Disparities in the Appropriateness of Medication Use

by

Md Motiur Rahman

A dissertation submitted to the Graduate Faculty of
Auburn University
in partial fulfillment of the
requirements for the Degree of
Doctor of Philosophy

Auburn, Alabama
December 15, 2018

Key words: REGARDS, potentially inappropriate medication, drug-drug interaction, anticholinergics, cognitive impairment, socioeconomic disparity

Approved by

Richard Hansen, Chair, Professor and Dean of the Harrison School of Pharmacy
Jingjing Qian, Associate Professor of Health Outcomes Research and Policy
Kimberly Garza, Associate Professor of Health Outcomes Research and Policy
Ash Abebe, Professor of Mathematics and Statistics
George Howard, Professor of Biostatistics, University of Alabama at Birmingham

Abstract

Background: Prior work has identified disparities in the quality and outcomes of health care across socioeconomic subgroups. Medication use may be subject to similar disparities.

Objectives: The objectives of this study were to assess the association between 1) potentially inappropriate medication (PIM) use and different disparity parameters (gender, age, race, income, education, and rural or urban areas), 2) PIM use and all-cause mortality and the effect of disparity parameters on this relationship, and 3) anticholinergic drug use and cognitive impairment and the effect of disparity parameters on this relationship.

Methods: The study included 30,239 US adults aged ≥ 45 years from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study (recruited 2003-2007). The appropriateness of medication use was measured by the presence of drug-drug interactions (DDIs) measured by the known clinically significant drug interactions list by Ament et al. and use of potentially inappropriate medications (PIMs) in older adults measured by the 2015 Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Multivariable logistic regressions were used to assess the association of disparity parameters with DDIs and PIM use stratified across prescription only and over-the-counter drugs (aim 1). In addition, Cox proportional hazards time-to-event analysis followed the participants until their death (all-cause) on or before March 31, 2016,

iteratively adjusting for disparity parameters and other covariates (aim 2). Furthermore, multivariable logistic regression models assessed disparities in cognitive impairment with the use of anticholinergic drugs (ACHs), the largest subset of PIMs in the Beers Criteria, iteratively adjusting for disparity parameters and other covariates (aim 3).

Results: High prevalence of PIM use (87% of the participants) was observed in our study. White females compared with white males and black males compared with white males had higher odds of receiving prescription-only PIMs. We also found that females compared with males, blacks compared with whites, and individuals with lower income, lower education, and residing in rural areas had higher PIM prevalence. Additionally, we observed that PIM use increased the risk of all-cause mortality among whites. Higher PIM use was independently associated with higher mortality risks.

Conclusion: Demographic and socioeconomic disparities in PIM use and DDIs exist. Our fully adjusted analyses also suggest the presence of disparities in all-cause mortality with PIM use. We also observed demographic and socioeconomic disparities in ACH use and in cognitive impairment, individually. Future studies should seek to better understand factors contributing to the disparities in order to guide development of interventions.

Table of Contents

Lists of Tables

Aim 3 Results

List of Figures

Chapter One | Introduction

1.1. Overview

In the United States (US), approximately 40% of people aged 65 or over are prescribed at least five medications per month.[1] Although potentially inappropriate medication (PIM) prescribing occurs in persons of all ages, adults aged ≥ 65 years are at increased risk for experiencing adverse drug events (ADEs) in the presence of PIM.[2,3] PIM's are defined as medications that have an increased risk of an ADE when an alternative drug exists that is equally efficacious with fewer risks.[2] High comorbidity, altered drug metabolism, and potential drug-drug-interactions (DDI) can make older adults more susceptible to ADEs than younger populations.[4,5] Prolonged exposure to multiple prescriptions can cause cognitive impairments in older adults. The use of PIM prescribing can contribute to prolonged hospital stay, re-hospitalization, mortality, and increased overall healthcare costs.[5] It has been found that the rate of re-hospitalization among Medicare beneficiaries were 19.6% and 34.0% following the discharge from a hospital within 30 days and 90 days, respectively.[6] Adults aged 65 and over account for 53.1% of inpatient hospitalizations resulting from drug-related adverse outcomes.[7] Moreover, to overcome the burden of excessive drug costs, people may opt to use other's remaining medications which can even lead to inappropriate use of medication.[4] Although older adults account for only 13% of the total US population, they are responsible for more than 33% of the total outpatient prescription drug expenditure.[4] Moreover, older adults

are the biggest consumers of over-the-counter (OTC) medications.[8] Excessive use of OTC medications along with other dietary supplements could increase the risk of adverse events associated with nonmedical use of prescription drugs.[4,8]

The American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (described as “Beers Criteria”) is a guideline to aid healthcare practitioners in prescribing medications to patients 65 years or older.[9] This contains a list of medications that are deemed ‘potentially inappropriate’ due to their harmful effects in older adults. Another measure of potentially inappropriate drug use is based on known DDIs which could be an indicator of PIM use. Although most pharmacies have software to detect DDIs, it is often very hard to measure clinical significance.[10] Polypharmacy and the resultant DDIs can be associated with higher risks of mortality.[11,12] Older adults are more susceptible to these DDIs[13] and are at increased risk of ADEs, hospitalization, morbidity and mortality.[2] And thus, identifying clinically significant DDIs is an important healthcare quality indicator. The largest subset of PIMs in the Beers Criteria is the use of anticholinergics (ACHs) in older adults. Although many anticholinergic (ACH) drugs are contraindicated in older adults, they are very frequently prescribed in this population.[14] Previous research have found the association of falls, delirium, dementia, and constipation with the use of ACH drugs.[14,15] Hence, the study of ACH use in older adults is an important aspect of quality of medication use.

The quality of healthcare is sometimes characterized by the frequency in which PIMs are prescribed in older adults,[16] and prior work has suggested that there may be a disparity in which people are prescribed PIMs.[17,18] Although disparities are generally considered in terms of race and ethnicity, they cover a broader dimension. Disparities can

occur across socioeconomic status, age, gender, income, education, geographic location, language, disability status, citizenship status, and sexual identity and orientation.[19] Such disparities, known as health disparities, are frequently observed in populations with negative health outcomes.[20] For example, an increased mortality rates, disability, and poor quality of life has been observed among patients who receive disparate medical care and treatment.[20] Moreover, health disparities can affect healthcare expenditures. One study found that health disparities contributed about 30% extra in direct medical costs for blacks, Hispanics, and asians.[21] Disparities can also contribute to the increase in indirect costs due to loss of productivity and untimely death.[19]

"Healthy People", a nationwide health promotion campaign, encompasses the continuous improvement of health for all Americans.[22] This is actually a guiding document launched by the Department of Health and Human Sciences which provides science-based national objectives aimed at improving health for all Americans.[22] One of the major goals of this campaign is to improve the overall healthcare quality for all by eliminating disparities and accomplishing health equity.[22] "Healthy People 2020", a continuation of this project, calls for eliminating disparities in terms of race, socioeconomic status, geographic location, disability status, and sexual orientation, and promoting health equity and better quality of life.[23]

Studying health disparities requires access to unique data that can identify disparities and measure longitudinal outcomes. One useful study is the REasons for Geographic And Racial Differences in Stroke (REGARDS) which is a longitudinal cohort study initially designed to assess health disparities in stroke treatment and outcomes in the Southeastern US ("Stroke Belt") compared to the other parts of the US.[24] 30,239 US

adults aged ≥ 45 years (42% black and 58% white) were recruited in the study from January 2003 to October 2007, providing information regarding patient demographics, socioeconomic status, complete medication lists, diagnostic reports and physicians' adjudicated health status. Age, gender, race, education, household income, and residential history were obtained by self-report. Cognitive impairment was assessed by the Six-Item Cognitive Screener[25] by the telephone interviewer. Information regarding both prescription and nonprescription medication taken within the past two weeks were obtained during the in-home exam provided by Examination Management Services, Inc. (EMSI). Since REGARDS is rigorously designed with a diverse patient population, we believe that REGARDS is appropriate for studying disparities in PIM prescribing and for measuring the association of PIM use with mortality and cognitive impairment.

1.2 Central research question

The overall research question of the study is whether the number of patients being prescribed at least one potentially inappropriate medication (PIM) and the resulting association of PIM use with mortality and cognitive impairment will be higher for those with lower income and education, residing in rural areas, and characterized as racial minorities compared to those with higher income and education, residing in non-rural areas, and not characterized as racial minorities, respectively.

1.3 Specific Aims

We have three specific aims to study the outcomes of potentially inappropriate medication (PIM). The aims of this study are as follows-

Specific Aim 1: To assess the association of health disparities with PIM use.

PIM use was coded using 2015 Beers Criteria. Another measure of PIM use is based on known drug-drug interactions (DDIs) which can also be an indicator of inappropriate drug use. Cross-sectional baseline data was used to compare the PIM use across population subgroups defined by race, income, education, and location of residence. For each of the two measures, PIM use was coded as a binary variable (yes/no) and count variable (number per person). Multivariable logistic regression models assessed the relationship between PIM/DDI use and the disparity parameters. Multivariable Poisson regression model was used to assess the impact of disparity parameters on the number of PIMs received (or prescribed).

Specific Aim 2: To assess the association between PIM use and all-cause mortality and to evaluate the effect of health disparities on this relationship.

A Kaplan-Meier estimator and Cox proportional Hazard Ratio (HR) was used to calculate the survival probability and the association between PIM use and mortality, respectively.

Specific Aim 3: To assess the association between anticholinergic drug use and cognitive impairment and to evaluate the effect of health disparities on this relationship.

Cognitive impairment was assessed by the Six-Item Cognitive Screener.[24] Multivariable logistic regression models assessed the disparities across cognitive impairment with anticholinergic drug use.

1.4 Significance

The United States spends more per capita on health care than any other nation,[26] yet health-related quality indicators lag behind many other countries.[27] A low quality score is partly attributed to inequalities among subpopulations within the US.[28] These inequalities, or health disparities, are defined as being significant differences in the treatment, diagnosing, and prevention of certain health conditions that are more prevalent among subpopulations versus the overall population.[29] The subpopulations affected can be defined by different domains of health disparities, including: 1) socioeconomic status; 2) location of residence (e.g., rural vs urban setting); and 3) obstacles related to race or ethnicity.[29] These factors are not mutually exclusive of one another and often occur simultaneously.

Previous research has explored the relationship between health disparities and various quality indicators reflecting health care structure, process, and outcome measures. For structure measures, for example, in 2015, the Agency for Healthcare Research and Quality (AHRQ) reported that blacks and people with low income had more limited access to care than whites and high income people.[30] Geographic variations in inappropriate medication use were also reported in previous research. For example, 21.1% and 32.7% of PIM was observed among the residents of elderly long term care in Japan[31] and Malaysia,[32] respectively. In another study, it was found that, in the US and Europe, 12% of community dwelling elders and 40% of nursing home residents received at least one PIM.[33]

For process measures, for example, uninsured and low coverage individuals report poor communication with health providers compared with those with private insurance

status. Uninsured adults and those with Medicaid reported that health providers did not always seek the patient's help when making treatment decisions nor did they spend enough time clarifying explanations with the patients.[34] For instance, while provider-patient interactions are vital in educating patients about their overall lifestyle, less than 40% of uninsured, obese adults report ever having their health provider give advice on dietary suggestions.[34]

In terms of outcome measures, numerous health disparities have been documented in terms of disease-specific outcomes, morbidity, and mortality. For stroke, for instance, health disparities due to race and ethnicity are prevalent in stroke care and management. Among adults 25 to 44 years of age, blacks and Native Americans/American Indians have a higher hemorrhage mortality rate with stroke.[35,36] Similarly, blacks and Hispanics are 70% more likely and Native Americans/American Indians are 20% more likely to be diagnosed with diabetes than whites, respectively.[37] In the case of cancer, for example, the incidence rate of cancers of the stomach, liver, cervix, kidney, and gallbladder were higher for American Indians/Alaska Native people.[38] Prior studies also found the association of low socioeconomic status with morbidity and mortality.[39-42]

One important but understudied quality measure revolves around the appropriateness of medication prescribing and use. While some studies have documented health disparities in terms of the appropriateness of medication prescribing and the quality of population-based medication use (e.g., which drugs are being used by specific populations and medication adherence), data are limited to support systematic assessment of the appropriateness of medication use across health disparities defined

on the basis of socioeconomic factors, rural vs. urban residence, and race. In part, this gap in the literature is caused by lack of appropriate population-level data, and in part this gap is related to lack of consensus of ways to define the "appropriateness of medication use". We used baseline data from the REGARDS study to evaluate the appropriateness of medication use across three domains of health disparities, comparing possible disparities across a variety of previously published measures that have been used to define the appropriateness of medication use.

