic Black	0.930	(0.820,1.054)	0.064	0.253	0.960	(0.846,1.090)	0.064	0.529
Hispanic	0.946	(0.808,1.109)	0.080	0.494	0.972	(0.831,1.137)	0.080	0.720
Non-Hispanic Asian	0.502	(0.367,0.689)	0.160	0.000	0.514	(0.373,0.710)	0.164	0.000
Non-Hispanic Other	1.052	(0.780,1.417)	0.152	0.740	1.037	(0.769,1.399)	0.152	0.817
Region [ref: Northeast]								
Midwest	1.077	(0.948,1.223)	0.065	0.253	1.063	(0.935,1.209)	0.065	0.347
South	0.896	(0.807,0.994)	0.053	0.039	0.882	(0.794,0.979)	0.053	0.018
West	0.896	(0.789,1.017)	0.064	0.089	0.895	(0.789,1.015)	0.064	0.083
Dual Eligible [ref: No]								
Yes	1.101	(0.978,1.239)	0.060	0.110	1.079	(0.958,1.215)	0.061	0.212
Comorbidity Index Severity Level [ref: Mild]								
Moderate	1.456	(1.306,1.624)	0.055	0.000	1.419	(1.273,1.581)	0.055	0.000
Severe	1.686	(1.486,1.913)	0.064	0.000	1.599	(1.410,1.813)	0.064	0.000
Perceived Health Status [ref: Excellent]								
Very Good	1.128	(0.950,1.339)	0.087	0.168	1.118	(0.943,1.327)	0.087	0.199
Good	1.429	(1.203,1.698)	0.088	0.000	1.385	(1.166,1.645)	0.088	0.000
Fair	1.863	(1.557,2.229)	0.091	0.000	1.757	(1.465,2.107)	0.092	0.000
Poor	2.573	(2.122,3.119)	0.098	0.000	2.435	(2.006,2.956)	0.099	0.000
Multum Therapeutic Class #1 [ref: Anti-Infectives]								
Antineoplastics	0.510	(0.181,1.438)	0.527	0.202	0.518	(0.184,1.458)	0.526	0.212
Cardiovascular Agents	0.993	(0.745,1.324)	0.146	0.964	0.966	(0.723,1.291)	0.147	0.816
Central Nervous System Agents	1.210	(0.902,1.621)	0.149	0.202	1.164	(0.866,1.563)	0.15	0.313
Coagulation Modifiers	1.348	(0.928,1.958)	0.190	0.117	1.392	(0.961,2.017)	0.189	0.080
Gastro-Intestinal Agents	0.978	(0.680,1.407)	0.185	0.905	0.972	(0.674,1.402)	0.186	0.880
Hormone Modifiers	0.856	(0.616,1.189)	0.167	0.352	0.863	(0.621,1.200)	0.168	0.380
Miscellaneous Agents	1.120	(0.535,2.345)	0.376	0.763	1.119	(0.521,2.405)	0.389	0.772
Genitourinary Agents	1.023	(0.521,2.008)	0.343	0.948	1.040	(0.529,2.046)	0.344	0.909
Nutritional Products	0.824	(0.520,1.306)	0.234	0.409	0.830	(0.518,1.330)	0.240	0.437
Respiratory Agents	0.972	(0.685,1.378)	0.178	0.871	0.947	(0.667,1.343)	0.178	0.758
Topical Agents	0.657	(0.465,0.928)	0.176	0.017	0.640	(0.454,0.902)	0.175	0.011
Psychotherapeutic Agents	0.965	(0.672,1.386)	0.184	0.847	0.984	(0.684,1.414)	0.184	0.929
Immunological Agents	0.934	(0.143,6.116)	0.955	0.943	0.939	(0.145,6.079)	0.949	0.948
Metabolic Agents	0.874	(0.655,1.166)	0.147	0.359	0.857	(0.642,1.145)	0.147	0.296
Year Fixed Effects Estimator [ref: 2010]								
2011	0.961	(0.821,1.124)	0.080	0.616	0.946	(0.807,1.109)	0.081	0.495
2012	0.879	(0.658,1.173)	0.147	0.380	0.897	(0.672,1.198)	0.147	0.462
2013	1.001	(0.819,1.225)	0.102	0.989	0.965	(0.788,1.823)	0.103	0.733
2014	1.009	(0.846,1.205)	0.090	0.917	1.034	(0.868,1.233)	0.089	0.706
2015	1.074	(0.875,1.319)	0.104	0.492	1.040	(0.847,1.276)	0.104	0.710
2016	1.013	(0.844,1.216)	0.093	0.888	1.015	(0.845,1.219)	0.093	0.874
2017	1.068	(0.901,1.266)	0.086	0.446	1.067	(0.901,1.263)	0.086	0.453
2018	1.067	(0.922,1.236)	0.075	0.384	1.067	(0.922,1.234)	0.074	0.382
2019	1.062	(0.916,1.232)	0.076	0.423	1.096	(0.943,1.273)	0.076	0.231

Note: Table displays relative risk ratios, 95% confidence intervals, robust standard errors, and p-values for two regression models: 1) w/binary polypharmacy variable 2) w/categorical polypharmacy variable. Both regression models utilize MEPS Survey Design and Time Fixed Effects Modified Poisson Regression. Person-level MEPS weights were re-scaled by dividing the weights by ten (PW/10) to account for ten years of pooled data. Calendar years corresponding to each year of MEPS data were used to account for potential observable and unobservable systematic differences between the appended years of data included in the study.

Sub-aim

Findings from our first sub-aim demonstrate classification models to offer substantial improvements in predictive capacity over random selection (see Figure 6.1). With AUCs above 0.8, all models were shown to have at least an 80% chance of correctly distinguishing a patient at risk for hospitalization from a patient who is not at risk; these results suggest at least a 30% improvement over random selection is gained with the use of classification models. In terms of AUC only, Boosting was shown to be the top performing classification method with an AUC of 0.825 or 82.5%. The lowest performing model with respect to AUC was Extreme Gradient Boosting with an AUC of 0.806 or 80.6%.

Figure 6.1
Predicting Admissions: Receiver Operating Charactristic curve comparison



Comparison of models across standard classification metrics illustrated the presence of differential benefits associated with the use of each model (see Table 6.2). Across accuracy, Boosting and Random Forest ensemble methods outperformed all others at 84.9%. All models performed extremely well in terms of specificity; however, Logistic Regression proved to be the best at correctly identifying those who are not at risk (96.5%). Every ensemble method outperformed Logistic Regression when it came to correctly classifying patients at risk for hospitalization; among the ensemble methods, however, Bagging delivered the best results at 41.7%.

Table 6.2
Performance metrics by model

Model Type	*Accuracy (%)*	*Sensitivity (%)*	*Specificity (%)*	*AUC (%)*
Boosting	84.9%	39.1%	94.6%	82.5%
XG Boosting	84.2%	35.4%	94.5%	80.6%
Bagging	84.6%	41.7%	93.7%	81.5%
Random Forest	84.9%	41.4%	94.1%	81.8%
Logistic Regression	84.6%	28.5%	96.5%	81.2%

Note: Random Forest (mtry = 2*sqrt(26), Bagging (RF w/mtry = 26)

Sensitivity analysis performed using different cutoff scores showed 0.5 to be associated with the highest accuracy and sensitivity values across all models. Incremental increases in cutoff scores from 0.5 to 0.8 was marked by gradual decreases across both accuracy and sensitivity; lowest values for both metrics (83.6% and 10.6%, respectively) were observed at a cutoff score of 0.8 using Logistic Regression. Specificity, however, continued to improve as the threshold increased. The highest specificity value (99.0%) was also observed at a cutoff score of 0.8 using Logistic Regression. Lastly, the exclusion of polypharmacy from our models was associated with 0.3% reductions across accuracy and specificity and a 1.2% reduction in sensitivity. This finding shows removal of polypharmacy from among our

predictors to have the greatest impact on our ability to correctly identify the at-risk population.

Table 6.3
Comparative Cost Analysis by model (Hospital Admissions)

	Predicted	
Actual	TP 273	FN 425
	FP 179	TN 3,125

	Predicted	
Actual	TP 247	FN 451
	FP 183	TN 3,121

	Predicted	
Actual	TP 291	FN 407
	FP 208	TN 3,096

	Predicted	
Actual	TP 289	FN 409
	FP 194	TN 3,110

	Predicted	
Actual	TP 199	FN 499
	FP 116	TN 3,188

Model (*N*=4,002)	Expected Cost ($)	
	Total ($)	Per Capita ($)
Boosting	$ 9,658,635.00	$ 2,413.45
XG Boosting	$ 9,715,965.00	$ 2,427.78
Bagging	$ 9,618,945.00	$ 2,403.53
Random Forest	$ 9,623,355.00	$ 2,404.64
Logistic	$ 9,821,805.00	$ 2,454.22
Current State	$ 10,260,600.00	$ 2,563.87
Cost Averted (max)	**$ 641,655.00**	**$ 160.33**

* Totals for predictive models calculated by applying the national average Medicare admission cost ($14,700) in 2017 to False Negatives and a 15% cost reduction to True Positives (.85*N*14,700). Best performing model acheives a 6.3% reduction in admission costs valued at $641,655 (sample) and $6.29 billion (nationally).
HCUP, 2020

Findings from our second sub-aim indicate the use of Bagging methods to be associated with the lowest expected cost ($9,618,945) across the sample population (see Table 6.3). Random Forest methods delivered the second lowest cost at $9,623,335, a mere $4,410 more than the best performing model. The use of classification models to identify patients at-risk for hospitalization delivered a total savings of $641,655 across the sample; this amount constitutes a 6.3% reduction in expenditures related to hospital admissions. Through extrapolation of the results, we estimate the potential cost-savings associated with nationwide use of classification models to be valued at $6.29 billion annually. Lastly, the sensitivity loss (1.2%)

associated with excluding polypharmacy from our training model reduced cost-savings by $17,000 and $200 million at the sample and national levels, respectively.