1.5 Innovation

We intend to shift current research paradigms of PIM prescription to focus on the population at risk for health disparities. Our research was focused on assessing the PIM use and associated all-cause mortality across population subgroups defined by sociodemographic variables, urban/rural residence, and race. We also assessed the association between the use of anticholinergic drugs, which are the largest subset in the Beers list,[9] and cognitive impairment and evaluate the effect of health disparities on this relationship. This research project was innovative for three reasons. First, to the best of our knowledge, this is the first study to assess the relationship between health disparities and PIM use as a whole along with the specific subset of PIM in the Beers list. This study has informed us about both prescription and nonprescription PIM use patterns in the minority population and will increase awareness among prescribers, which we believe, has the potential to shift clinical practice paradigms.

The 2012 Beers Criteria were updated in 2015 with several changes, such as changes in prescribing recommendations, inclusion of new medications, information regarding dose adjustments, and addition of DDIs.[9] Previous studies used the 2012 or earlier Beers Criteria to identify a specific subset of PIM and assess its relationship with specific disparities. This is the first study that used 2015 Beers Criteria to identify PIM use and assess its relationship with health disparities.

Another measure of PIM use is based on known DDIs which could be an indicator of inappropriate drug use. This is the first study that assessed the relationship between health disparities and the use of interacting drugs together.

1.6 Impact

Although health disparities are known to exist in the US, very little is known regarding the disparities in PIM use and related adverse outcomes. This study has helped to identify both prescription and nonprescription drug utilization patterns in the minority groups. Dissemination of the research findings will increase awareness among the prescribers which may help in changing their prescribing behavior. Additionally, this study will inform action for regulatory agencies, help achieve Healthy People 2020 goals, and in turn will help improve the overall health care quality and equity for all.

Chapter Two | Background and Literature Review

2.1. Quality of care

According to the Institute of Medicine (IOM), the quality of care is defined as "the degree to which health care services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[43] The Agency for Healthcare Research and Quality (AHRQ) defines quality of care as, “doing the right thing, at the right time, in the right way to, for the right person and having the best possible results.”[44] In general, quality of care refers to the use of scientific and medical judgement to improve the health and quality of life of the patients being treated.

2.1.1. Domains of quality of care

The six domains of quality of care according to IOM are- safety, effectiveness, efficiency, patient centeredness, timeliness, and equity.[43,45]

- **Safety**: This refers to avoiding actual or potential harms from the care.
- **Effectiveness**: This is providing care based on scientific knowledge and achieving desired outcomes by avoiding underuse and misuse.

- **Efficiency**: Efficiency refers to the return on investment, that is, maximizing the utilization of healthcare resources. In other words, efficiency is avoiding wastage of the resources such as equipment, medication, ideas, energy, etc.
- **Patient centeredness**: This refers to making clinical decisions by being respectful to individual patients' needs, preferences, and values.
- **Timeliness**: This is related to providing care by reducing waiting time and harmful delays.
- **Equity**: This refers to providing equal quality healthcare regardless of gender, race, socioeconomic status, and geographic location.

IOM also categorized the quality of care based on the consumers' perspective.[43] They are-

- **Staying healthy**: This refers to getting appropriate care to avoid illness and remain healthy.
- **Getting better**: This refers to getting appropriate care to recover from an existing illness or injury.
- **Living with illness or disability**: This refers to getting appropriate care to manage ongoing chronic conditions or getting help with managing an ongoing, chronic condition or coping with an existing disability.
- **Coping with the end of life**: This refers to getting necessary help to deal with a terminal illness.

All of these quality domains interplay for the overall wellbeing of the patients and hence, the measurement of quality is quite essential in order to help guide improvement of the overall healthcare quality.

2.1.2. Necessity of measuring quality of care

Measuring quality of care is necessary to know the performance of the health system which ultimately results in improved care. Different stakeholders such as consumers, healthcare providers, insurance companies, regulatory agencies, employers, and business groups are interested in quality measurement for different reasons; however, they have one common goal of improving patients' wellbeing.[46]

Consumers are getting more involved in healthcare decision making and want to know about the cost-effectiveness of current practice and alternative treatment options. Hence, individual consumers and/or different consumer interest groups look for information regarding quality of healthcare.

Hospitals seek quality information to measure physicians' performance, cost-effectiveness of procedures, patients' outcomes, and overall decision making and marketing. In 2009-2010, the Center for Medicare & Medicaid Services (CMS) changed its reimbursement policy to lower the hospital payments for unplanned readmission.[46] These changes prompted hospitals to measure their quality of care to avoid loss of revenue.

Insurance companies need data regarding costs, usage patterns, and practicing behavior in order to assess the performance of the concerned providers. All of these help the insurance companies to select preferred providers and sell their products to appropriate customers.

Both federal and state government fund effectiveness research and want to know about the costs and outcomes of medical care. This helps them to make decisions on

payment systems and funding. Additionally, government regulators in many states mandate the submission of specific hospital data to the state repository. This helps in assessing the quality of care and develop improvement strategies.

As a whole, quality measurement can be used to improve health care in the following ways [47]

- By ensuring patients' safety through preventing overuse, underuse, and misuse of health care services
- To identify the best operating methods in health care to facilitate improvement
- By formulating better health insurance plans and guiding health care providers to provide high-quality care
- By keeping consumers involved in healthcare decision making
- Through evaluating and addressing disparities across healthcare delivery and outcomes

2.1.3. Healthcare quality measures

There are different tools to measure healthcare quality. Some of the most commonly used tools are described below-

The Health Plan Employer Data and Information Set (HEDIS)

Around 90% of health plans in the US use HEDIS as a measure of quality of care.[48,49] It contains 7 domains and 94 measures of quality of care.[49] This helps

organizations to measure performance of the care provided against some accepted standards. HEDIS measures may include, for example, percentage of patients with diabetes given statin therapy and percentage of children that received follow-up care who were prescribed ADHD medications.[50]

The Consumer Assessment of Healthcare Providers and Systems (CAHPS)

This is a measure of health care quality from the patient's perspective.[51] CAHPS consist of a group of surveys that ask patients about their experience with care. In general, the topics covered by the surveys include communication with health providers, customer service, coordination of care, and access to care.[51]

ORYX

ORYX was developed by The Joint Commission, a non-profit organization, that measures the quality of care of its accredited health care organizations.[52,53] This measures performance of the processes and outcomes of care provided by the hospitals, nursing homes, home care agencies, and mental health providers.[48]

The Medicare Health Outcomes Survey (HOS)

HOS evaluates physical and mental wellbeing of managed care plan enrollees.[48] This is regarded as the first patient reported outcome measure used in Medicare managed care.[54] HOS is conducted annually from a random sample of Medicare beneficiaries who are enrolled in Medicare Advantage plans. The purpose of this survey

is to obtain data from the Medicare Advantage program in order to use it in quality improvement activities, pay for performance, reporting to public, and as a whole to improve health.[54]

Nursing Home Compare

This evaluates the quality of care in nursing homes. This measures the health states of nursing home residents which include their pain status, physical restraints, mobility, urinary tract infection, and depression or anxiety.[48]

Although there are a multitude of quality measures available to evaluate the quality of healthcare, they can broadly be classified into three standardized categories as suggested by Avedis Donabedian, M.D., a pioneering scientist in the field of quality measurement (widely known as the Donabedian framework).[43,47,55]

2.1.3.1 The Donabedian framework

Donabedian provided an excellent model that covers different aspects of quality of healthcare into three broad categories. This helps to comprehend the concept of quality in a broader manner and measure the quality of care in different settings. The Donabedian framework is shown in figure 2.1.[56]

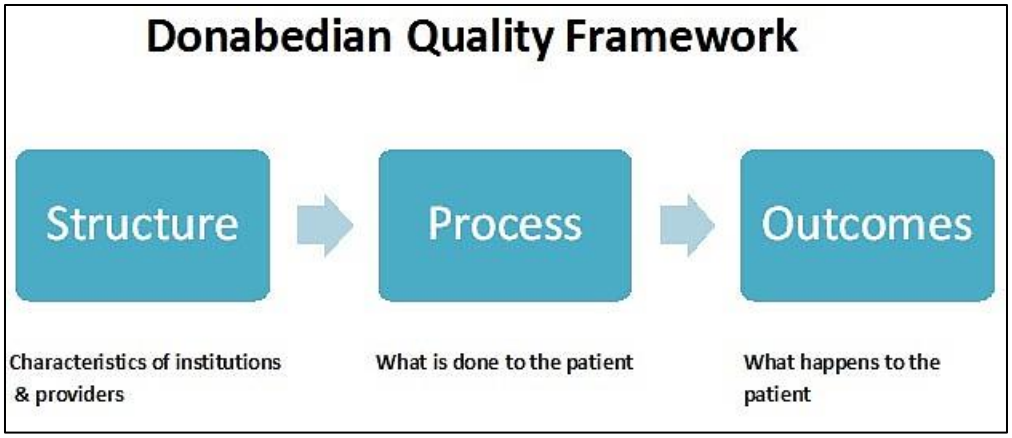

Figure 2.1. The Donabedian quality framework[56]

According to the Donabedian model, any improvement in the structure of care results in an improvement in clinical processes which ultimately increases the likelihood of improving patients' outcomes.[55,57] The following sections elaborated on these element of the Donabedian framework.

Structure measures [47]

This is a measure of the infrastructure of the healthcare facility, that is, whether the healthcare setting is equipped with the necessary infrastructure to deliver the intended standard care. This evaluates the features of the settings, facilities, personnel, resource availability, and the overall policies of the healthcare institution. One structure measure, for example, could be if the hospital has an electronic prescription delivery system or not. These measures are very important for insurance companies and regulatory bodies to assess the capabilities of the healthcare facility which may ultimately guide policy decisions and/or accreditation. However, the infrastructure cannot be considered as the

sole measure of quality since it cannot ensure whether the care was actually delivered or whether it actually improved the patient's health.

Process measures [47]

This measures the consistency of the care provided to the patients according to the established and recommended guidelines. In other words, this evaluates whether processes of care are consistent with best practices.[58] An example of a process measure could be if the physicians are prescribing the appropriate medication for their diabetic patients. For diabetes care, performing a hemoglobin A1C (HbA1c) test at least twice a year for the patients who are meeting treatment goal, performing HbA1c test quarterly for the patients who do not have glycemic control, and getting an eye exam in an appropriate time window also are examples of process measures.[59] Additional examples include whether a patient with high blood pressure receives guidance on lifestyle modification along with appropriate drugs and if a heart attack patient is prescribed aspirin prior to hospital discharge.[48] Care coordination such as alignment of the treatment with patients' physical and mental conditions is an important aspect of this measure which is often overlooked during the process measures. A good process measure would ensure whether the standards of care translate into predicted outcomes.

Outcome measures [47]

Outcome measures include whether the goals of the care were achieved or not. This is a measure of patients' health resulting from the care obtained. Commonly

measured outcome indicators include but are not limited to the measures of mortality, morbidity, and health-related quality of life.[47] One outcome measure, for example, could be the five-year survival rate of cancer patients following a treatment. However, genetic variations and social factors such as economic condition, adequate housing, and social support can have significant effects on health outcomes and are often overlooked. An outcome measure should consider these important factors. Additionally, definition of outcome (intermediate outcomes vs. main outcomes) may vary depending on the study. For diabetes care, for example, differences in opinions exist as to whether HbA1c measurement should be considered as a primary outcome or an intermediate outcome.[60] According to the US Food and Drug Administration (FDA), drugs that lower HbA1c are expected to lower the microvascular complications and can be considered as primary efficacy endpoint for the drugs seeking approval for the treatment of diabetes.[60,61] However, several clinical trials demonstrated differences in patient outcomes even though the drugs under trial lowered HbA1c to a similar level.[62-66] For example, empagliflozin and liraglutide significantly reduced cardiovascular events and mortality compared to placebo; however, the reduction in HbA1c were similar between the groups.[64,66] These findings pose a question mark to the use of HbA1c as a primary outcome measure in clinical studies. Similarly, numerous studies have shown that reduction in blood pressure (BP) has been linked with lower incidence of cardiovascular events.[67-70] For example, a 10 mmHg reduction in systolic BP or 5 mmHg reduction in diastolic BP was associated with 22% reduction in coronary heart disease and 41% reduction in stroke.[69,71] In this case, the outcomes should be cardiovascular events, not the BP reduction. So, we should be cautious about how to define outcomes and how to measure them.

Another measure of the quality of care is the measure of patients' experience of the care received.[47] The patient-centered approach helps patients communicate with their healthcare providers and in shared decision making.[72] Picker's eight principles of patient-centered care are as follows: respect for patients' values, preferences and expressed needs, coordination and integration of care, information and education, physical comfort, emotional support and alleviation of fear and anxiety, involvement of family and friends, continuity and transition, and access to care.[73] This measure evaluates, for example, the interaction of the patients with their doctors, the extent and comprehensibility of the information shared, and ease of getting an appointment. It has been reported that patients with better experience are more involved with the treatment plan and adherent to an appropriate course of action.[74] This measure is being recommended by many experts as a key element of health care quality measurement.[47]

2.1.4. Quality of care in the US

The quality of care in the US is often questioned and considered as substandard by many experts.[47] Previous research found that only around 55% of patients receive the appropriate diagnosis and care.[75] Moreover, variations in access to care and outcomes exist.[30] Underuse, overuse, and misuse of healthcare resources and services were also reported in previous research.[47] Additionally, in many cases the healthcare delivery system is unorganized and very complicated.

The US spends more per capita on health care than any other nation,[26] yet health-related quality indicators lag behind many other countries.[27] A low quality score is partly

attributed to inequalities among subpopulations within the US.[28] These inequalities, or health disparities, are defined as being significant differences in the treatment, diagnosis, and prevention of certain health conditions that are more prevalent among subpopulations versus the overall population.[29] The subpopulations affected can be defined by different domains of health disparities, including: 1) socioeconomic status; 2) location of residence (e.g., rural vs urban setting); and 3) obstacles related to race or ethnicity.[29] These factors are not mutually exclusive of one another and often occur simultaneously.

2.2. Disparities in healthcare

According to the AHRQ, any differences among the populations in healthcare is considered as health disparities.[76] According to the IOM, differences in healthcare services between the two groups without the evidence of medical conditions or health preferences are defined as health disparities.[76] Previous research has explored the relationship between health disparities and various quality indicators reflecting health care structure, process, and outcome measures.

2.2.1. Disparities in structure

For structure measures, for example, in 2015, the AHRQ reported that blacks and people with low income had less access to care than whites and high income people.[30] It has been reported that healthcare providers, patients, healthcare plan managers, and the health system can contribute to racial/ethnic disparity.[77] Moreover, bias, stereotyping, and prejudice from the healthcare provider also can lead to racial disparities. Racial disparities in fee-for-service and managed care settings have been identified in different studies.[77-

[82] For example, economically solvent white male Medicare beneficiaries use more services and have better health conditions compared to the members of the minority groups.[80]

It has been reported that there is a lack of physicians in the areas with higher proportions of minorities.[83] Additionally, individuals with lower income and education tend to reside in the neighborhoods with low healthcare facilities.[84] These group of patients often have limited availability to subspecialty physicians. Poor access to care among the individuals residing in rural areas also was reported in prior studies. Poor timely access to healthcare providers, limited access to subspecialty physicians, and poor management of chronic conditions are pretty common among rural residents.[85] A study by Pollard and Jacobsen found that 15% of the residents in the Appalachian area did not have a health insurance compared to 14% in the nation.[86] Lower physician density in this area also was reported in Yao et al.[87] In terms of gender inequality, women than men had delayed or no care, and experienced trouble in getting mental health treatments.[88] Poor access to care and/or lack of technical knowledge among the providers can lead to substandard delivery of care which ultimately can lead to undesirable consequences. Thus, along with the reduction in disparities in terms of structure measures, attention should be given to exercise appropriate processes of care among all patient groups.

2.2.2. Disparities in process

For process measures, for example, uninsured and low coverage individuals reported poor communication with health providers compared with those with private insurance. Uninsured adults and those with Medicaid reported that health providers did

not always seek the patient's help when making treatment decisions, nor did they spend enough time clarifying explanations with the patients.[34] For instance, while provider-patient interactions are vital in educating patients about their overall lifestyle, less than 40% of uninsured, obese adults report ever having their health provider give advice on dietary suggestions.[34] Prior research also found that African-American patients have a less participatory relationship with their physicians than whites.[89] Oliver et al. found that white physicians spent more time with white patients than African-American patients for planning a treatment, evaluating health literacy, providing health education, and answering questions.[90]

Disparities in health service utilization have been documented in previous studies as well. It has been found that blacks were less likely than whites to receive eye examination after diabetes diagnosis, post hospitalization mental illness follow-up, and flu vaccination.[79,91,92] One study among veterans treated for war-related post-traumatic stress disorders (PTSD) found that black veterans were less likely than white veterans to receive antidepressants and showed less improvement in controlling violent behavior.[93] A study among patients hospitalized for acute myocardial infarction found that blacks had a lower rate of catheterization than whites.[94] McBean et al. found that blacks had a significantly lower rate of the 17 most commonly used surgical procedures than whites.[95] For example, blacks compared to whites had 72% and 68% lower rate of coronary artery bypass grafting and angioplasty, respectively.[95] In general, blacks compared to whites utilized less preventive services, had fewer diagnostic and surgical procedures, and underwent more procedures that are associated with poor chronic disease management such as partial or complete lower limb amputations.[80] Additionally, it has been reported

that individuals with lower income and residing in rural areas are more affected by opioid epidemic throughout the country.[96] Prior research also showed that females compared to males had more postponed preventive health services, skipped medical tests or treatments, and did not fill prescriptions or skipped medication doses.[88]

One important but understudied quality measure revolves around the appropriateness of medication prescribing and use. While some studies have documented health disparities in terms of the appropriateness of medication prescribing and the quality of population-based medication use (e.g., which drugs are being used by specific populations and medication adherence), data are limited to support systematic assessment of the appropriateness of medication use across health disparities defined on the basis of socioeconomic factors, rural vs. urban residence, and race. In part, this gap in the literature is caused by lack of appropriate population-level data, and in part, this gap is related to lack of consensus of ways to define the "appropriateness of medication use".

The IOM suggests that assuring evidence-based uniform clinical practice guidelines; incentivizing the doctors to promote preventive services such as flu shots, cancer screening, and immunization; and improving communication with the patients can help reduce process-related disparities and improve patient outcomes.[77]

2.2.3. Disparities in outcomes

In terms of outcome measures, numerous health disparities have been documented in terms of disease-specific outcomes, morbidity, and mortality. For stroke, for instance, health disparities due to race and ethnicity are present in stroke care and

management. Among adults 25 to 44 years of age, blacks and Native Americans/American Indians had a higher stroke mortality rate with stroke.[35,36] Research also showed higher prevalence of diabetes, asthma, and cardiovascular diseases among blacks and American Indians/Alaska Natives.[19] Disparities across the burden of HIV/AIDS diagnosis and death rates were prominent among blacks with an eight to ten times higher rate of HIV/AIDS than whites.[97] Blacks and American Indians/Alaska Natives have higher infant mortality rates than whites[19] and black males had the lowest life expectancy among subpopulations defined by race and gender.[98] However, low income individuals across all races had comparatively poor health status than higher income individuals.[99] Similarly, an increase in the number of premature deaths has been reported among the individuals residing in rural counties.[96] Moreover, rural dwellers than their urban counterparts demonstrated higher rates of obesity, diabetes, and injury.[100]

The focus of our study is to examine the appropriateness of medication use among different demographic and socioeconomic subgroups of the US population. Although medication prescription is a process measure, inappropriate prescription can lead to poor outcomes especially in older adults due to physiological vulnerabilities. However, debate exists among researchers regarding the definition of "appropriateness of medication use". Understanding the concept of appropriate medication use and following clinical guidelines while prescribing are important aspects of healthcare quality.

2.3. Potentially inappropriate medications (PIMs)

Around one hundred thousand Americans get injured or die in hospitals, doctors' offices, nursing homes, and other healthcare settings each year due to "avoidable"

medication errors at a cost around $17-$29 billion each year.[48,101] One form of avoidable medication error is the use of potentially inappropriate medications (PIMs).

2.3.1. Definition

PIM's are defined as utilization of medications that have an increased risk of adverse drug events (ADEs) when an alternative exists that is equally efficacious with fewer risks.[2,33] Irrational use of medicine such as use of medications at a higher dose/frequency, for longer duration than clinically indicated, under use of medicine for no clinical reasons, and use of multiple medications that are known to have clinically significant drug–drug interactions or drug–disease interactions are also considered under the umbrella of PIM use.[33,101]

2.3.2. Burden of PIM

In the United States, approximately 37% of older adults use at least five prescription medications.[1] Prescribing of PIMs occurs in persons of all ages; however, adults aged 65 years or more, who are more susceptible to physiological vulnerabilities, are at increased risk for experiencing adverse drug reactions.[2,3] In older adults, PIM prescribing can contribute to an increased risk of ADEs, prolonged hospital stay, re-hospitalization, mortality, and increased overall healthcare costs.[5] Older adults account for approximately 35% of hospital admissions[3] of which many of them are being prescribed PIM that are known to cause ADEs as well as drug-drug and drug-disease interactions.[5] Adults aged 65 and over account for 53.1% of inpatient hospitalizations resulting from drug-related adverse outcomes.[7]

2.3.3 Risk factors for PIM prescribing

Older adults are often exposed to unnecessary medications, multiple providers, specialists, and limited hospital formularies that cause the need for reconciliation with home medications.[102,103] All of these factors can contribute to higher PIM prescribing. Previous research on hospitalized patients demonstrated that polypharmacy, multiple comorbidities, and altered pharmacokinetics with advanced age are the major contributing factors for increased ADEs.[104-107]