Discussion

Findings from our primary aim suggest polypharmacy to have a practically and statistically significant association with hospital admissions after fully adjusting for comorbidity and medication class (RR: 1.592, $p < 0.001$). These findings comport with previous studies that also found polypharmacy to be positively associated with hospital admissions (Chang et al., 2020; Davies et al., 2020; Khezrian et al., 2020; Linkens et al., 2020). The findings of our study further suggest degree of polypharmacy to play a role in determining its impact on admissions. Using polypharmacy's categorical construct, we find hyperpolypharmacy's practical significance of association to be 51.7% (2.106:1.388) greater than that of standard polypharmacy. This result bolsters the findings of previous studies that have alluded to the negative health impacts of excessive prescribing among the elderly (Calderón-Larrañaga et al., 2012; Cantlay et al., 2016; Dhalwani et al., 2017). Lastly, by including comorbidity severity and medication class to our model, we addressed gaps in the research and alleviated uncertainty regarding the robustness of previous findings (Davies et al., 2020).

Findings from our first sub-aim illustrates the potential benefits associated with the use of classification models to identify elderly patients at risk for hospitalization. With corresponding AUCs above 0.80 (80%), all classification models exhibited excellent discriminatory capacity when compared with random selection (Mandrekar, 2010; Safari et al., 2016). Cross-study comparisons using

AUC scores found our results to mirror the findings of several studies that applied classification models to healthcare data with the intent of predicting hospital admissions (King et al., 2022; Patel et al., 2022; Soy Chen et al., 2020). When compared with a study by Orchard et al. (AUC: 0.68), however, our models were actually shown to exhibit greater discriminatory performance (Orchard et al., 2018).

Cross-study comparisons using the standard classification metrics of accuracy, sensitivity, and specificity demonstrated a high degree of variability among results. It was evident from our comparisons that AUC scores were preferred over traditional measures of accuracy as the primary measure of model performance; the mention of accuracy within most studies was either non-existent or stated in terms of AUC values (Jones et al., 2018; King et al., 2022; Orchard et al., 2018; Patel et al., 2022). Among the studies reviewed, only Shahid et al. examined accuracy in terms of traditional error rates using sample predictions (Shahid et al., 2019). Additionally, despite arriving at comparable results in terms of AUC scores, the studies showed considerable variation in terms of sensitivity and specificity. With respect to sensitivity, values ranged from 34.8% to 73.0% (Patel et al., 2022; Soy Chen et al., 2020). Likewise, specificity values varied greatly with a range of 43.8% to 97.1% (Jones et al., 2018; Patel et al., 2022).

The combination of consistency across AUC scores and disparities among sensitivity and specificity values are explained by the tradeoff between true positive and false positive rates used to calculate a model's respective AUC (Hajian-Tilaki, 2013). Since the combination of two metrics are used in AUC estimation, its overall score is relatively robust to changes in sensitivity and specificity that result from

cutoff score variation; the robust nature of AUC scores makes them a valuable measure of overall model performance. Furthermore, the importance of appropriate cutoff score selection cannot be overstated. Although 0.5 is used as the standard cutoff score in many studies, its selection should be made relative to the intended purpose of the classification model (Brownlee, 2020).

Further comparison of studies revealed ensemble methods to consistently outperform standard logistic regression across both standard classification metrics and AUC (King et al., 2022; Patel et al., 2022). Among ensemble methods, both Random Forest and Boosting techniques were represented in the studies (Jones et al., 2018; King et al., 2022; Patel et al., 2022). Upon review of existing results, no one ensemble method was found to consistently deliver optimal results over the others (King et al., 2022; Peterson et al., 2021); however, Boosting techniques appeared to have a slight advantage with respect to sensitivity rates in some studies (Jones et al., 2018). This result runs contrary to our findings which showed Bagging and Random Forest models to outperform both Boosting and Extreme Gradient Boosting across the sensitivity metric (see Table 6.2).

Findings from our second sub-aim illustrate the potential cost-savings associated with the use of classification models to identify elderly patients at-risk for hospitalization. These calculations imply the use of targeted intervention strategies to reduce preventable hospitalizations among those designated to be at-risk. While unplanned admissions among the elderly population are impacted by many factors, opportunities for targeted intervention may exist through deprescribing measures that

address potentially inappropriate medication use and seek to reduce the incidence of polypharmacy (Alcusky et al., 2021; Dahal & Bista, 2023).

Classification model performance evaluation using comparative cost-analysis was shown to rely almost exclusively on a model's ability to maximize true positive rates. Since our estimation assigned costs only to patients who were admitted to the hospital, the best performing model in terms of sensitivity optimized at-risk patient identification. Through advanced identification, greater potential exists for targeted intervention and the reduction of admissions. Given our approach to estimation, it was conceivable that the model associated with the highest sensitivity (Bagging) would be expected to deliver the greatest cost savings.

Our approach to estimation omits a vital component needed to derive truly accurate estimations of cost-savings, intervention costs. If sensitivity of our model were the only factor of concern, we would optimize our ability to correctly classify at-risk patients by drastically reducing the cutoff score. By reducing the cutoff score used in our model to 0.3, we boost our sensitivity to 60.5% and increase within sample cost-savings to $930,510; this new amount represents a 9.1% reduction in total admission costs. Through extrapolation of these results, we estimate national savings to approach $9.08 billion per year. Although AUCs of all models are nearly identical at cutoff scores of 0.3 and 0.5, declining specificity rates lead to a 116% increase in false positives at a cutoff of 0.3. As false positives represent intervention costs for which there are no returns on investment, each entity employing the use of classification models must decide the cutoff score that optimizes their savings. Lastly, the 1.2% increase in sensitivity and $200 million (national) increase in cost-savings

gained by including polypharmacy status within our training model provides strong support for its ongoing use within healthcare-related prediction models.

Limitations

Limitations specific to our third aim stem from both the data and methods used in our analyses. Primary limitations related to the data result from its cross-sectional composition. The use of cross-sectional data to train classification models may limit their ability to recognize consistent patterns between predictors and the outcome variable due to both intrinsic health differences (unmeasured confounding) among patients and limited exposure to similar patterns; this limitation could potentially lead to a loss in predictive capacity across our models. Similar predictive analysis studies have all used longitudinal data obtained from Electronic Health Records to train their models; this methodological difference may provide an explanation for the low sensitivity rates observed across all models. Lastly, estimation methods used to calculate potential cost-savings in our second sub-aim may have led to artificially inflated savings estimates. Given the absence of both similar studies on the topic and standardized intervention costs, no monetary value was assigned to false positives. By excluding intervention-related expenditures from our calculations, our estimates fail to accurately portray the monetary investment required to realize reduced admissions.

Chapter 7: Conclusion

The overarching goal of this dissertation was to provide a comprehensive assessment of polypharmacy's impact on the elderly population. Using nationally representative survey data, this study explored the predictors of polypharmacy, the association between polypharmacy and medical expenditures, and the association between polypharmacy and hospital admissions. This chapter provides a summary of the findings and offers suggestions regarding policy implications and the direction of future studies.

Summary of Findings

Overall findings from our study indicate polypharmacy to carry independent associations with both cost and utilization-based outcomes. The positive associations found between polypharmacy and both metrics point to the potential negative impacts of polypharmacy on the elderly population.

Aim 1: Explore the predictors of polypharmacy among individuals aged 65 and older

Findings from this aim suggest both socio-demographic and clinic factors to be associated with polypharmacy. Females, dual eligible beneficiaries, residents of the South, high income earners, patients prescribed cardiovascular agents, and patients with moderate and severe levels of comorbidity were all associated with higher risks of polypharmacy. Conversely, patients over 80 years old, married individuals, non-Hispanic Blacks, non-Hispanic Asians, and those routinely treated by medical specialists were associated with lower relative risks of polypharmacy.

Aim 2: Estimate the association between polypharmacy and total medical expenditures among individuals aged 65 and older

Findings from this aim indicate polypharmacy to have statistically significant positive associations with total, inpatient, outpatient, and prescription expenditures. Practical significance of the association between hyperpolypharmacy and total medical expenditures was found to be even greater (Coef: 0.865) while remaining statistically significant at the $p < 0.001$ level. Lastly, average marginal effects associated with polypharmacy of $3,504.92, $4,052.19, and $788.41 were seen across total, inpatient, and prescription expenditures, respectively.

Aim 3: Estimate the association between polypharmacy and hospital admissions among individuals aged 65 and older

Findings from this aim show polypharmacy to be positively associated with hospital admissions (RR: 1.592, $p < 0.001$) after adjusting for comorbidity severity and medication class. Practical significance of the association was found to be even greater among hyperpolypharmacy patients (RR: 2.106, $p < 0.001$).
Additionally, results demonstrated classification models to offer substantial improvements in predictive capacity (AUCs > 0.8) over random selection. Bagging delivered the highest sensitivity rate (41.7%) and cost savings (6.3% reduction) among models. Lastly, including polypharmacy status within our training models improved sensitivity by 1.2% and increased potential cost-savings by $200 million per year nationally.

Policy Implications

Findings from this study provide new impetus for the enactment of policies aimed at reducing the incidence of polypharmacy and its negative effects on the elderly population. Unfortunately, ongoing efforts to expand medication access by reducing drug costs have the potential to further exacerbate the problem in the absence of strict medication reconciliation policies. By ensuring comprehensive medication reviews are completed along the continuum of care, providers and care teams can reduce errors associated with incorrect dosing and drug-drug interactions (Barnsteiner, 2008). To streamline the process and improve its accuracy, machine learning methods should be leveraged to identify potential risks at the patient level. Applied to electronic health records, machine learning models are able to predict clinical outcomes with greater accuracy when compared with traditional statistical methods (Ouchi et al., 2018). To ensure consistency across organizations, prospective healthcare policy should establish guidelines for the use of these methods and ensure compliance as part of the hospital reaccreditation process.