Polypharmacy

Older adults often present with multiple chronic conditions that may require the use of multiple drugs concomitantly which in turn can increase the risk of drug-drug and drug-disease interactions.[108] It has been found that patients taking two medications face a 13% risk of drug-drug interactions (DDIs). This percentage rises up to 38% for patients taking four medications and rises up to 82% if seven or more medications are given concomitantly.[109] Additionally, polypharmacy may result in medication non-adherence and may lead to poor clinical outcomes.[110] Furthermore, duplicate prescribing in the same drug class may be unrecognized and increase the risk of ADEs as a result of polypharmacy.[108,109] Particular emphasis should be given to drugs such as atypical and typical antipsychotic agents and benzodiazepines as these medications can lower the patients' functioning and increase morbidity and mortality.[3,5,111-113]

Multiple comorbidities

It has been reported that 84% of patients aged ≥ 65 years have at least two comorbid conditions as compared to 35% of patients aged 45 to 65 years.[114] Previous research has found that the risk of an ADE increases by 2.9-12.6 times with the presence of three or more comorbid conditions.[106] Additionally, patients with multiple comorbidities are at higher risk of being exposed to lots of medications as well as multiple prescribers and specialists.[115] One study on Medicare beneficiaries found that on an average, patients with heart failure can see around 15-23 providers in a given year.[116] Lack of coordination or miscoordination in the overall care system for these patients may lead to prescribing of unnecessary medication, duplication of medication, and potential DDIs.[5]

Altered pharmacokinetics with advanced age

In general, older adults have decreased lean body mass and body water and increased total body fat. This results in a decreased volume of distribution for hydrophilic drugs such as lithium and digoxin and increased volume of distribution for lipophilic drugs such as long-acting benzodiazepines and certain narrow therapeutic index (NTI) drugs.[5] This in turn results in higher plasma drug concentration, possible toxicity, and potential accumulation, respectively if dosing is not adjusted.[5]

Drugs with substantial hepatic first pass metabolism such as beta-blockers, nitrates, and tricyclic antidepressants may have higher bioavailability due to the age-related reduction in hepatic mass and blood flow and thus call for dose adjustment.[5] Decreased oxidation of certain drug metabolizing enzymes such as Cytochrome P450 can result in increased risk of toxicity and DDIs for the drugs that are substrates of this

enzyme.[117] Aging is also linked with compromised renal function. A reduction in serum albumin may cause an increase in the drug concentration of highly protein-bound NTI drugs such as phenytoin, theophylline, warfarin, and digoxin which also call for dose adjustment in older adults.[5]

Advanced age is also associated with a decreased sensitivity to beta-receptors which may result in a lower response to beta-blockers and beta agonists. Moreover, older adults become more susceptible to the centrally acting drugs such as opioids, benzodiazepines, and psychotropic drugs.[118]

All these factors have contributed to the inclusion of these types of drugs in the list of “potentially inappropriate medication” for older adults.

2.3.4 Tools for PIM identification

The tools for PIM identification are guidelines to aid healthcare practitioners in prescribing medications to patients 65 years or older. These contain lists of medications that could potentially cause harmful effects in older populations. The tools for identifying or assessing PIMs in older adults can be classified into two broad categories: explicit criteria and implicit criteria.[119,120] Explicit criteria can be used with little clinical knowledge and mainly contain the list of medications that are to be avoided in older adults .[121] However, individual differences across patients are generally overlooked in these criteria.[121] On the contrary, use of implicit criteria involve professional and/or clinical judgement and require patient specific data which are very time consuming and difficult to execute.[122,123] The commonly used explicit criteria include the following: Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (Beers Criteria),[2,9] Screening

Tool of Older Persons (STOPP) and Screening Tool to Alert to Right Treatment (START)[124], Improved Prescribing in the Elderly Tool (IPET),[125] and EU (7)- PIM list.[5,119,123] The implicit criteria include the following:[126] Assessing Care of Vulnerable Elders-3 (ACOVE-3),[127-129] Medication Appropriateness Index (MAI),[130] Good Palliative–Geriatric Practice Algorithm (GPGPA),[131,132] Screening Medications in the Older Drug User (SMOG),[133] Assess, Review, Minimize, Optimize, Reassess (ARMOR),[134] Tool to Improve Medications in the Elderly via Review (TIMER),[135] and Assessment of Underutilization (AOU).[136,137] Recently, a new tool for identifying PIMs, The Systematic Tool to Reduce Inappropriate Prescribing (STRIP),[120] has emerged which combines both explicit and implicit criteria and is supposed to improve the general practitioners' quality of prescribing. However, its usefulness is still under investigation.[120] Another popular tool is STOPP and START which are mainly used in European countries since many drugs in the Beers list are not available in the European market.[124] For our study, we focused on the Beers Criteria for identifying PIM use among the older adults. Since the Beers Criteria was developed in the US and is the most widely used tool for PIM identification,[124] we consider this to be an appropriate tool for our study.

The Beers Criteria

The Beers Criteria was first published my Dr. Mark Beers and colleagues in 1991 to identify PIM use in nursing home residents.[138] The initial list contained 30 medications that are to be avoided in nursing home residents irrespective of diagnoses. A revised version of this list was published in 1997.[139] The new list was more comprehensive and applicable for all patients aged 65 years and older. Along with medications to be generally

avoided in older adults, this list contained two other categories of PIMs: inappropriate prescription based on dose/duration/frequency and drugs to be avoided with some particular comorbidities. The next update of the Beers List was published in 2003.[140] This list contained 48 medications/classes of medications to be avoided in older adults. This version also contained another 20 condition specific medications to be avoided for their potential harmful effects in older adults. In 2012, the American Geriatric Society (AGS) updated the Beers Criteria for PIM use in older adults.[2] This list included 53 medications/medication classes to be avoided in older adults. A new addition to this list was the medications that are to be used with caution in older adults. The latest update of this list was published in 2015.[9]

Anticholinergics (ACHs) are the largest subset of PIMs listed in the Beers Criteria. Older adults often suffer from multiple chronic conditions, require multiple prescription-only and over-the-counter (OTC) medications to manage them, and are at an increased risk of developing dementia.[141-143] These factors often expose them to the drugs with anticholinergic properties.[144,145] ACHs are routinely used for the treatment of depression, psychosis, Parkinson's disease, muscle spasms, allergy, intestinal motility disorders, and urinary incontinence.[144,145] ACHs account for a wide variety of peripheral and central nervous system (CNS) AEs due to the broad distribution of muscarinic acetylcholine receptors across the CNS and rest of the body.[146,147] Peripheral AEs include constipation, dry mouth, dry eyes, tachycardia and urinary retention whereas the CNS AEs include agitation, confusion, delirium, falls, hallucinations and cognitive dysfunction.[145] Older adults are more sensitive to the CNS AEs due to the reduction in cholinergic neurons in brains, decreased hepatic metabolism and renal drug excretion, and increased

permeability of the blood-brain barriers.[148] For these reasons, many ACHs are considered potentially inappropriate in older adults.[9] Many researchers, thus, expressed their concerns particularly regarding the CNS anticholinergic effects in the older patients, especially with pre-existing cognitive impairments.[142,148] Hence, the study of appropriateness of ACH use in older adults is an important aspect of the quality of medication use.

Previous studies also found significant association between the use of other medications in the Beers Criteria and poor patients' outcomes such as ADEs, hospitalization, and mortality.[119,149-155] Additionally, some medications in this list are proven to have less effectiveness in older adults and are associated with gastrointestinal bleeding, delirium, falls and fracture.[150,153] However, debate exists as to whether the Beers list medications can be a sole predictor of adverse outcomes in older adults.[5] A study among 389 hospitalized patients revealed that only 9.2% of the ADEs were attributable to the Beers list medications.[156] Moreover, some researchers argue that the PIM issue is not a major problem compared to other inappropriate prescribing such as duplication of medications, over/under use of medications, and drug-drug and drug-disease interactions.[5]

Drug-drug interactions (DDIs)

One measure of potentially inappropriate drug use is based on known DDIs. Use of contraindicated drugs together can lead to therapeutic failure and life-threatening ADEs. Polypharmacy and the resultant DDIs can increase the risk of mortality.[11,12] Older adults are more susceptible to these DDIs[13] and are at increased risk of ADEs,

hospitalization, morbidity and mortality.[2] Additionally, prior research has found that older adults admitted to an intensive care unit or who underwent surgery are at increased risk of DDIs.[157] And thus, identifying clinically significant DDIs is an important healthcare quality indicator. Although most pharmacies have software to detect DDIs, it is often very hard to measure clinical significance and thus many alerts are over-ridden.[10] Moreover, above 30 medications are introduced into the market each year.[10] It is quite impossible for physicians and pharmacists to memorize all the possible interactions. Ament et al. published a comprehensive list of clinically significant DDIs of commonly prescribed medications[10]. This could help the healthcare practitioners in prescribing medications to their patients. For our study, we use this list as a measure of identifying clinically significant DDIs.

Although the harmful effects of PIMs and DDIs are well documented, disparities in these regards and resultant adverse clinical outcomes are yet to be studied. Such studies are of huge importance in order to develop interventions to eliminate health disparities. Studying health disparities requires access to unique data that can identify disparities and measure longitudinal outcomes. One useful study is the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

2.4 The REGARDS study

The REasons for Geographic And Racial Differences in Stroke (REGARDS) is a longitudinal cohort study initially designed to assess health disparities in stroke treatment and outcomes in the Southeastern U.S. (“Stroke Belt”) compared to the other parts of the US.[24] 30,239 US adults aged ≥ 45 years (42% black and 58% white) were recruited in the

study from January 2003 to October 2007 and provided information regarding patient demographics, socioeconomic status, complete medication lists, diagnostic reports and physicians' adjudicated health status.[24] Baseline data in the REGARDS study were obtained through telephone interview, self-administered questionnaire, and in-home visits.[24] Age, gender, race, education, household income, and residential history were obtained by self-report.[24] Cognitive impairment was assessed by the Six-Item Cognitive Screener by the telephone interviewer.[24] Information regarding both prescription and nonprescription medications taken within the past two weeks were obtained through in-home exam provided by Examination Management Services, Inc. (EMSI).

We believe that REGARDS is appropriate for studying disparities in PIM prescribing also. This dissertation uses longitudinal data from the REGARDS study to evaluate the appropriateness of medication use across different domains of health disparities, including: 1) socioeconomic status; 2) location of residence (e.g., rural vs urban setting); and 3) obstacles related to race, comparing possible disparities across a variety of previously published measures that have been used to define the appropriateness of medication use. We leveraged REGARDS' infrastructure to quantify health disparities on PIM use and resulting association of PIM use with mortality and cognitive deficiency.

Chapter Three | Methods

3.1 Overview

The purpose of the study is to evaluate the association of health disparities with the rate of potentially inappropriate medication (PIM) use; assess the association between PIM use and mortality and the impact of disparities in this relationship; and to assess the association between anticholinergic drug use and cognitive impairment and the impact of disparities in this relationship. Data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study was used for this purpose. In this section, the aims were discussed in general context and were elaborated in the subsequent sections with more details.

3.2 Aims

Specific Aim 1: To assess the association of health disparities with PIM use.

PIM use was coded using 2015 Beers Criteria. Another measure of PIM use is based on known drug-drug interactions (DDIs) which can also be an indicator of inappropriate drug use. Cross-sectional baseline data was used to compare the PIM use across population subgroups defined by race, income, education, and location of residence. For each of the two measures, PIM use was coded as a binary variable (yes/no) and count variable (number per person). Multivariable logistic regression models

assessed the relationship between PIM/DDI use and the disparity parameters. Multivariable Poisson regression model was used to assess the impact of disparity parameters on the number of PIM use.