Advancements in machine learning methods have created new opportunities for their application at various stages along the continuum of care. Using both "upstream" and "downstream" predictive modeling, organizations improve their ability to identify at-risk populations for targeted intervention. Post-identification interventions should consider deprescribing as well as other methods to reduce the risk of medication-related adverse outcomes and improve the overall health of the elderly population. In cases where prospective outcomes are similar, alternative treatment modalities should be used in lieu of pharmaceutical intervention. By

enacting data-driven policy directives at multiple echelons of governance, we improve the possibility of achieving lasting reductions across utilization and cost.

Lastly, the results of this study point to the need for a renewed focus on prevention across the healthcare spectrum. The rise in polypharmacy prevalence is primarily a consequence of increasing comorbidity among the elderly population. Despite becoming more susceptible to illness with age, many patients suffer from preventable ailments caused by unhealthy lifestyles. Tied primarily to obesity, coronary heart disease and type II diabetes are two illnesses frequently treated using pharmaceutical intervention. To reduce demand for prescription medications and lessen the impacts of polypharmacy, prevention-related policies must be enacted that improve population health and reduce the burden of disease.

Future Research Priorities

This study addressed existing gaps in the research and added new findings that improve our understanding of the impact polypharmacy has on the elderly population. Despite our efforts, however, questions remain to be answered. Through our analyses, we identified several socio-demographic factors to be potential predictors of polypharmacy. To gain a better understanding of why these disparities exist, future research should explore these associations in depth. For example, why is it that non-Hispanic Blacks and non-Hispanic Asians have lower relative risks of polypharmacy. Are the reasons tied to healthcare access among these groups? Or are there cultural components at play that would explain these findings. While this example highlights differences among racial/cultural aspects, similar levels of scrutiny must be used to

examine the reasons behind our findings across marital status, gender, and region of residence.

Our second aim indicates polypharmacy to be associated with increased expenditures across a variety of healthcare settings. While these findings point to the potential negative effects associated with polypharmacy, more clarity is needed regarding the specific pathways by which polypharmacy affects cost. While suppositions of increased utilization among polypharmacy patients is confirmed by our study, their likely exists a myriad of other factors that partially explain the differences in cost. Using sub-group analyses, future studies could attain new insights into factors outside the realm of utilization that coalesce to increase medical spending among polypharmacy patients.

Findings from our final aim strongly suggest polypharmacy to be associated with an increased risk of hospitalization. Given the consistency with which comparable results are found in the literature, future studies should focus their attention on harnessing knowledge of this relationship to reduce the risk of hospitalization among the elderly. Trained using predictive factors that include polypharmacy status, classification model proliferation within the healthcare industry represents a real opportunity to reduce both poor outcomes and healthcare spending within the target population. Future studies on this topic should employ the use of longitudinal data from Electronic Health Records to improve overall model performance.

Appendices

Table A.1
Baseline Characteristics Across Polypharmacy Level

	Total (N=13338)	Polypharmacy			P-value
		NONPOLYPHARMACY (N=5984)	POLYPHARMACY (N=5039)	HYPERPOLYPHARMACY (N=2315)	
Age (years)					
65-69	4335 (32.5%)	1985 (33.2%)	1589 (31.5%)	761 (32.9%)	0.009
70-74	3309 (24.8%)	1448 (24.2%)	1277 (25.3%)	584 (25.2%)	
75-79	2489 (18.7%)	1060 (17.7%)	950 (18.9%)	479 (20.7%)	
> 80	3205 (24.0%)	1491 (24.9%)	1223 (24.3%)	491 (21.2%)	
Gender					
MALE	5620 (42.1%)	2639 (44.1%)	2072 (41.1%)	909 (39.3%)	<0.001
FEMALE	7718 (57.9%)	3345 (55.9%)	2967 (58.9%)	1406 (60.7%)	
Marital Status					
NOT MARRIED	6439 (48.3%)	2695 (45.0%)	2524 (50.1%)	1220 (52.7%)	<0.001
MARRIED	6899 (51.7%)	3289 (55.0%)	2515 (49.9%)	1095 (47.3%)	
Race/Ethnicity					
NH WHITE	8981 (67.3%)	3973 (66.4%)	3402 (67.5%)	1606 (69.4%)	0.019
NH BLACK	1952 (14.6%)	902 (15.1%)	737 (14.6%)	313 (13.5%)	
HISPANIC	1416 (10.6%)	623 (10.4%)	547 (10.9%)	246 (10.6%)	
NH ASIAN	725 (5.4%)	375 (6.3%)	255 (5.1%)	95 (4.1%)	
NH OTHER/MULTI-RACE	264 (2.0%)	111 (1.9%)	98 (1.9%)	55 (2.4%)	
Education					
LESS THAN HIGH SCHOOL	2739 (20.5%)	1151 (19.2%)	1095 (21.7%)	493 (21.3%)	<0.001
HIGH SCHOOL	6084 (45.6%)	2669 (44.6%)	2314 (45.9%)	1101 (47.6%)	
AA OR OTHER DEGREE	1009 (7.6%)	464 (7.8%)	366 (7.3%)	179 (7.7%)	
BACHELORS	1935 (14.5%)	944 (15.8%)	699 (13.9%)	292 (12.6%)	
MASTERS OR DOCTORAL	1571 (11.8%)	756 (12.6%)	565 (11.2%)	250 (10.8%)	
Poverty Level					
POOR	1769 (13.3%)	767 (12.8%)	682 (13.5%)	320 (13.8%)	<0.001
NEAR POOR	829 (6.2%)	341 (5.7%)	321 (6.4%)	167 (7.2%)	
LOW INCOME	2245 (16.8%)	987 (16.5%)	822 (16.3%)	436 (18.8%)	
MIDDLE INCOME	3846 (28.8%)	1692 (28.3%)	1466 (29.1%)	688 (29.7%)	
HIGH INCOME	4649 (34.9%)	2197 (36.7%)	1748 (34.7%)	704 (30.4%)	
Residence Region					
NORTHEAST	2427 (18.2%)	1130 (18.9%)	912 (18.1%)	385 (16.6%)	<0.001
MIDWEST	2840 (21.3%)	1246 (20.8%)	1074 (21.3%)	520 (22.5%)	
SOUTH	5159 (38.7%)	2219 (37.1%)	1964 (39.0%)	976 (42.2%)	
WEST	2912 (21.8%)	1389 (23.2%)	1089 (21.6%)	434 (18.7%)	
Dual Eligible					
NO	11340 (85.0%)	5264 (88.0%)	4261 (84.6%)	1815 (78.4%)	<0.001
YES	1998 (15.0%)	720 (12.0%)	778 (15.4%)	500 (21.6%)	
Comorbidity Index Level					
MILD	6944 (52.1%)	3639 (60.8%)	2482 (49.3%)	823 (35.6%)	<0.001
MODERATE	4555 (34.2%)	1782 (29.8%)	1848 (36.7%)	925 (40.0%)	
Perceived Health Status					
EXCELLENT	2165 (16.2%)	1328 (22.2%)	685 (13.6%)	152 (6.6%)	<0.001
VERY GOOD	3874 (29.0%)	1952 (32.6%)	1463 (29.0%)	459 (19.8%)	
GOOD	4239 (31.8%)	1724 (28.8%)	1712 (34.0%)	803 (34.7%)	
FAIR	2351 (17.6%)	790 (13.2%)	901 (17.9%)	660 (28.5%)	
POOR	709 (5.3%)	190 (3.2%)	278 (5.5%)	241 (10.4%)	
Usual Source of Care Provider					
GENERAL PRACTICE	12726 (95.4%)	5677 (94.9%)	4817 (95.6%)	2232 (96.4%)	0.107
MEDICAL SPECIALIST	577 (4.3%)	287 (4.8%)	211 (4.2%)	79 (3.4%)	
ALTERNATIVE CARE	35 (0.3%)	20 (0.3%)	11 (0.2%)	4 (0.2%)	
Primary Pharmacy Type					
CLINIC/HOSPITAL	887 (6.7%)	383 (6.4%)	338 (6.7%)	166 (7.2%)	0.223
DRUG STORE	6676 (50.1%)	3018 (50.4%)	2535 (50.3%)	1123 (48.5%)	
OTHER STORE	3672 (27.5%)	1690 (28.2%)	1363 (27.0%)	619 (26.7%)	
MAIL-ORDER	1998 (15.0%)	845 (14.1%)	760 (15.1%)	393 (17.0%)	
ONLINE	105 (0.8%)	48 (0.8%)	43 (0.9%)	14 (0.6%)	

Multum Therapeutic Class #1					
ANTI-INFECTIVES	434 (3.3%)	330 (5.5%)	81 (1.6%)	23 (1.0%)	<0.001
ANTINEOPLASTICS	68 (0.5%)	44 (0.7%)	20 (0.4%)	4 (0.2%)	
CARDIOVASCULAR AGENTS	4728 (35.4%)	1694 (28.3%)	2052 (40.7%)	982 (42.4%)	
CNS AGENTS	1644 (12.3%)	667 (11.1%)	595 (11.8%)	382 (16.5%)	
COAGULATION MODIFIERS	292 (2.2%)	177 (3.0%)	99 (2.0%)	16 (0.7%)	
GI AGENTS	428 (3.2%)	236 (3.9%)	148 (2.9%)	44 (1.9%)	
HORMONE MODIFIERS	802 (6.0%)	486 (8.1%)	246 (4.9%)	70 (3.0%)	
MISCELLANEOUS AGENTS	42 (0.3%)	18 (0.3%)	19 (0.4%)	5 (0.2%)	
GENITOURINARY AGENTS	72 (0.5%)	40 (0.7%)	24 (0.5%)	8 (0.3%)	
NUTRITIONAL PRODUCTS	178 (1.3%)	94 (1.6%)	59 (1.2%)	25 (1.1%)	
RESPIRATORY AGENTS	397 (3.0%)	152 (2.5%)	157 (3.1%)	88 (3.8%)	
TOPICAL AGENTS	728 (5.5%)	392 (6.6%)	236 (4.7%)	100 (4.3%)	
PSYCHOTHERAPEUTIC AGENTS	400 (3.0%)	200 (3.3%)	151 (3.0%)	49 (2.1%)	
IMMUNOLOGICAL AGENTS	8 (0.1%)	7 (0.1%)	1 (0.0%)	0 (0%)	
METABOLIC AGENTS	3117 (23.4%)	1447 (24.2%)	1151 (22.8%)	519 (22.4%)	
Year Fixed Effects Estimator					
10	1502 (11.3%)	643 (10.7%)	573 (11.4%)	286 (12.4%)	<0.001
11	1210 (9.1%)	511 (8.5%)	449 (8.9%)	250 (10.8%)	
12	557 (4.2%)	325 (5.4%)	181 (3.6%)	51 (2.2%)	
13	760 (5.7%)	219 (3.7%)	311 (6.2%)	230 (9.9%)	
14	1443 (10.8%)	734 (12.3%)	544 (10.8%)	165 (7.1%)	
15	797 (6.0%)	257 (4.3%)	326 (6.5%)	214 (9.2%)	
16	1379 (10.3%)	622 (10.4%)	516 (10.2%)	241 (10.4%)	
17	1341 (10.1%)	556 (9.3%)	538 (10.7%)	247 (10.7%)	
18	2255 (16.9%)	969 (16.2%)	870 (17.3%)	416 (18.0%)	
19	2094 (15.7%)	1148 (19.2%)	731 (14.5%)	215 (9.3%)	

Table A.2
Aim 1 model comparison between modified poisson and logistic regression

	Modified Poisson				*Logistic*			
	OR	*95% CI*	*Robust SE*	*p-value*	*OR*	*95% CI*	*SE*	*p-value*
Age [ref: 65-69 years]								
70-74	0.986	(0.939,1.036)	0.025	0.576	0.967	(0.857,1.092)	0.062	0.589
75-79	0.963	(0.915,1.013)	0.026	0.146	0.906	(0.794,1.034)	0.067	0.143
> 80	0.875	(0.830,0.922)	0.027	0.000	0.704	(0.618,0.801)	0.066	0.000
Gender [ref: male]								
Female	1.088	(1.047,1.131)	0.020	0.000	1.236	(1.121,1.362)	0.049	0.000
Marital Status [ref: not married]								
Married	0.930	(0.894,0.968)	0.020	0.000	0.832	(0.752,0.920)	0.051	0.000
Race/Ethnicity [ref: Non-Hispanic White]								
Non-Hispanic Black	0.864	(0.818,0.914)	0.028	0.000	0.696	(0.608,0.796)	0.068	0.000
Hispanic	0.957	(0.897,1.020)	0.035	0.173	0.891	(0.759,1.047)	0.082	0.162
Non-Hispanic Asian	0.880	(0.788,0.982)	0.056	0.023	0.741	(0.583,0.941)	0.121	0.014
Non-Hispanic Other	1.007	(0.895,1.133)	0.060	0.905	1.040	(0.754,1.435)	0.164	0.811
Education [ref: Less than HS]								
High School	1.061	(1.015,1.108)	0.022	0.008	1.180	(1.050,1.325)	0.059	0.006
Associate's/Other Degree	0.975	(0.904,1.052)	0.039	0.515	0.966	(0.801,1.164)	0.095	0.713
Bachelor's Degree	1.040	(0.979,1.105)	0.031	0.202	1.126	(0.967,1.311)	0.077	0.126
Master's or Doctoral Degree	1.069	(0.955,1.148)	0.036	0.067	1.204	(1.007,1.440)	0.091	0.042
Poverty Level [ref: Poor]								
Near Poor	1.006	(0.926,1.092)	0.042	0.892	1.036	(0.836,1.284)	0.109	0.744
Low Income	1.028	(0.961,1.099)	0.034	0.428	1.087	(0.913,1.293)	0.088	0.347
Middle Income	1.077	(1.008,1.115)	0.034	0.029	1.219	(1.027,1.448)	0.087	0.024
High Income	1.107	(1.030,1.190)	0.037	0.006	1.300	(1.084,1.560)	0.092	0.005
Region [ref: Northeast]								
Midwest	1.035	(0.979,1.094)	0.028	0.222	1.086	(0.949,1.244)	0.069	0.229
South	1.060	(1.007,1.115)	0.026	0.026	1.155	(1.019,1.308)	0.064	0.024
West	1.021	(0.959,1.088)	0.032	0.509	1.048	(0.901,1.219)	0.077	0.541
Comorbidity Index Severity Level [ref: Mild]								
Moderate	1.217	(1.163,1.274)	0.023	0.000	1.609	(1.440,1.799)	0.057	0.000
Severe	1.306	(1.238,1.377)	0.027	0.000	2.066	(1.772,2.407)	0.078	0.000
Dual Eligible [ref: No]								
Yes	1.110	(1.051,1.173)	0.028	0.000	1.326	(1.135,1.549)	0.079	0.000
Perceived Health Status [ref: Excellent]								
Very Good	1.209	(1.119,1.305)	0.039	0.000	1.425	(1.228,1.653)	0.076	0.000
Good	1.426	(1.327,1.531)	0.036	0.000	2.144	(1.857,2.474)	0.073	0.000
Fair	1.524	(1.418,1.638)	0.037	0.000	2.641	(2.258,3.090)	0.080	0.000
Poor	1.561	(1.437,1.696)	0.042	0.000	3.039	(2.423,3.811)	0.115	0.000
Usual Source of Care Provider Type [ref: General Practice]								
Medical Specialist	0.893	(0.810,0.985)	0.050	0.024	0.766	(0.616,0.952)	0.110	0.016
Alternative Care	0.683	(0.433,1.079)	0.232	0.102	0.495	(0.242,1.014)	0.364	0.054
Primary Pharmacy Type Used [ref: Clinic/Hospital]								
Drug Store	0.967	(0.0.899,1.041)	0.037	0.375	0.923	(0.765,1.113)	0.095	0.399
Other Store	0.966	(0.888,1.052)	0.043	0.431	0.917	(0.740,1.137)	0.109	0.430
Mail-Order	1.041	(0.956,1.132)	0.043	0.354	1.112	(0.893,1.385)	0.111	0.342
Online	0.989	(0.799,1.224)	0.108	0.918	0.983	(0.593,1.628)	0.256	0.946
Multum Therapeutic Class #1 [ref: Anti-Infectives]								
Antineoplastics	1.136	(0.746,1.730)	0.214	0.552	1.111	(0.559,2.209)	0.349	0.763
Cardiovascular Agents	2.235	(1.885,2.651)	0.087	0.000	4.801	(3.743,6.157)	0.127	0.000
Central Nervous System Agents	1.939	(1.626,2.313)	0.090	0.000	3.264	(2.489,4.281)	0.138	0.000
Coagulation Modifiers	1.371	(1.073,1.751)	0.124	0.012	1.613	(1.085,2.398)	0.202	0.018
Gastro-Intestinal Agents	1.555	(1.257,1.923)	0.108	0.000	1.997	(1.409,2.830)	0.177	0.000
Hormone Modifiers	1.533	(1.260,1.865)	0.010	0.000	1.993	(1.470,2.702)	0.155	0.000
Miscellaneous Agents	1.807	(1.214,2.690)	0.202	0.004	2.743	(1.230,6.113)	0.407	0.014
Genitourinary Agents	1.452	(1.010,2.089)	0.185	0.044	1.706	(0.859,3.389)	0.349	0.127
Nutritional Products	1.650	(1.290,2.109)	0.125	0.000	2.195	(1.414,3.407)	0.223	0.000
Respiratory Agents	2.081	(1.705,2.540)	0.101	0.000	3.924	(2.686,5.733)	0.193	0.000
Topical Agents	1.742	(1.446,2.099)	0.095	0.000	2.592	(1.938,3.468)	0.148	0.000
Psychotherapeutic Agents	1.598	(1.296,1.970)	0.106	0.000	2.072	(1.454,2.952)	0.180	0.000
Immunological Agents	0.519	(0.085,3.177)	0.921	0.477	0.469	(0.058,3.762)	1.059	0.475
Metabolic Agents	1.845	(1.544,2.205)	0.091	0.000	2.901	(2.220,3.791)	0.136	0.000

Year Fixed Effects Estimator [ref: 2010]

2011	1.043	(0.957,1.138)	0.044	0.337	1.111	(0.881,1.402)	0.118	0.373
2012	0.755	(0.667,0.854)	0.063	0.000	0.544	(0.423,0.701)	0.129	0.000
2013	1.194	(1.109,1.285)	0.038	0.000	1.780	(1.383,2.290)	0.128	0.000
2014	0.854	(0.784,0.930)	0.043	0.000	0.691	(0.567,0.842)	0.100	0.000
2015	1.168	(1.092,1.249)	0.034	0.000	1.612	(1.303,1.994)	0.108	0.000
2016	0.944	(0.878,1.014)	0.037	0.115	0.871	(0.726,1.045)	0.093	0.137
2017	0.988	(0.917,1.063)	0.038	0.740	0.972	(0.805,1.175)	0.096	0.770
2018	0.985	(0.928,1.046)	0.030	0.618	0.968	(0.826,1.133)	0.080	0.682
2019	0.782	(0.730,0.838)	0.035	0.000	0.578	(0.493,0.678)	0.081	0.000

Note: Table displays odds ratios, 95% confidence intervals, robust standard errors, and p-values for two Time Fixed Effects Logistic Regression models: 1) w/MEPS Survey Design and 2) w/out MEPS Survey Design. Person-level MEPS weights were re-scaled by dividing the weights by ten (PW/10) to account for ten years of pooled data. Calendar years corresponding to each year of MEPS data were used to account for potential observable and unobservable systematic differences between the appended years of data included in the study.