Sub-aim 1.a. *Evaluate all PIM use across different population subgroups*

Sub-aim 1.b. *Evaluate prescription versus nonprescription PIM use across different population subgroups*

Sub-aim 1.c. *Evaluate drug-drug interactions (DDIs) across different population subgroups*

Hypothesis

The number of patients being prescribed at least one PIM and DDIs will be higher for females and those with lower income and education, residing in rural areas, and characterized as racial minorities compared to males and those with higher income and education, residing in non-rural areas, and not characterized as racial minorities, respectively.

Specific Aim 2: To assess the association between PIM use and all-cause mortality and to evaluate the effect of health disparities on this relationship.

A Kaplan-Meier estimator and Cox proportional Hazard Ratio (HR) was used to calculate the survival probability and the association between PIM use and mortality, respectively. Multivariable statistical analysis was used to assess the impact of different population subgroups on mortality.

Sub-aim 2.a. *Evaluate the association between all PIM use and all-cause mortality across different population subgroups.*

Sub-aim 2.b. *Evaluate the association between drug-drug interactions (DDIs) and all-cause mortality across different population subgroups*

Hypothesis

The risks of all-cause mortality with PIM use and DDIs will be higher for females and those with lower income and education, residing in rural areas, and characterized as racial minorities compared to males and those with higher income and education, residing in non-rural areas, and not characterized as racial minorities, respectively.

Specific Aim 3: To assess the association between anticholinergic drug use and cognitive impairment and to evaluate the effect of health disparities on this relationship.

Cognitive impairment was assessed by the Six-Item Cognitive Screener (SIS).[24,25] The SIS score ranges from 0 to 6 and a score of ≤ 4 suggests cognitive impairment.[25] Multivariable logistic regression models assessed the disparities across cognitive impairment with anticholinergic drug use.

Sub-aim 3.a. *Evaluate the association between <u>all</u> anticholinergic drug use and cognitive impairment across different population subgroups.*

Sub-aim 3.b. *Evaluate the association between <u>different classes of anticholinergic drug use</u> and cognitive impairment across different population subgroups.*

Hypothesis

The odds of cognitive impairment with anticholinergic drug use will be higher for females and those with lower income and education, residing in rural areas, and characterized as racial minorities compared to males and those with higher income and education, residing in non-rural areas, and not characterized as racial minorities, respectively.

3.3 Data Source and Study Population

The REasons for Geographic And Racial Differences in Stroke (REGARDS) is a national, biracial, longitudinal cohort study initially designed to assess health disparities in stroke treatment and outcomes in the Southeastern US ("Stroke Belt") compared to the other parts of the US.[24] Participants were randomly selected from a commercially available list purchased through Genesys Inc. Potential participants were introduced to the study via mailed letter and study brochure. To prevent underrepresentation of the head of households, trained interviewers made up to 15 contact attempts during the day, evening, weekdays, and weekends.

Exclusion criteria included, race other than blacks or whites, active treatment for cancer, residing or on a waiting list for a nursing home, or inability to communicate in English. After the verbal consent, patients were interviewed via computer-assisted telephone interviewing (CATI). The response rate was 33%.[158] Written informed consents were taken during the further in-home visit. A total of 30,239 US adults with age ≥ 45 years (42% black and 58% white) were recruited in the study from January 2003 to

October 2007. The study sample included 21% of participants from the Stroke Buckle (coastal plain region of North Carolina, South Carolina, and Georgia), 35% from the Stroke Belt states (remainder of North Carolina, South Carolina, and Georgia, plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana), and rest of the 44% from the other 40 neighboring states which are referred to as non-Belt. REGARDS study was approved by the Institutional Review Boards of all the participating institutions. Baseline data collection information of the REGARDS study relevant to our work is given in table 3.1.

Table 3.1. Components of the REGARDS baseline data.[24]

Components	**Telephone interview**	**In-home exam**	**Self-administered**
Medical history	X		
Personal history, demographic data, socioeconomic status	X		
Stroke-free status	X		
Physical activity	X		
Depression	X		
Cognitive screening	X		
Social support	X		
Laboratory assays [a]		X	
Urine		X	
Height, weight, waist circumference		X	
Blood pressure, pulse		X	
Electrocardiography		X	
Medications in the past 2 weeks		X	
Residential history			X

[a] Lipid profile, glucose, creatinine, C-reactive protein

3.4 Variables[24]

The REGARDS dataset contains information regarding patient demographics, socioeconomic status, complete medication lists, diagnostic reports and physicians' adjudicated health status. Age, gender, race, education, household income, and residential history were obtained by self-report. Medical history and cognitive impairment was assessed by the Six-Item Cognitive Screener (SIS) by the telephone interviewer. Information regarding both prescription and nonprescription medication taken within the past two weeks were obtained through in-home exam provided by Examination Management Services, Inc. (EMSI).[24] Information from the telephone interview was transferred to EMSI in order to schedule an in-home visit. The in-home visit took place in the morning between Monday to Thursday by EMSI technicians trained on methods of the REGARDS study protocol. Patients' written informed consents were obtained during the home visit. The trained technicians collected patients' medication lists and other laboratory information (described in table 3.1) during the visit. After the visit, a self-administered questionnaire was left with the participants along with a prepaid envelope in order to return the filled questionnaire to the REGARDS facility. A thank-you letter with a $30 check was mailed to each participant after the in-home visit. A list of the relevant variables for our study is given in table 3.2.

Table 3.2 Partial list of the relevant variables from the REGARDS study.

Number	Variables	Description
1.	id_num	Unique subject identifier
2.	Afib_SR_ECG	Atrial Fibrillation (Self-reported or ECG evidence)
3.	Age	Participants' age
4.	Alc_NIAA	Alcohol use group
5.	ARICStroke	ARIC Stroke Risk Score: 10 years probability of Ischemic Stroke (%)
6.	CAD_SR_ECG	History of heart disease (self-reported MI, CABG, bypass, angioplasty, or stenting or evidence of MI via ECG
7.	CESD	Center for epidemiological studies depression scale
8.	Cholest	Total cholesterol (g/dL)
9.	CogScore	Computed cognitive score
10.	CogStatus	Cognitive Status
11.	Creatinine_urine	Urinary creatinine (mg/dL)
12.	Diabetes_SR	Self-reported diabetes
13.	Ed_Cat	Education categories
14.	EGFR_CKDEPI	Estimated GFR from the CKD-Epi equation
15.	Exercise_cat	Times per week of exercise
16.	Falls	Self-reported falls in the past year
17.	Gender	Self-reported gender
18.	Income	Income
19.	Income_4cat	Income categories based on income
20.	MCS	MCS-12: SF- 12
21.	PCS	PCS-12: SF- 12 Mental
22.	PSS	Perceived stress scale
23.	Race	Race (black or white)
24.	Stroke_SR	Participant reported stroke at baseline
25.	Ruca_4cat	Four category residence status (isolated, small rural, large rural, urban)
26.	death_indicator	Dead or alive indicator
27.	last_fudate	For participants dead, the last follow up date was their death date; for the rest of the participants, this was the most recent follow up date

ECG- electrocardiogram; ARIC- Atherosclerosis Risk in Communities Study; MI- myocardial infarction; CABG- coronary artery bypass grafting; GFR- glomerular filtration rate; CKD- chronic kidney disease; MCS-12 SF-12- mental component summary of the short-form 12 health survey; PCS-12 SF-12- physical component summary of the short-form 12 health survey.

3.5 Approach

3.5.1. Specific Aim 1: To assess the association of health disparities with PIM use

Sub-aim 1.a. Evaluate <u>all</u> PIM use across different population subgroups

Study Population

We used the data collected in the REGARDS study which accounted for a total of 30,239 US adults with age ≥ 45 years (42% black and 58% white). 3,441 participants were excluded due to missing drug information. So, a total of 26,798 participants were present in the overall cohort out of which 13,623 were of age ≥ 65 years (38% black). For this sub-aim 1.a., we used only the patients aged ≥ 65 years since Beers Criteria contain medications that are considered potentially inappropriate for the patients aged 65 or over.

Measures

PIM use was coded using the 2015 Beers Criteria which includes a list of medications that are potentially harmful and are to be avoided in older adults (age ≥ 65 years).[9] Any drug appearing in the patients' medication list was matched with the Beers Criteria for their presence or absence in it and coded as binary variables (yes/no). Total number of medications per patient and total number of PIMs per patient also were calculated. Total number of medications per person was converted into quartiles.

Variables of interest

PIM use (yes/no) was considered as a dependent variable and the disparity parameters (gender, race, income, education, location of residence) and the total number

of medications per person was considered as independent variables in the overall model. The categorization of the disparity parameters is given in table 3.3.

Table 3.3 Categorization of the disparity parameters

Variables	**Categories**
Gender	Male
	Female
Race	Black
	White
Income (per year)	Less than $20,000
	$20,000- $34,999
	$35,000- $74,999
	≥ $75,000
Education	Less than high school
	High school
	Some college
	Greater than college
Location of residence	Isolated
	Small rural
	Large rural
	Urban

Statistical analysis

Descriptive statistics were used to report the rate of PIM use stratified across different population subgroups.

Multivariable logistic regression was used to assess the association between any PIM use and the disparity parameters. Interaction variables was created to test for interaction between race x gender; race x income; race x education; race x region, and race x total number of medications per person. The resultant odds ratios (OR) and 95%

confidence intervals were assessed as a measure of significance of association. Similar analyses were applied for PIM use across prescription-only and OTC drugs.

Interactions were considered significant at alpha = 0.1 level.[159] A significant interaction will render it as an effect modifier.[160] Let us consider the interaction between race and gender. Both are categorical variables. For this we can take the categorical by categorical interaction approach.[161-163] Let us consider a logistic model for the risk of PIM use in terms of gender and race:

$$logit\ PIM\ (Y = 1) = \beta_0 + \beta_1\, gender + \beta_2\, race + \beta_3\, (gender \times race) \quad \ldots\ldots\ldots\ldots (3.1)$$

Here,

gender: male=0, female=1; race: white=0, black=1.

For interpreting β_3, equation 3.1 can be rewritten as follow:

$$logit\ PIM\ (Y = 1) = \beta_0 + \beta_1\, gender + [\beta_2 + \beta_3\, gender]\ race \quad \ldots\ldots\ldots\ldots\ldots\ldots (3.2)$$

β_3 is the difference between the log-odds ratio comparing black vs white in males and the log-odds ratio comparing black vs white in females. In other words, β_3 can be interpreted as the difference between the log-odds ratio comparing female vs male in blacks and the log-odds ratio comparing female vs male in whites. So, two ways of effect modification is possible here:

- Effect modification of race by gender
- Effect modification of gender by race.

This results in four types of odds ratios. They are as follow:

- female vs male; race = black
- female vs male; race = white
- black vs. white; gender = female
- black vs. white; gender = male

All other interaction terms was interpreted in a similar way.

We conducted a multivariable Poisson regression as a measure of sensitivity analysis to assess the effect of different disparity parameters on total number of medications and total number of PIMs use. The resultant prevalence ratio (PR) and 95% confidence interval was assessed as a measure of significance of association. Interaction of race with other disparity parameters also were tested as described before. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Handling missing data

Missing data in covariates were replaced by multivariable multiple imputation technique using chain equations in 10 datasets with sample bootstrapping.[164,165]

Sub-aim 1.b. Evaluate prescription versus nonprescription PIM use across different population subgroups

Study population

The population described in sub-aim 1.a. was used here.

Measures

Our data contained an indicator variable that defined whether it was an OTC or prescription-only drug. This information was collected by the trained EMSI technicians

during the in-home visit. For example, omeprazole, a proton pump inhibitor, is available both as an OTC and prescription drug. If it was prescribed by a physician, it was considered as a prescription drug and if it was purchased by the patient without a prescription, it was considered as an OTC drug. All other measurements was carried out according to the methods described in sub-aim 1.a. stratified across OTC and prescription-only drugs.