Bibliography

2020 Profile of Older Americans. (n.d.). 21.

Abe, T., Tamiya, N., Kitahara, T., & Tokuda, Y. (2015). Polypharmacy as a risk factor for hospital admission among ambulance-transported old-old patients. *Acute Medicine & Surgery*, *3*(2), 107–113. https://doi.org/10.1002/ams2.153

Admi, H., Shadmi, E., Baruch, H., & Zisberg, A. (2015). From Research to Reality: Minimizing the Effects of Hospitalization on Older Adults. *Rambam Maimonides Medical Journal*, *6*(2). https://doi.org/10.5041/RMMJ.10201

Alcusky, M., Thomas, R. B., Jafari, N., Keith, S. W., Kee, A., Del Canale, S., Lombardi, M., & Maio, V. (2021). Reduction in unplanned hospitalizations associated with a physician focused intervention to reduce potentially inappropriate medication use among older adults: A population-based cohort study. *BMC Geriatrics*, *21*(1), Article 1. https://doi.org/10.1186/s12877-021-02172-3

Alhawassi, T. M., Krass, I., Bajorek, B. V., & Pont, L. G. (2014). A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clinical Interventions in Aging*, *9*, 2079–2086. https://doi.org/10.2147/CIA.S71178

Alshabanat, A., Zafari, Z., Albanyan, O., Dairi, M., & FitzGerald, J. M. (2015). Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. *PloS One*, *10*(9), e0136065. https://doi.org/10.1371/journal.pone.0136065

Ambrose, A. F., Paul, G., & Hausdorff, J. M. (2013). Risk factors for falls among older adults: A review of the literature. *Maturitas*, *75*(1), 51–61. https://doi.org/10.1016/j.maturitas.2013.02.009

Andersen, R. M. (1995a). Revisiting the Behavioral Model and Access to Medical Care: Does it Matter? *Journal of Health and Social Behavior*, *36*(1), 1–10. https://doi.org/10.2307/2137284

Andersen, R. M. (1995b). Revisiting the behavioral model and access to medical care: Does it matter? *Journal of Health and Social Behavior*, *36*(1), 1–10.

Andersen, R., & Newman, J. F. (1973). Societal and Individual Determinants of Medical Care Utilization in the United States. *The Milbank Memorial Fund Quarterly. Health and Society*, *51*(1), 95–124. https://doi.org/10.2307/3349613

Barnason, S., Zimmerman, L., Hertzog, M., & Schulz, P. (2010). Pilot testing of a medication self-management transition intervention for heart failure patients. *Western Journal of Nursing Research*, *32*(7), 849–870. https://doi.org/10.1177/0193945910371216

Barnsteiner, J. H. (2008). Medication Reconciliation. In R. G. Hughes (Ed.), *Patient Safety and Quality: An Evidence-Based Handbook for Nurses*. Agency for Healthcare Research and Quality (US). http://www.ncbi.nlm.nih.gov/books/NBK2648/

Beers, M. H., Ouslander, J. G., Rollingher, I., Reuben, D. B., Brooks, J., & Beck, J. C. (1991). Explicit criteria for determining inappropriate medication use in

nursing home residents. UCLA Division of Geriatric Medicine. *Archives of Internal Medicine*, *151*(9), 1825–1832.

Blanes-Selva, V., Ruiz-García, V., Tortajada, S., Benedí, J.-M., Valdivieso, B., & García-Gómez, J. M. (2021). Design of 1-year mortality forecast at hospital admission: A machine learning approach. *Health Informatics Journal*, *27*(1), 1460458220987580. https://doi.org/10.1177/1460458220987580

Brownlee, J. (2020, February 9). A Gentle Introduction to Threshold-Moving for Imbalanced Classification. *MachineLearningMastery.Com*. https://machinelearningmastery.com/threshold-moving-for-imbalanced-classification/

Budnitz, D. S., Lovegrove, M. C., Shehab, N., & Richards, C. L. (2011). Emergency hospitalizations for adverse drug events in older Americans. *The New England Journal of Medicine*, *365*(21), 2002–2012. https://doi.org/10.1056/NEJMsa1103053

Bureau, U. C. (n.d.). *Demographic Turning Points for the United States: Population Projections for 2020 to 2060*. Census.Gov. Retrieved April 6, 2023, from https://www.census.gov/library/publications/2020/demo/p25-1144.html

By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. (2019). American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults: 2019 AGS BEERS CRITERIA® UPDATE EXPERT PANEL. *Journal of the American Geriatrics Society*, *67*(4), 674–694. https://doi.org/10.1111/jgs.15767

Calderón-Larrañaga, A., Poblador-Plou, B., González-Rubio, F., Gimeno-Feliu, L. A., Abad-Díez, J. M., & Prados-Torres, A. (2012). Multimorbidity, polypharmacy, referrals, and adverse drug events: Are we doing things well? *British Journal of General Practice*, *62*(605), e821–e826. https://doi.org/10.3399/bjgp12X659295

Cantlay, A., Glyn, T., & Barton, N. (2016). Polypharmacy in the elderly. *InnovAiT*, *9*(2), 69–77. https://doi.org/10.1177/1755738015614038

Cashion, W., McClellan, W., Howard, G., Goyal, A., Kleinbaum, D., Goodman, M., Prince, V., Muntner, P., McClure, L. A., McClellan, A., & Judd, S. (2015). Geographic region and racial variations in polypharmacy in the United States. *Annals of Epidemiology*, *25*(6), 433-438.e1. https://doi.org/10.1016/j.annepidem.2015.01.018

Castell, M.-V., Sánchez, M., Julián, R., Queipo, R., Martín, S., & Otero, Á. (2013). Frailty prevalence and slow walking speed in persons aged 65 and older: Implications for primary care. *BMC Family Practice*, *14*, 86. https://doi.org/10.1186/1471-2296-14-86

Chang, T. I., Park, H., Kim, D. W., Jeon, E. K., Rhee, C. M., Kalantar-Zadeh, K., Kang, E. W., Kang, S.-W., & Han, S. H. (2020). Polypharmacy, hospitalization, and mortality risk: A nationwide cohort study. *Scientific Reports*, *10*(1), 18964. https://doi.org/10.1038/s41598-020-75888-8

Changes in Hospitalizations and In-Hospital Deaths for Adults Aged 65 Years and Older in the Initial Period of the COVID-19 Pandemic (April-September 2020), 13 States #285. (n.d.). Retrieved March 31, 2022, from

https://www.hcup-us.ahrq.gov/reports/statbriefs/sb285-COVID-19-OverAge64Hosptl.jsp

Charlson, M. E., Carrozzino, D., Guidi, J., & Patierno, C. (2022). Charlson Comorbidity Index: A Critical Review of Clinimetric Properties. *Psychotherapy and Psychosomatics*, *91*(1), 8–35. https://doi.org/10.1159/000521288

Charlson, M., Szatrowski, T. P., Peterson, J., & Gold, J. (1994). Validation of a combined comorbidity index. *Journal of Clinical Epidemiology*, *47*(11), 1245–1251. https://doi.org/10.1016/0895-4356(94)90129-5

Chhetri, J. K., Zheng, Z., Xu, X., Ma, C., & Chan, P. (2017). The prevalence and incidence of frailty in Pre-diabetic and diabetic community-dwelling older population: Results from Beijing longitudinal study of aging II (BLSA-II). *BMC Geriatrics*, *17*(1), 47. https://doi.org/10.1186/s12877-017-0439-y

Coleman, J. J., & Pontefract, S. K. (2016). Adverse drug reactions. *Clinical Medicine*, *16*(5), 481–485. https://doi.org/10.7861/clinmedicine.16-5-481

Courtney, M. D., Edwards, H. E., Chang, A. M., Parker, A. W., Finlayson, K., & Hamilton, K. (2011). A randomised controlled trial to prevent hospital readmissions and loss of functional ability in high-risk older adults: A study protocol. *BMC Health Services Research*, *11*, 202. https://doi.org/10.1186/1472-6963-11-202

Dahal, R., & Bista, S. (2023). Strategies To Reduce Polypharmacy in the Elderly. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK574550/

Davies, L. E., Spiers, G., Kingston, A., Todd, A., Adamson, J., & Hanratty, B. (2020). Adverse Outcomes of Polypharmacy in Older People: Systematic Review of Reviews. *Journal of the American Medical Directors Association*, *21*(2), 181–187. https://doi.org/10.1016/j.jamda.2019.10.022

De Paepe, P., Petrovic, M., Outtier, L., Van Maele, G., & Buylaert, W. (2013). Drug interactions and adverse drug reactions in the older patients admitted to the emergency department. *Acta Clinica Belgica*, *68*(1), 15–21. https://doi.org/10.2143/ACB.68.1.2062714

Deandrea, S., Lucenteforte, E., Bravi, F., Foschi, R., La Vecchia, C., & Negri, E. (2010). Risk factors for falls in community-dwelling older people: A systematic review and meta-analysis. *Epidemiology (Cambridge, Mass.)*, *21*(5), 658–668. https://doi.org/10.1097/EDE.0b013e3181e89905

Deb, P., Manning, W. G., & Norton, E. C. (2014). *Modeling Health Care Costs and Counts*. ASHEcon, Los Angeles. http://econ.hunter.cuny.edu/parthadeb/wp-content/uploads/sites/4/2014/05/ASHEcon_LosAngeles_minicourse.pdf

Deb, P., & Norton, E. C. (2018). Modeling Health Care Expenditures and Use. *Annual Review of Public Health*, *39*, 489–505.

Dhalwani, N. N., Fahami, R., Sathanapally, H., Seidu, S., Davies, M. J., & Khunti, K. (2017). Association between polypharmacy and falls in older adults: A longitudinal study from England. *BMJ Open*, *7*(10), e016358. https://doi.org/10.1136/bmjopen-2017-016358

Donabedian, A. (1988). The quality of care. How can it be assessed? *JAMA*, *260*(12), 1743–1748. https://doi.org/10.1001/jama.260.12.1743

Dunn, P., & Smyth, G. (2001). *Tweedie Family Densities: Methods of Evaluation*.