Variables of interest

The same variables described in sub-aim 1.a. was used here.

Statistical analysis

The same data analyses techniques described in sub-aim 1.a. also was used here stratified across OTC and prescription-only drugs.

Sub-aim 1.c. Evaluate drug-drug interactions (DDIs) across different population subgroups

Study population

The total population of the REGARDS study cohort after excluding the participants with missing drug information were included in this study. So, a total of 26,798 US adults aged ≥ 45 years were included for this sub-aim.

Measures

DDIs was coded using known clinically significant drug interactions list published by Ament et al.[10] A complete list of commonly known interacting drugs is provided in **appendix A.**

The list of interacting drugs was matched with the patient's complete medication list for identifying the presence of possible interacting drugs together. Any interaction present was coded as "Interaction = yes" or else "Interaction = no" if absent. This coded and clean medication list data was merged back to the patients' sociodemographic and health status data based on their unique patient identification number for further analyses.

Variables of interest

DDIs (yes/no) was considered as a dependent variable and the disparity parameters (age, gender, race, income, education, location of residence) and the total number of medications per person were considered as independent variables in the overall model. Age was stratified as <60 years, 60-64 years, 65- 75 years, and greater than 75 years. The other disparity variables were categorized as described in table 3.3.

Statistical analysis

Multivariable logistic regression was used to evaluate the association between DDIs and the disparity parameters. Interaction variables was created to test for interaction between race x gender; race x income; race x education; race x region; and race x total number of medications per person. Interaction terms were interpreted following the method described in sub-aim 1.a. The resultant odds ratio (OR) and 95% confidence interval was assessed as a measure of significance of association.

3.5.2. Specific Aim 2: To assess the association between PIM use and all-cause mortality and to evaluate the effect of health disparities on this relationship

Sub-aim 2.a. Evaluate the association between all PIM use and all-cause mortality across different population subgroups

Study population

We used the data collected in the REGARDS study which accounted for a total of 30,239 US adults with age ≥ 45 years (42% black and 58% white). A total of 3,441 participants were excluded due to the missing drug information. Additional 399 patients also were excluded due to the missing death indicators. So, a total of 26,399 participants were included in the study out of which 13,475 were of age ≥ 65 years.

Measures

Measures described in sub-aim 1.a. was used here.

Study outcome

Our study outcome is all-cause mortality. We assessed whether there are any disparities in this outcome with the PIM and DDI use. For participants who died during follow-up, the last follow-up date was their death date. For the rest of the participants, this was the most recent follow-up date. The last follow-up date for our study was March 31, 2016.

Variables of interest

The disparity parameters (gender, race, income, education, and location of residence) were categorized as described in the table 3.3. Other than the disparity

variables, patients' medical condition, physiologic risk factors, total number of medications, and total PIM use were considered as covariates.

Medical condition included self-reported diabetes, atrial fibrillation (Afib) defined as self-reported history or evidence on an ECG performed during the in-home assessment, chronic kidney disease (CKD) defined as estimated glomerular filtration rate (eGFR) <60 ml/min/ 1.73 m^2,[166] self-reported history of stroke, and history of cardiovascular diseases (CVD) defined by self-reported myocardial infarction (MI), coronary artery bypass grafting (CABG), bypass, angioplasty, or stenting or evidence of MI via ECG.

Physiologic risk factors included dyslipidemia defined as total cholesterol (TC) ≥ 240 mg/dL or low-density lipoprotein (LDL) ≥ 160 mg/dL or high-density lipoprotein (HDL) ≤ 40 mg/dL or on any cholesterol lowering medication, Atherosclerosis Risk in Communities (ARIC) study stroke risk score, total cholesterol, and urinary creatinine levels.

In our study, diabetes, Afib, CKD, history of stroke, CVD, and dyslipidemia were coded as binary variables (yes/no) whereas the total cholesterol, ARIC stroke risk scores, urinary creatinine levels, total number of medication, and total PIM use were converted into quartiles for further analyses.

Statistical analysis

Descriptive statistics were obtained for PIM use by using chi-square statistics for categorical characteristics and Student *t* test for continuous characteristics. Time-to-event

analyses were performed for all-cause mortality where the participants were followed-up until the event of interest through March 31, 2016.

The association of all-cause mortality with PIM use was studied by sequentially adjusted Cox proportional Hazard models. The resultant hazard ratio (HR) and corresponding 95% confidence intervals (CI) were reported as a measure of significance of association.

The hazard rate is given by the following equation: [167]

$$h(t)=h_0(t)\, r(x, \beta_x) \quad \ldots\ldots\ldots\ldots\ldots\ldots (3.3)$$

Here,

$h_0(t)$ = baseline hazard rate which depends on time alone

$r(x, \beta_x)$ = describes hazard rates dependent on other x covariates

Since the expression of hazard rate depending on its covariates is an exponential function, the hazard function is given by the equation 3.4.

$$h(t)=h_0(t)\, exp(x\beta_x) \quad \ldots\ldots\ldots\ldots\ldots\ldots (3.4)$$

The HR is given by the equation 3.5.

$$HR = \frac{h(t|x_2)}{h(t|x_1)} = \frac{h_0(t)exp(x_2\beta_x)}{h_0(t)exp(x_1\beta_x)} \quad \ldots\ldots\ldots\ldots\ldots\ldots (3.5)$$

Since the hazard rates between two groups with fixed covariates will stay constant over time, it is called the proportional HR.[167] Equation 3.5 shows the ratio between two hazard rates at time t. When $x = x1$, the hazard rate at time t is $h(t|x1) = h_0(t)\, exp(x1\beta_x)$ and when $x = x2$, the hazard rate at time t is $h(t|x2) = h_0(t)\, exp(x2\beta_x)$. The $h_0(t)$ cancels each other out and HR is given by equation 3.6.

$$HR = exp(\beta_x(x_2 - x_1)) \quad \ldots\ldots\ldots\ldots\ldots\ldots (3.6)$$

Thus, the HR does not depend on time t and remains constant over time with fixed covariates. This is the biggest assumption of the Cox proportional hazard model. For example, if blacks have twice the hazard rate than whites at day 1, the Cox proportional hazard model assumes that the hazard rate between blacks and whites was the same at 500 days.[167] Proportional hazard assumptions were tested via Schoenfeld Residuals method.[167-169]

The sequentially adjusted Cox proportional hazard models were developed as follows: model 1 was the unadjusted Cox proportional hazard model that accounted for only the PIM exposure. Model 2 was adjusted for demographics and socioeconomic characteristics. Model 3 adjusted for all the model 2 covariates plus patients' medical condition, physiologic risk factors, total number of medication use, and total PIM use. The summary of all the models are shown in figure 3.1.

Model 1. Unadjusted model: only the PIM exposure

Mortality = PIM

Model 2. Adjusted for demographic and socioeconomic characteristics

Mortality = PIM + demographics + socioeconomic variables

Model 3. Adjusted for model 2 covariates, medical conditions, and physiologic risk factors + medication count + PIM count

Mortality = PIM + demographics + socioeconomic variables + medical condition [a] + physiologic risk factors [a] + total number of medications + total PIM use

[a] covariates described in sub-aim 2. a.

Figure 3.1. Summary of the analyses plan to evaluate the association between PIM use and mortality

Due to the cross-sectional nature of the PIM exposure, we conducted a series of predictive modelling to test the impact of censoring follow-up intervals.[164] We stratified

the follow-up time intervals as 0-2 years, 0-4 years, 0-6 years, and 0 to end of follow-up time. To study the effect of disparity parameters on the relationship of PIM use and all-cause mortality, interaction variables were created to test for interaction between PIM use and all the disparity variables. We also tested the interaction between PIM use and other covariates. Interactions were considered significant at alpha= 0.1 level.[159,170]

And finally, Kaplan-Meier survival curves and log-rank tests were performed[167,171,172] to test the effect of PIM use, total number of medication use, and total number of PIM use per person on the survival probability. We also studied the impact of disparity variables on survival probability among participants with PIM use using the Kaplan-Meier estimator. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Handling missing data

Missing data in covariates were replaced by multivariable multiple imputation technique using chain equations in 10 datasets with sample bootstrapping.[164,165]

Sub-aim 2.b. Evaluate the association between drug-drug interactions (DDIs) and all-cause mortality across different population subgroups

Study population

We used the data collected in the REGARDS study which accounted for a total of 30,239 US adults with age ≥ 45 years (42% black and 58% white). A total of 3,441participants were excluded due to the missing drug information. Additional 399

patients also were excluded due to the missing death indicators. So, a total of 26,399 participants were included in the study.

Measures

The measures described in sub-aim 1.c. was used here.

Variables of interest

We used DDI (yes/no) as the main predictor variable. The other covariates described in sub-aim 2.a. was used here. Additionally, since we did not restrict our cohort to ≥ 65 years for this sub-aim, we stratified the age as less than 60 years, 60-64 years, 65-75 years, and greater than 75 years and used as a covariate in the study.

Statistical analysis

Data analyses techniques described in sub-aim 2.a. was used here. The summary of all the models are shown in figure 3.2.

Model 1. Unadjusted model: only the DDI exposure

Mortality = DDI

Model 2. Adjusted for demographic and socioeconomic characteristics

Mortality = DDI + demographics + socioeconomic variables

Model 3. Adjusted for model 2 covariates, medical conditions, and physiologic risk factors + medication count

Mortality = DDI + demographics + socioeconomic variables + medical condition [a] + physiologic risk factors [a] + total number of medications

[a] covariates described in sub-aim 2.a. and 2.b.

Figure 3.2. Summary of the analyses plan to evaluate the association between DDIs and mortality

3.5.3. Specific Aim 3: To assess the association between anticholinergic drug use and cognitive impairment and to evaluate the effect of health disparities on this relationship

Sub-aim 3.a. Evaluate the association between <u>all</u> anticholinergic drug use and cognitive* impairment *across different population subgroups

Study population

The population described in sub-aim 1.a. was used here.

Measures

Anticholinergic drug use was coded using the 2015 Beers Criteria which contains a list of drugs with strong anticholinergic properties.[9] The list of anticholinergic drugs was matched with the patient's clean and complete medication list for identifying the presence or absence of these drugs. A complete list of the anticholinergic drugs that was studied is given in **appendix B**. Any anticholinergics present was coded as "ACH=yes" or else "ACH =no" if absent. This coded analytic dataset was used for further analyses.

Cognitive impairment was defined by the participants' most recent score in the Six-Item Cognitive Screener (SIS) which is a test of cognitive function derived from the Mini-Mental State Exam (MMSE).[173] In this screener, the scores range from 0 to 6. A score ≤ 4 denotes cognitive impairment.[174,175] If the score is > 4 then the cognitive status was coded as "Normal" or else if the score is ≤ 4, the cognitive status was coded as "Impaired".

Variables of interest

Cognitive impairment (Impaired / Normal) was considered as the dependent variable and ACH (yes/no) and the disparity parameters (gender, race, income, education, location of residence) was considered as independent variables in the overall model. The disparity variables were categorized as described in table 3.3.

Other covariates included patients' medical condition, physiologic risk factors, health behaviors, and markers of mental health were considered as covariates. Medical condition included self-reported diabetes and chronic kidney disease (CKD) defined as estimated glomerular filtration rate (eGFR) <60 ml/min/ 1.73 m^2.[166] Physiologic risk factors included atherosclerosis risk in communities (ARIC) study stroke risk score and urinary creatinine levels. Measures of health behaviors included alcohol use defined as none; moderate: 1-7 for women, 1-14 for men; and heavy: ≥7 drinks/week for women, ≥14 drinks/week for men[164] and exercise defined as none; 1 to 3 times; and 4 or more times/week. Finally, markers of mental health were assessed by the mental component scores (MCS) of the Short Form-12 (SF-12), presence of depressive symptoms defined as a score ≥4 of the Centers for Epidemiologic Study Depressive Scale (CES-D),[176] and Cohen's Perceived Stress Scale(PSS) score.[164]

Prior studies showed that complete abstinence from alcohol, lack of exercise, and depression were associated with cognitive impairment.[177,178] Also, the stress level was found to be associated with depression.[179] Similarly, higher creatinine level was found to be associated with CKD[166] and CKD was associated with cognitive impairment.[173,180] Diabetes and stroke increases the permeability of the blood-brain barrier and increase the penetration of anticholinergic drugs.[181,182] Prior studies also found the association of

cognitive impairment with diabetes and stroke.[173,178,183] All of these factors contributed to the selection of covariates for this study.

In our study, diabetes, CKD, and depressive symptoms were coded as binary variables (yes/no) whereas the ARIC stroke risk scores, urinary creatinine levels, MCS, and PSS scores were converted into quartiles for further analyses.

Statistical analysis

Descriptive statistics were used to report the rate of anticholinergic drug use in different population subgroups.

The association between cognitive impairment and ACH use were studied by sequentially adjusted multivariable logistic regression models. The resultant odds ratio (OR) and corresponding 95% confidence intervals (CI) were reported as a measure of significance of association. Model 1 was the unadjusted logistic regression model that accounted for only the ACH exposure. Model 2 was adjusted for demographics and socioeconomic characteristics. Model 3 adjusted for all the model 2 covariates plus patients' medical condition, and physiologic risk factors. Model 4 was adjusted for model 3 covariates plus measures of health behaviors. And finally, model 5 was adjusted for all the model 4 covariates plus markers of mental health.

To study the effect of disparity parameters on the relationship of ACH exposure and cognitive impairment, interaction variables were created to test for interaction between ACH use and all the disparity variables and covariates. Interaction of race with other disparity variables also were considered to study disparities across ACH use only.

Interactions were considered significant at alpha= 0.1 level. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC). The summary of all the models are shown in figure 3.3.

Model 1. Unadjusted model: only the ACH exposure

Cognitive Impairment = ACH

Model 2. Adjusted for demographic and socioeconomic characteristics

Cognitive Impairment = ACH + demographics + socioeconomic variables

Model 3. Adjusted for model 2 covariates, medical conditions, and physiologic risk factors

Cognitive Impairment = ACH + demographics + socioeconomic variables + medical condition [a] + physiologic risk factors [a]

Model 4. Adjusted for model 3 covariates and health behaviors

Cognitive Impairment = ACH + demographics + socioeconomic variables + medical condition [a] + physiologic risk factors [a] + alcohol use [a] + exercise per week [a]

Model 5. Adjusted for model 4 covariates, and markers of mental health

Cognitive Impairment = ACH + demographics + socioeconomic variables + medical condition [a] + physiologic risk factors [a] + alcohol use [a] + exercise per week [a] + PSS + MCS + depression [a]

[a] covariates described in sub-aim 3. a.

Figure 3.3. Summary of the analyses plan to evaluate the association between anticholinergic drug use and cognitive impairment.

Handling missing data

Similar to the method describe din sub-aim 2.a.

Sub-aim 3.b. Evaluate the association between different classes of anticholinergic drug use and cognitive* impairment *across different population subgroups

Study population

The population described in sub-aim 1.a. was used here.

Measures

Different classes of anticholinergic drug use was coded using the 2015 Beers Criteria which include antihistamines, antidepressants, antimuscarinics, antiparkinsonian agents, antipsychotics, antispasmodics, skeletal muscle relaxants, antiarrhythmics, and antiemetic drug classes.[9] Any drug classified as antihistamine in the Beers list was matched with the patient's clean and complete medication list for identifying the presence of these drugs. Any antihistamines present was coded as "antihistamine=yes" or else "antihistamine =no" if absent. The same approach was taken for all the classes of anticholinergic drugs. All other measures described in sub-aim 3.a. was used here.

Variables of interest

The other covariates described in sub-aim 3.a. was used here as well.

Statistical analysis

Data analyses techniques described in sub-aim 3.a. also was applied here. The analyses were stratified across different classes of anticholinergic drugs. The summary of all the models are shown in figure 3.4.

Model 1. Unadjusted model: only the ACH exposure

Cognitive Impairment = ACH class

Model 2. Adjusted for demographic and socioeconomic characteristics

Cognitive Impairment = ACH class + demographics + socioeconomic variables

Model 3. Adjusted for model 2 covariates, medical conditions, and physiologic risk factors

Cognitive Impairment = ACH class + demographics + socioeconomic variables + medical condition [a] + physiologic risk factors [a]

Model 4. Adjusted for model 3 covariates and health behaviors

Cognitive Impairment = ACH class + demographics + socioeconomic variables + medical condition [a] + physiologic risk factors [a] + alcohol use [a] + exercise per week [a]

Model 5. Adjusted for model 4 covariates, and markers of mental health

Cognitive Impairment = ACH class + demographics + socioeconomic variables + medical condition [a] + physiologic risk factors [a] + alcohol use [a] + exercise per week [a] + PSS + MCS + depression [a]

* ACH classes include antihistamines, antidepressants, antimuscarinics, antiparkinsonian agent, antipsychotics, antispasmodics, skeletal muscle relaxants, antiarrhythmic, and antiemetic drug classes

[a] covariates described in sub-aim 3. a.

Figure 3.4. Summary of the analyses plan to evaluate the association between anticholinergic drug classes use and cognitive impairment.

Chapter Four | Results

Aim 1

ABSTRACT

Background: Prior work has identified disparities in the quality and outcomes of health care across socioeconomic subgroups. Medication use may be subject to similar disparities.

Objective: To assess the association between demographic factors and socioeconomic status (gender, age, race, income, education, and rural or urban areas) and appropriateness of medication use.

Methods: The analyses included 26,798 black and white US adults aged ≥ 45 years from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, of which 13,623 participants were of age ≥ 65 years (recruited 2003-2007). The appropriateness of medication use was measured by the presence of drug-drug interactions (DDIs) measured by the known clinically significant drug interactions list published by Ament et al. and use of potentially inappropriate medications (PIMs) in older adults measured by the 2015 Beers Criteria. Multivariable logistic regressions were used to assess the association of disparity parameters with PIM use and DDIs. Multivariable Poisson regression assessed the effect of different disparity parameters on total number of medications and total number of PIMs use. The full models included interaction terms

between race and other disparity variables. Similar analyses were applied for PIM use across prescription-only and OTC drugs.

Results: Approximately 87% of the participants aged ≥ 65 years used at least one drug listed in the Beers criteria, and 3.8% of all participants used two or more drugs with DDIs. For prescription-only drugs, income (<$20,000 vs. ≥$75,000: OR=1.26, 95% CI 1.01-1.57; ($20,000-$34,999 vs. ≥$75,000: OR=1.24, 95% CI 1.02-1.51) and education (< high school vs. >college: OR=1.31, 95% CI 1.09-1.56; high school vs. >college: OR=1.17, 95% CI 1.01-1.34; some college vs. >college: OR=1.19, 95% CI 1.04-1.37) were significantly associated with PIM use. Significant gender-race interaction revealed that white females had higher odds of PIM use than white males (OR=1.33, 95% CI 1.20-1.48) and black males had higher odds of PIM use than white males (OR=1.60, 95% CI 1.41-1.82). For OTC drugs, gender (female vs. male: OR=0.61, 95% CI 0.56-0.67), education (< high school vs. >college: OR=1.16, 95% CI 1.01-1.33), and rural residence (small rural vs. urban: OR=1.29, 95% CI 1.07-1.54; large rural vs. urban: OR=1.18, 95% CI 1.03-1.35) were significant predictors of PIM use. DDIs also were significantly associated with gender (female vs. male: OR= 0.55, 95% CI 0.48-0.63) and location of residence (small rural vs. urban: OR=1.37, 95% CI 1.07-1.76). Total number of medication use was a significant predictor of PIM use and DDIs (P<0.01). Sensitivity analyses also revealed that females compared to males, blacks compared to whites, and individuals with lower income, education, and residing in rural areas had higher PIM prevalence (P<0.01).

Conclusion: Demographic and socioeconomic disparities in PIM use and DDIs exist, and future studies should seek to better understand factors contributing to the disparities in order to guide development of interventions.

Key words: REGARDS, potentially inappropriate medication, drug-drug interaction, socioeconomic disparity

Introduction

The United States (US) spends more per capita on health care than any other nation,[1] yet health-related quality indicators lag behind many other countries.[2] The quality of care in the US is often questioned and considered as substandard by many experts.[3] Previous research found that only around 55% of patients receive the appropriate diagnosis and care.[4] Variations in access to care and outcomes also exist.[5] Underuse, overuse, and misuse of healthcare resources and services are relatively common.[3] Additionally, in many cases, the healthcare delivery system is unorganized and very complicated.

A low healthcare quality score is partly attributed to inequalities among subpopulations within the US.[6] These inequalities, or health disparities, are defined as being significant differences in the treatment, diagnosis, and prevention of certain health conditions that are more prevalent among subpopulations versus the overall population.[7] The subpopulations affected can be defined by different domains of health disparities, including: 1) socioeconomic status; 2) location of residence (e.g., rural vs urban setting); and 3) obstacles related to race or ethnicity.[7] These factors are not mutually exclusive of one another and often occur simultaneously.

Previous research has explored the relationship between health disparities and various quality indicators reflecting health care structure, process, and outcome measures. For structure measures, for example, in 2015, the Agency for Healthcare Research and Quality (AHRQ) reported that blacks and people with low income had worse access to care than whites and high income individuals.[5] Additionally, people

residing in rural areas have limited access to care which is often attributed to the lack of providers.[8]

For process measures, for example, uninsured and low coverage individuals report poor communication with health providers compared with those with private insurance status. Uninsured adults and those with Medicaid reported that health providers did not always seek the patient's help when making treatment decisions nor did they spend enough time clarifying explanations with patients.[9] For instance, while provider-patient interactions are vital in educating patients about their overall lifestyle, less than 40% of uninsured, obese adults report ever having their health provider give advice on dietary suggestions.[9]

In terms of outcome measures, numerous health disparities have been documented in terms of disease-specific outcomes, morbidity, and mortality. For stroke, for instance, health disparities due to race and ethnicity are prevalent in stroke care and management. Among adults 25 to 44 years of age, blacks and Native Americans/American Indians have a higher hemorrhage mortality rate with stroke.[10,11] Similarly, blacks and Hispanics are 70% more likely and Native Americans/American Indians are 20% more likely to be diagnosed with diabetes than whites, respectively.[12] Prior studies also found the association of low socioeconomic status with morbidity and mortality.[13-16]

One important but understudied quality measure revolves around the appropriateness of medication prescribing and use. While some studies have documented health disparities in terms of the appropriateness of medication prescribing and the quality of population-based medication use (e.g., which drugs are being used by

specific populations and medication adherence), data are limited to support systematic assessment of the appropriateness of medication use across health disparities defined on the basis of socioeconomic factors, rural vs. urban residence, and race. In part, this gap in the literature is caused by lack of appropriate population-level data, and in part this gap is related to lack of consensus of ways to define the "appropriateness of medication use".