Edwards, I. R., & Aronson, J. K. (2000). Adverse drug reactions: Definitions, diagnosis, and management. *The Lancet*, *356*(9237), 1255–1259. https://doi.org/10.1016/S0140-6736(00)02799-9

Ellenbogen, M. I., Wang, P., Overton, H. N., Fahim, C., Park, A., Bruhn, W. E., Carnahan, J. L., Linsky, A. M., Balogun, S. A., & Makary, M. A. (2020). Frequency and Predictors of Polypharmacy in US Medicare Patients: A Cross-Sectional Analysis at the Patient and Physician Levels. *Drugs & Aging*, *37*(1), 57–65. https://doi.org/10.1007/s40266-019-00726-0

Florence, C. S., Bergen, G., Atherly, A., Burns, E., Stevens, J., & Drake, C. (2018). Medical Costs of Fatal and Nonfatal Falls in Older Adults. *Journal of the American Geriatrics Society*, *66*(4), 693–698. https://doi.org/10.1111/jgs.15304

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W. J., Burke, G., McBurnie, M. A., & Cardiovascular Health Study Collaborative Research Group. (2001). Frailty in older adults: Evidence for a phenotype. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *56*(3), M146-156. https://doi.org/10.1093/gerona/56.3.m146

Fried, T. R., O'Leary, J., Towle, V., Goldstein, M. K., Trentalange, M., & Martin, D. K. (2014). Health Outcomes Associated with Polypharmacy in Community-Dwelling Older Adults: A Systematic Review. *Journal of the American Geriatrics Society*, *62*(12), 2261–2272. https://doi.org/10.1111/jgs.13153

Gill, T. M., Allore, H. G., Holford, T. R., & Guo, Z. (2004). Hospitalization, Restricted Activity, and the Development of Disability Among Older Persons. *JAMA*, *292*(17), 2115–2124. https://doi.org/10.1001/jama.292.17.2115

Gnjidic, D., Hilmer, S. N., Blyth, F. M., Naganathan, V., Cumming, R. G., Handelsman, D. J., McLachlan, A. J., Abernethy, D. R., Banks, E., & Le Couteur, D. G. (2012). High-risk prescribing and incidence of frailty among older community-dwelling men. *Clinical Pharmacology and Therapeutics*, *91*(3), 521–528. https://doi.org/10.1038/clpt.2011.258

Gnjidic, D., Hilmer, S. N., Blyth, F. M., Naganathan, V., Waite, L., Seibel, M. J., McLachlan, A. J., Cumming, R. G., Handelsman, D. J., & Le Couteur, D. G. (2012). Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *Journal of Clinical Epidemiology*, *65*(9), 989–995. https://doi.org/10.1016/j.jclinepi.2012.02.018

Guthrie, B., Makubate, B., Hernandez-Santiago, V., & Dreischulte, T. (2015). The rising tide of polypharmacy and drug-drug interactions: Population database analysis 1995-2010. *BMC Medicine*, *13*, 74. https://doi.org/10.1186/s12916-015-0322-7

Gutiérrez-Valencia, M., Izquierdo, M., Cesari, M., Casas-Herrero, Á., Inzitari, M., & Martínez-Velilla, N. (2018). The relationship between frailty and polypharmacy in older people: A systematic review. *British Journal of Clinical Pharmacology*, *84*(7), 1432–1444. https://doi.org/10.1111/bcp.13590

Haddad, Y. K., Bergen, G., & Florence, C. (2019). Estimating the Economic Burden Related to Older Adult Falls by State. *Journal of Public Health Management and Practice : JPHMP*, *25*(2), E17–E24. https://doi.org/10.1097/PHH.0000000000000816

Hajian-Tilaki, K. (2013). Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. *Caspian Journal of Internal Medicine*, *4*(2), 627–635.

Halli-Tierney, A., Scarbrough, C., & Carroll, D. G. (2019). Polypharmacy: Evaluating Risks and Deprescribing. *American Family Physician*, *100*(1), 32–38.

Hammami, S., Zarrouk, A., Piron, C., Almas, I., Sakly, N., & Latteur, V. (2020). Prevalence and factors associated with frailty in hospitalized older patients. *BMC Geriatrics*, *20*, 144. https://doi.org/10.1186/s12877-020-01545-4

Hammond, T., & Wilson, A. (2013). Polypharmacy and Falls in the Elderly: A Literature Review. *Nursing and Midwifery Studies*, *2*(2), 171–175.

Hanley, J. A., & McNeil, B. J. (1982). The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*, *143*(1), 29–36. https://doi.org/10.1148/radiology.143.1.7063747

Hartman, M., Martin, A. B., Benson, J., Catlin, A., & The, N. H. E. A. T. (2020). National Health Care Spending In 2018: Growth Driven by Accelerations in Medicare and Private Insurance Spending. *Health Affairs*, *39*(1), 8–17. https://doi.org/10.1377/hlthaff.2019.01451

Health Policy Data Requests—Percent of U.S. Adults 55 and Over with Chronic Conditions. (2019, February 7). https://www.cdc.gov/nchs/health_policy/adult_chronic_conditions.htm

Heffernan, C. J. (1988). Social foundations of thought and action: A social cognitive theory, Albert Bandura Englewood Cliffs, New Jersey: Prentice Hall, 1986, xiii + 617 pp. Hardback. US$39.50. *Behaviour Change*, *5*(1), 37–38. https://doi.org/10.1017/S0813483900008238

Held, F., Le Couteur, D. G., Blyth, F. M., Hirani, V., Naganathan, V., Waite, L. M., Seibel, M. J., Handelsman, D. J., Cumming, R. G., Allore, H. G., & Gnjidic, D. (2017). Polypharmacy in older adults: Association Rule and Frequent-Set Analysis to evaluate concomitant medication use. *Pharmacological Research*, *116*, 39–44. https://doi.org/10.1016/j.phrs.2016.12.018

Herr, M., Robine, J.-M., Pinot, J., Arvieu, J.-J., & Ankri, J. (2015). Polypharmacy and frailty: Prevalence, relationship, and impact on mortality in a French sample of 2350 old people. *Pharmacoepidemiology and Drug Safety*, *24*(6), 637–646. https://doi.org/10.1002/pds.3772

Herr, M., Sirven, N., Grondin, H., Pichetti, S., & Sermet, C. (2017). Frailty, polypharmacy, and potentially inappropriate medications in old people: Findings in a representative sample of the French population. *European Journal of Clinical Pharmacology*, *73*(9), 1165–1172. https://doi.org/10.1007/s00228-017-2276-5

Herzog, R., Álvarez-Pasquin, M. J., Díaz, C., Del Barrio, J. L., Estrada, J. M., & Gil, Á. (2013). Are healthcare workers' intentions to vaccinate related to their

knowledge, beliefs and attitudes? A systematic review. *BMC Public Health*, *13*, 154. https://doi.org/10.1186/1471-2458-13-154

Hilmer, S. N., Tran, K., Rubie, P., Wright, J., Gnjidic, D., Mitchell, S. J., Matthews, S., & Carroll, P. R. (2011). Gentamicin pharmacokinetics in old age and frailty. *British Journal of Clinical Pharmacology*, *71*(2), 224–231. https://doi.org/10.1111/j.1365-2125.2010.03825.x

Hofner, B., Hothorn, T., Kneib, T., & Schmid, M. (2011). A Framework for Unbiased Model Selection Based on Boosting. *Journal of Computational and Graphical Statistics*, *20*(4), 956–971.

IPUMS MEPS. (n.d.). Retrieved February 28, 2023, from https://meps.ipums.org/meps/userNotes_linking_to_MEPS.shtml

Johnell, K., Jonasdottir Bergman, G., Fastbom, J., Danielsson, B., Borg, N., & Salmi, P. (2017). Psychotropic drugs and the risk of fall injuries, hospitalisations and mortality among older adults. *International Journal of Geriatric Psychiatry*, *32*(4), 414–420. https://doi.org/10.1002/gps.4483

Jokanovic, N., Tan, E. C. K., Dooley, M. J., Kirkpatrick, C. M., & Bell, J. S. (2015). Prevalence and Factors Associated with Polypharmacy in Long-Term Care Facilities: A Systematic Review. *Journal of the American Medical Directors Association*, *16*(6), 535.e1-535.e12. https://doi.org/10.1016/j.jamda.2015.03.003

Jones, A., Costa, A. P., Pesevski, A., & McNicholas, P. D. (2018). Predicting hospital and emergency department utilization among community-dwelling older

adults: Statistical and machine learning approaches. *PLoS ONE*, *13*(11), e0206662. https://doi.org/10.1371/journal.pone.0206662

Jyrkkä, J., Enlund, H., Korhonen, M. J., Sulkava, R., & Hartikainen, S. (2009). Patterns of Drug Use and Factors Associated with Polypharmacy and Excessive Polypharmacy in Elderly Persons. *Drugs & Aging*, *26*(6), 493–503. https://doi.org/10.2165/00002512-200926060-00006

Kaufman, G. (2011). Polypharmacy in older adults. *Nursing Standard (through 2013); London*, *25*(38), 49–55; quiz 58.

Kennel, P. J., Kneifati-Hayek, J., Bryan, J., Mehta, K., Banerjee, S., Sobol, I., Safford, M., & Goyal, P. (2018). Prevalence and Determinants of Hyperpolypharmacy in Adults with Heart Failure. *Journal of Cardiac Failure*, *24*(8, Supplement), S33. https://doi.org/10.1016/j.cardfail.2018.07.096

Khezrian, M., McNeil, C. J., Murray, A. D., & Myint, P. K. (2020). An overview of prevalence, determinants and health outcomes of polypharmacy. *Therapeutic Advances in Drug Safety*, *11*, 2042098620933741. https://doi.org/10.1177/2042098620933741

Kim, Y. J., & Park, H. (2019). Improving Prediction of High-Cost Health Care Users with Medical Check-Up Data. *Big Data*, *7*(3), 163–175. https://doi.org/10.1089/big.2018.0096

King, Z., Farrington, J., Utley, M., Kung, E., Elkhodair, S., Harris, S., Sekula, R., Gillham, J., Li, K., & Crowe, S. (2022). Machine learning for real-time aggregated prediction of hospital admission for emergency patients. *Npj Digital Medicine*, *5*(1), Article 1. https://doi.org/10.1038/s41746-022-00649-y

Kojima, G., Bell, C., Tamura, B., Inaba, M., Lubimir, K., Blanchette, P., Iwasaki, W., & Masaki, K. (2012). Reducing Cost by Reducing Polypharmacy: The Polypharmacy Outcomes Project. *Journal of the American Medical Directors Association*, *13*. https://doi.org/10.1016/j.jamda.2012.07.019

Kojima, G., Iliffe, S., & Walters, K. (2018). Frailty index as a predictor of mortality: A systematic review and meta-analysis. *Age and Ageing*, *47*(2), 193–200. https://doi.org/10.1093/ageing/afx162

Kwak, M. J., Chang, M., Chiadika, S., Aguilar, D., Avritscher, E., Deshmukh, A., Goyal, P., Kim, D. H., Aparasu, R., & Holmes, H. M. (2022). Healthcare Expenditure Associated with Polypharmacy in Older Adults with Cardiovascular Diseases. *American Journal of Cardiology*, *169*, 156–158. https://doi.org/10.1016/j.amjcard.2022.01.012

Laflamme, L., Monárrez-Espino, J., Johnell, K., Elling, B., & Möller, J. (2015). Type, Number or Both? A Population-Based Matched Case-Control Study on the Risk of Fall Injuries among Older People and Number of Medications beyond Fall-Inducing Drugs. *PLOS ONE*, *10*(3), e0123390. https://doi.org/10.1371/journal.pone.0123390

Lee, T. C., Shah, N. U., Haack, A., & Baxter, S. L. (2020). Clinical Implementation of Predictive Models Embedded within Electronic Health Record Systems: A Systematic Review. *Informatics (MDPI)*, *7*(3), 25. https://doi.org/10.3390/informatics7030025

Li, W., Lipsky, M. S., Hon, E. S., Su, W., Su, S., He, Y., Holubkov, R., Sheng, X., & Hung, M. (2021). Predicting all-cause 90-day hospital readmission for dental

patients using machine learning methods. *BDJ Open*, *7*, 1. https://doi.org/10.1038/s41405-021-00057-6

Linkens, A. E. M. J. H., Milosevic, V., van der Kuy, P. H. M., Damen-Hendriks, V. H., Mestres Gonzalvo, C., & Hurkens, K. P. G. M. (2020). Medication-related hospital admissions and readmissions in older patients: An overview of literature. *International Journal of Clinical Pharmacy*, *42*(5), 1243–1251. https://doi.org/10.1007/s11096-020-01040-1

Linsky, A., Gellad, W. F., Linder, J. A., & Friedberg, M. W. (2019). Advancing the Science of Deprescribing: A Novel Comprehensive Conceptual Framework. *Journal of the American Geriatrics Society*, *67*(10), 2018–2022. https://doi.org/10.1111/jgs.16136

Ludvigsson, J. F., Appelros, P., Askling, J., Byberg, L., Carrero, J.-J., Ekström, A. M., Ekström, M., Smedby, K. E., Hagström, H., James, S., Järvholm, B., Michaelsson, K., Pedersen, N. L., Sundelin, H., Sundquist, K., & Sundström, J. (2021). Adaptation of the Charlson Comorbidity Index for Register-Based Research in Sweden. *Clinical Epidemiology*, *13*, 21–41. https://doi.org/10.2147/CLEP.S282475

Machine-learning algorithms for predicting hospital re-admissions in sickle cell disease—Patel—2021—British Journal of Haematology—Wiley Online Library. (n.d.). Retrieved April 11, 2022, from https://onlinelibrary-wiley-com.proxy-um.researchport.umd.edu/doi/10.1111/bjh.17107

Mahmoudi, E., Kamdar, N., Furgal, A., Sen, A., Zazove, P., & Bynum, J. (2020). Potentially Preventable Hospitalizations Among Older Adults: 2010-2014. *Annals of Family Medicine*, *18*(6), 511. https://doi.org/10.1370/afm.2605

Malet-Larrea, A., Goyenechea, E., Gastelurrutia, M. A., Calvo, B., García-Cárdenas, V., Cabases, J. M., Noain, A., Martínez-Martínez, F., Sabater-Hernández, D., & Benrimoj, S. I. (2017). Cost analysis and cost-benefit analysis of a medication review with follow-up service in aged polypharmacy patients. *The European Journal of Health Economics*, *18*(9), 1069–1078. https://doi.org/10.1007/s10198-016-0853-7

Malik, D., & Munjal, G. (2021). Reviewing Classification Methods on Health Care. In S. Bhatia, A. K. Dubey, R. Chhikara, P. Chaudhary, & A. Kumar (Eds.), *Intelligent Healthcare: Applications of AI in eHealth* (pp. 127–142). Springer International Publishing. https://doi.org/10.1007/978-3-030-67051-1_8

Mandrekar, J. N. (2010). Receiver Operating Characteristic Curve in Diagnostic Test Assessment. *Journal of Thoracic Oncology*, *5*(9), 1315–1316. https://doi.org/10.1097/JTO.0b013e3181ec173d

Marcum, Z. A., & Hanlon, J. T. (2012). Commentary on the New American Geriatric Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *The American Journal of Geriatric Pharmacotherapy*, *10*(2), 151–159. https://doi.org/10.1016/j.amjopharm.2012.03.002

Masnoon, N., Shakib, S., Kalisch-Ellett, L., & Caughey, G. E. (2017). What is polypharmacy? A systematic review of definitions. *BMC Geriatrics*, *17*, 230. https://doi.org/10.1186/s12877-017-0621-2

McDermott, C. L., Fedorenko, C. R., Sun, Q., Curtis, J. R., Kreizenbeck, K. L., Conklin, T., Smith, B., Lyman, G. H., & Ramsey, S. D. (2018). Polypharmacy and medication costs at end of life among commercially insured adults aged 65 and older with cancer. *Journal of Clinical Oncology*, *36*(34_suppl), 65–65. https://doi.org/10.1200/JCO.2018.36.34_suppl.65

McMaughan, D. J., Oloruntoba, O., & Smith, M. L. (2020). Socioeconomic Status and Access to Healthcare: Interrelated Drivers for Healthy Aging. *Frontiers in Public Health*, *8*, 231. https://doi.org/10.3389/fpubh.2020.00231

Medical Expenditure Panel Survey Background. (n.d.). Retrieved November 24, 2020, from https://meps.ahrq.gov/mepsweb/about_meps/survey_back.jsp

Medical Expenditure Panel Survey Home. (n.d.). Retrieved May 2, 2022, from https://www.meps.ahrq.gov/mepsweb/

Medical Expenditure Panel Survey Household Component Response Rates. (n.d.). Retrieved July 6, 2022, from https://meps.ahrq.gov/survey_comp/hc_response_rate.jsp

Medicare Advantage Versus the Traditional Medicare Program: Costs of Inpatient Stays, 2009-2017. (2017).

Medicare Advantage Versus the Traditional Medicare Program: Costs of Inpatient Stays, 2009-2017 #262. (n.d.). Retrieved April 22, 2023, from https://hcup-us.ahrq.gov/reports/statbriefs/sb262-Medicare-Advantage-Costs-2009-2017.jsp

Midão, L., Brochado, P., Almada, M., Duarte, M., Paúl, C., & Costa, E. (2021). Frailty Status and Polypharmacy Predict All-Cause Mortality in Community

Dwelling Older Adults in Europe. *International Journal of Environmental Research and Public Health*, *18*(7), 3580. https://doi.org/10.3390/ijerph18073580

Mihaylova, B., Briggs, A., O'hagan, A., & Thompson, S. G. (2011). Review of Statistical Methods for Analysing Healthcare Resources and Costs. *Health Economics*, *20*, 987–916. https://doi.org/10.1002/hec.1653

Montero-Odasso, M., Sarquis-Adamson, Y., Song, H. Y., Bray, N. W., Pieruccini-Faria, F., & Speechley, M. (2019). Polypharmacy, Gait Performance, and Falls in Community-Dwelling Older Adults. Results from the Gait and Brain Study. *Journal of the American Geriatrics Society*, *67*(6), 1182–1188. https://doi.org/10.1111/jgs.15774

Morin, L., Larrañaga, A. C., Welmer, A.-K., Rizzuto, D., Wastesson, J. W., & Johnell, K. (2019, June 24). * Polypharmacy and injurious falls in older adults: A nationwide nested case-control study *. Clinical Epidemiology; Dove Press. https://doi.org/10.2147/CLEP.S201614

Mudge, A. M., O'Rourke, P., & Denaro, C. P. (2010). Timing and Risk Factors for Functional Changes Associated with Medical Hospitalization in Older Patients. *The Journals of Gerontology: Series A*, *65A*(8), 866–872. https://doi.org/10.1093/gerona/glq069

Nardi, M. D., French, E., Jones, J. B., & McCauley, J. (2016). Medical Spending of the US Elderly. *Fiscal Studies*, *37*(3–4), 717–747. https://doi.org/10.1111/j.1475-5890.2016.12106

NHE Fact Sheet | CMS. (n.d.). Retrieved September 23, 2020, from https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NHE-Fact-Sheet

Norton, E. C., & Dowd, B. E. (2018a). Log Odds and the Interpretation of Logit Models. *Health Services Research*, *53*(2), 859–878. https://doi.org/10.1111/1475-6773.12712

Norton, E. C., & Dowd, B. E. (2018b). Log Odds and the Interpretation of Logit Models. *Health Services Research*, *53*(2), 859–878. https://doi.org/10.1111/1475-6773.12712

Orchard, P., Agakova, A., Pinnock, H., Burton, C. D., Sarran, C., Agakov, F., & McKinstry, B. (2018). Improving Prediction of Risk of Hospital Admission in Chronic Obstructive Pulmonary Disease: Application of Machine Learning to Telemonitoring Data. *Journal of Medical Internet Research*, *20*(9), e263. https://doi.org/10.2196/jmir.9227

Ouchi, K., Lindvall, C., Chai, P. R., & Boyer, E. W. (2018). Machine Learning to Predict, Detect, and Intervene Older Adults Vulnerable for Adverse Drug Events in the Emergency Department. *Journal of Medical Toxicology*, *14*(3), 248–252. https://doi.org/10.1007/s13181-018-0667-3

Ouellet, G. M., Ouellet, J. A., & Tinetti, M. E. (2018). Principle of rational prescribing and deprescribing in older adults with multiple chronic conditions. *Therapeutic Advances in Drug Safety*, *9*(11), 639–652. https://doi.org/10.1177/2042098618791371

Palmer, K., Marengoni, A., Russo, P., Mammarella, F., & Onder, G. (2016). Frailty and Drug Use. *The Journal of Frailty & Aging*, *5*(2), 100–103. https://doi.org/10.14283/jfa.2016.84

Patel, D., Cheetirala, S. N., Raut, G., Tamegue, J., Kia, A., Glicksberg, B., Freeman, R., Levin, M. A., Timsina, P., & Klang, E. (2022). Predicting Adult Hospital Admission from Emergency Department Using Machine Learning: An Inclusive Gradient Boosting Model. *Journal of Clinical Medicine*, *11*(23), Article 23. https://doi.org/10.3390/jcm11236888

Patton, D. E., Hughes, C. M., Cadogan, C. A., & Ryan, C. A. (2017). Theory-Based Interventions to Improve Medication Adherence in Older Adults Prescribed Polypharmacy: A Systematic Review. *Drugs & Aging*, *34*(2), 97–113. https://doi.org/10.1007/s40266-016-0426-6

Payne, R. A., & Avery, A. J. (2011). Polypharmacy: One of the greatest prescribing challenges in general practice. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners*, *61*(583), 83–84. https://doi.org/10.3399/bjgp11X556146

Peterson, D. J., Ostberg, N. P., Blayney, D. W., Brooks, J. D., & Hernandez-Boussard, T. (2021). Machine Learning Applied to Electronic Health Records: Identification of Chemotherapy Patients at High Risk for Preventable Emergency Department Visits and Hospital Admissions. *JCO Clinical Cancer Informatics*, *5*, CCI.21.00116. https://doi.org/10.1200/CCI.21.00116

Poudel, A., Peel, N. M., Nissen, L. M., Mitchell, C. A., Gray, L. C., & Hubbard, R. E. (2016). Adverse Outcomes in Relation to Polypharmacy in Robust and Frail

Older Hospital Patients. *Journal of the American Medical Directors Association*, *17*(8), 767000000000. https://doi.org/10.1016/j.jamda.2016.05.017

Research, C. for D. E. and. (2019). National Drug Code Database Background Information. *FDA*. https://www.fda.gov/drugs/development-approval-process-drugs/national-drug-code-database-background-information

Richardson, K., Moore, P., Peklar, J., Galvin, R., Bennett, K., & Kenny, R. A. (2012). *Polypharmacy in adults over 50 in Ireland: Opportunities for cost saving and improved healthcare*. The Irish Longitudinal Study on Ageing. https://doi.org/10.38018/TildaRe.2012-02

Rieckert, A., Trampisch, U. S., Klaaßen-Mielke, R., Drewelow, E., Esmail, A., Johansson, T., Keller, S., Kunnamo, I., Löffler, C., Mäkinen, J., Piccoliori, G., Vögele, A., & Sönnichsen, A. (2018). Polypharmacy in older patients with chronic diseases: A cross-sectional analysis of factors associated with excessive polypharmacy. *BMC Family Practice*, *19*(1), 113. https://doi.org/10.1186/s12875-018-0795-5

Ryvicker, M. (2018). A conceptual framework for examining healthcare access and navigation: A behavioral-ecological perspective. *Social Theory & Health*, *16*(3), 224–240. https://doi.org/10.1057/s41285-017-0053-2

Safari, S., Baratloo, A., Elfil, M., & Negida, A. (2016). Evidence Based Emergency Medicine; Part 5 Receiver Operating Curve and Area under the Curve. *Emergency*, *4*(2), 111–113.

Salive, M. E. (2013). Multimorbidity in older adults. *Epidemiologic Reviews*, *35*, 75–83. https://doi.org/10.1093/epirev/mxs009

Seppala, L. J., Wermelink, A. M. A. T., de Vries, M., Ploegmakers, K. J., van de Glind, E. M. M., Daams, J. G., van der Velde, N., & EUGMS task and Finish group on fall-risk-increasing drugs. (2018). Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. *Journal of the American Medical Directors Association*, *19*(4), 371.e11-371.e17. https://doi.org/10.1016/j.jamda.2017.12.098

Shahid, N., Rappon, T., & Berta, W. (2019). Applications of artificial neural networks in health care organizational decision-making: A scoping review. *PLoS ONE*, *14*(2), e0212356. https://doi.org/10.1371/journal.pone.0212356

Shehab, N., Lovegrove, M. C., Geller, A. I., Rose, K. O., Weidle, N. J., & Budnitz, D. S. (2016). US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *JAMA*, *316*(20), 2115–2125. https://doi.org/10.1001/jama.2016.16201

Sikdar, K. C., Dowden, J., Alaghehbandan, R., MacDonald, D., Peter, P., & Gadag, V. (2012). Adverse drug reactions in elderly hospitalized patients: A 12-year population-based retrospective cohort study. *The Annals of Pharmacotherapy*, *46*(7–8), 960–971. https://doi.org/10.1345/aph.1Q529

Sompayrac, J., & Linehart Trundle, K. (2018). Obesity: The Elephant in the Room We Can No Longer Afford to Ignore. *Online Journal of Health Ethics*, *14*(2). https://doi.org/10.18785/ojhe.1402.02

Soy Chen, M. S., Danielle Bergman, B. S. N., Kelly Miller, D. N. P., Allison Kavanagh, M. S., John Frownfelter, M. D., & John Showalter, M. D. (2020). *Using Applied Machine Learning to Predict Healthcare Utilization Based on Socioeconomic Determinants of Care*. http://www.ajmc.com/view/using-applied-machine-learning-to-predict-healthcare-utilization-based-on-socioeconomic-determinants-of-care

Staffa, S. J., & Zurakowski, D. (2021). Statistical Development and Validation of Clinical Prediction Models. *Anesthesiology*, *135*(3), 396–405. https://doi.org/10.1097/ALN.0000000000003871

Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*, *25*(9), 603–605. http://dx.doi.org/10.1007/s10654-010-9491-z

Tang, Q., Lu, J., Wu, W., Liu, Z., Zhao, S., Li, C., Chen, G., & Lu, J. (2022). Risk prediction model of polypharmacy for community-dwelling elderly patients: An assessment tool for early detection. *Frontiers in Pharmacology*, *13*. https://www.frontiersin.org/articles/10.3389/fphar.2022.977492

Thompson, W., Reeve, E., Moriarty, F., Maclure, M., Turner, J., Steinman, M. A., Conklin, J., Dolovich, L., McCarthy, L., & Farrell, B. (2019). Deprescribing: Future directions for research. *Research in Social & Administrative Pharmacy: RSAP*, *15*(6), 801–805. https://doi.org/10.1016/j.sapharm.2018.08.013

Tinetti, M. E., Bogardus, S. T., & Agostini, J. V. (2004). Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *The New England Journal of Medicine*, *351*(27), 2870–2874. https://doi.org/10.1056/NEJMsb042458

Tinetti, M. E., Han, L., Lee, D. S. H., McAvay, G. J., Peduzzi, P., Gross, C. P., Zhou, B., & Lin, H. (2014). Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA Internal Medicine*, *174*(4), 588–595. https://doi.org/10.1001/jamainternmed.2013.14764

Todd, A., Jansen, J., Colvin, J., & McLachlan, A. J. (2018). The deprescribing rainbow: A conceptual framework highlighting the importance of patient context when stopping medication in older people. *BMC Geriatrics*, *18*(1), 295. https://doi.org/10.1186/s12877-018-0978-x

Varghese, D., Ishida, C., & Haseer Koya, H. (2023). Polypharmacy. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK532953/

Vincent Rajkumar, S. (2020). The high cost of prescription drugs: Causes and solutions. *Blood Cancer Journal*, *10*(6), 71. https://doi.org/10.1038/s41408-020-0338-x

Wester, K., Jönsson, A. K., Spigset, O., Druid, H., & Hägg, S. (2008). Incidence of fatal adverse drug reactions: A population-based study. *British Journal of Clinical Pharmacology*, *65*(4), 573–579. https://doi.org/10.1111/j.1365-2125.2007.03064.x

Wongpakaran, N., Wongpakaran, T., Sirirak, T., Jenraumjit, R., Jiraniramai, S., & Lerttrakarnnon, P. (2018). Predictors of polypharmacy among elderly Thais

with depressive and anxiety disorders: Findings from the DAS study. *BMC Geriatrics*, *18*, 309. https://doi.org/10.1186/s12877-018-1001-2

Woolcott, J. C., Richardson, K. J., Wiens, M. O., Patel, B., Marin, J., Khan, K. M., & Marra, C. A. (2009). Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Archives of Internal Medicine*, *169*(21), 1952–1960. https://doi.org/10.1001/archinternmed.2009.357

Young, E. H., Pan, S., Yap, A. G., Reveles, K. R., & Bhakta, K. (2021). Polypharmacy prevalence in older adults seen in United States physician offices from 2009 to 2016. *PLOS ONE*, *16*(8), e0255642. https://doi.org/10.1371/journal.pone.0255642

Zaninotto, P., Huang, Y. T., Di Gessa, G., Abell, J., Lassale, C., & Steptoe, A. (2020). Polypharmacy is a risk factor for hospital admission due to a fall: Evidence from the English Longitudinal Study of Ageing. *BMC Public Health*, *20*(1), 1804. https://doi.org/10.1186/s12889-020-09920-x

Zhou, Z.-H. (2012). *Ensemble Methods: Foundations and Algorithms* (1st ed.). Chapman and Hall/CRC.

Zou, G. (2004). A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *American Journal of Epidemiology*, *159*(7), 702–706. https://doi.org/10.1093/aje/kwh090