Roughly 100,000 Americans are injured or die in hospitals, doctors' offices, nursing homes, and other healthcare settings each year due to "avoidable" medication errors at a cost around $17-$29 billion each year.[17,18] One form of avoidable medication error is the use of potentially inappropriate medications (PIMs). PIM's are defined as utilization of medications that have an increased risk of adverse drug events (ADEs) when an alternative exists that is equally efficacious with fewer risks.[19,20] Improper use of medicine such as use of medications at a higher dose/frequency, for longer duration than clinically indicated, under use of medicine for no clinical reasons, and use of multiple medications that are known to have clinically significant drug–drug interactions (DDIs) are also considered under the umbrella of PIM use.[18,21] Although most pharmacies have software to detect DDIs, it is often hard to measure the clinical significance.[22] Older adults are more susceptible to these DDIs and are at increased risk of ADEs, hospitalization, morbidity and mortality.[19,23] And thus, identifying clinically significant DDIs is an important healthcare quality indicator.

The quality of healthcare is sometimes characterized by the frequency in which PIMs are prescribed in older adults,[24] and prior work has suggested that there may be a disparity in which people are prescribed PIMs.[25,26] The focus of our study is to evaluate

the frequency of medication use across three domains of health disparities, comparing possible disparities across a variety of previously published measures that have been used to define the appropriateness of medication use.

Methods

Data source

Data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study was used for this study. REGARDS is a population-based study initially designed to assess health disparities in stroke treatment and outcomes in the Southeastern US ("Stroke Belt") compared to the other parts of the US.[27] Participants in this study were randomly selected via mail and telephone contacts from a commercially available list purchased through Genesys Inc.. Potential participants were introduced to the study via mailed letter and study brochure. To prevent underrepresentation of the head of households, trained interviewers made up to 15 contact attempts during the day, evening, weekdays, and weekends.

Demographic and socioeconomic characteristics were obtained via computer-assisted telephone interviewing (CATI). Information regarding both prescription and nonprescription medications taken within the past two weeks were obtained through in-home exam provided by the Examination Management Services, Inc. (EMSI). Patients' written informed consents were obtained during the home visit. The REGARDS study was approved by the Institutional Review Boards (IRB) of all the participating institutions.

Complete methodological details of the REGARDS study are published elsewhere.[27] This retrospective analysis was approved by the Auburn University IRB.

Study population

This study included a total of 30,239 US adults age ≥ 45 years (42% black) who were recruited from January 2003 to October 2007. Exclusion criteria included race other than blacks or whites, active treatment for cancer, residing or on a waiting list for a nursing home, or inability to communicate in English. 3,441 participants were excluded due to missing drug information. So, a total of 26,798 participants were present in the overall cohort out of which 13,623 were of age ≥ 65 years (38% black).

Measures

PIM use was coded using the American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (described as “Beers Criteria” from here forward) which includes a list of medications that are potentially harmful and are to be avoided in older adults (age ≥ 65 years).[28] Any drug appearing in the patients’ medication list was matched with the Beers Criteria for their presence or absence in it and coded as binary variables (yes/no). The total number of medications per patient and the total number of PIMs per patient also were calculated. The total number of medications per person was converted into quartiles. The PIM use was stratified across over-the-counter (OTC) and prescription-only drugs. This was determined and coded by the trained technicians of EMSI during the in-home visit.

Another measure of PIM use is based on known DDIs which could be an indicator of inappropriate drug use. DDIs were coded using a known clinically significant drug

interactions list published by Ament et al.[22] A complete list of commonly known interacting drugs is provided in **appendix A**. The list of interacting drugs was matched with the patient's complete medication list for identifying the presence of possible interacting drugs together. Any interaction present was coded as "Interaction= yes" or else "Interaction = no" if absent. The clean and coded medication list data was merged with the patients' demographic and socioeconomic status data based on their unique patient identifier for further analyses.

The disparity parameters for this study were defined as gender (male/female), race (black/white), annual income (stratified as less than $20,000, $20,000- $34,999, $35,000- $74,999, and ≥ $75,000), education (stratified as less than high school, high school, some college, and greater than college), and location of residence (stratified as isolated, small rural, large rural, and urban).

For PIM analyses using the Beers Criteria, we restricted the patient's cohort to age ≥ 65 years since the medications listed as PIM in this list are only applicable for this patient group. However, there is no such age restriction for the analyses of DDIs using the list provided by Ament et al. To study the disparities across DDIs, we used age as a disparity parameter and stratified it as less than 60 years, 60-64 years, 65-75 years, and greater than 75 years.

Statistical analyses

Descriptive statistics were used to report the rate of PIM use stratified across different disparity parameters. Multivariable logistic regression was used to assess the association between any PIM use and the disparity parameters. Interaction variables

were created to test for interaction between race x gender; race x income; race x education; race x region, and race x total number of medications per person. Interactions were considered significant at alpha= 0.1 level. The resultant odds ratios (OR) and 95% confidence intervals were assessed as a measure of significance of association. Similar analyses were applied for PIM use across prescription-only and OTC drugs. Income and location of residence had around 12% and 9% of missing data, respectively. In our study, missing data in covariates were replaced by multivariable multiple imputation technique using chain equations in 10 datasets with sample bootstrapping.[29,30] Prior studies recommended multiple imputation in case of data where 10 to 60% of values are missing.[31,32]

We conducted a multivariable Poisson regression as a measure of sensitivity analysis to assess the effect of different disparity parameters on total number of medications and total number of PIM use. The resultant prevalence ratio (PR) and 95% confidence interval was assessed as a measure of significance of association. The interaction of race with other disparity parameters also were tested as described before. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

3,441 out of the 30,239 participants were excluded due to missing drug information. So, a total of 26,798 participants were present in the overall cohort out of which 13,623 were of age ≥ 65 years (38% black).

Out of 13,623 participants aged ≥ 65 years, a total of 11,912 (87.4%) used at least one drug listed in the Beers criteria, and out of all the participants (n=26,798), 1014 (3.8%)

used two or more drugs with DDIs. On an average, each participant aged 65 and over used 6.5 medications which ranged from 1 to 20. The mean number of PIM use per person aged ≥ 65 years was 2.4 which ranged from 0 to 14. Characteristics of the PIM and DDI users and non-users are shown in Table 1.

Significant differences were observed between PIM users and non-users. For example, PIM users compared to the non-users were older (mean age 72.8 vs 72.3 years) and more likely whites (62.3% vs 59.6%). PIM users had lower income, education, and mainly resided in rural areas compared with non-users. No differences were seen by gender. Similar differences were observed for DDI users and non-users. For example, DDI users compared to non-users were older (mean age 67.4 vs 65.2 years), more likely male (54.8% vs 43.4%), whites (76.5% vs 58.5%), and resided in rural areas.

We also studied PIM use across prescription-only and OTC drugs. For prescription only drugs, higher rates of PIM use were observed for females compared with males, blacks compared with whites, and individuals with lower income and education (Table 2). However, for OTC drugs, higher rates of PIMs were observed for males compared with females and whites compared with blacks. We did not find any consistent pattern for PIM use across OTC drugs in terms of income, education, and location of residence.

We conducted multivariable logistic regression to assess the association between PIM use in older adults and disparity parameters (gender, race, income, education, and location of residence) and total number of medications per person stratified across prescription-only and OTC drugs (Table 3). The total number of medications was converted into quartiles for the analyses. Interaction of race with other disparity variables and total number of medication use also were conducted. For PIM use across all the

drugs (both prescription-only and OTC), gender-race and the total number of medications-race interactions were found to be significant. White males demonstrated higher odds of having PIMs compared with white females (female vs. male among whites: OR= 0.84, 95% CI 0.74 – 0.96). Higher number of medication use was a significant predictor of PIM use in both blacks and whites. For example, when we compared the fourth quartile vs. the first quartile, the OR and 95% CI of PIM use for blacks was 65.53 (40.79 – 105.29) whereas for whites it was 38.13 (28.97 – 50.18).

For PIM use across prescription-only drugs, income and education were independent predictors of PIM use whereby individuals with lower income and education had higher odds of having a PIM prescription (Table 3). For example, the odds of PIM prescription among individuals with an annual income of less than $20,000 was 26% more than those with annual income ≥ $75,000. Similarly, participants with education level less than high school had 31% more odds of having a PIM prescription than the individuals with college degrees or above. A significant gender-race interaction indicated that black males compared with white males (OR= 1.60, 95% CI 1.41 – 1.82) and white females compared with white males (OR= 1.33, 95% CI 1.20 – 1.48) had higher odds of PIM prescription. Higher number of medications per person also was a significant predictor for PIM prescription in both blacks and whites.

The study of PIM use across OTC drugs showed that gender, education, and location of residence were independent predictors of PIM use (Table 3). Males compared with females (female vs male: OR= 0.61, 95% CI 0.56 – 0.67), individuals with lower education (less than high school vs college graduate and above: OR= 1.16, 95% CI 1.01 – 1.33), and people residing in rural areas (small rural vs urban: OR= 1.29, 95% CI 1.07

– 1.54); large rural vs urban: OR= 1.18, 95% CI 1.03 – 1.35) had higher odds of OTC PIM use. We also found that higher number of medication use was associated with a higher odds of OTC PIM use. A significant income-race interaction elucidated that blacks compared with whites had higher odds of OTC PIM use in the lower income subgroups (for annual income less than $20,000, black vs white: OR= 1.32, 95% CI 1.08 – 1.61). This relationship was not significant in the higher income subgroups.

We also found similar disparities across the use of interacting drugs together (Table 3). Males compared with females (female vs male: OR= 0.55, 95% CI 0.48 – 0.63) and individuals residing in rural areas (small rural vs urban: OR 1.37, 95% CI 1.07 – 1.76) had higher odds of having DDIs. Higher medication use also was a significant predictor of DDIs. A significant age-race interaction suggested that whites compared with blacks have higher odds of DDIs regardless of their age. However, higher age was a significant predictor for DDIs only among whites (Age ≥ 75 vs. < 60 years: OR= 1.48, 95% CI 1.16 – 1.90).

To assess the effect of different disparity parameters on total number of medications and the total number of PIM use, we conducted a multivariable Poisson regression as a sensitivity analysis. Interaction of race with other disparity parameters also was tested. For studying the factors affecting total medication count, we found that females compared with males, whites compared with blacks, and individuals with lower income, education and residing in rural areas had higher medication use across all drugs and also for prescription-only drugs (Table 4). In terms of OTC drugs, females compared with males, whites compared blacks, and individuals with lower education were more likely to use more medications.

Evaluation of factors affecting the total number of PIM use revealed that all the disparity parameters and total number of medications were significant predictors of total PIM count across all drugs, prescription-only, and OTC drugs except for gender (Table 5). Gender was not a significant predictor for OTC PIM count. We found that females compared with males, blacks compared with whites, and individuals with lower income, education, and residing in rural areas had higher PIM prevalence compared with the individuals with higher income and education, and urban dwellers. We also found that more medication use was associated with higher PIM prevalence. No interactions were found to be significant.

Discussion

High prevalence of PIM use (87% of the participants) was observed in our study. We also observed differences in the use of PIMs across gender, race, income, education, and location of residence. White females compared with white males and black males compared with white males had higher odds of receiving prescription-only PIMs. Lower income and education also were significant predictors of PIM prescription. Males compared with females, and individuals with lower education and residing in rural areas also demonstrated higher odds of using OTC PIMs. We consistently observed that individuals with higher medication use had higher odds of using PIMs in both blacks and whites. Similar results also were observed for the study of DDIs where males compared with females and individuals living in the rural areas had higher odds of having DDIs. Whites demonstrated higher odds of having DDIs compared with blacks. Sensitivity analyses also revealed that females compared with males, blacks compared with whites,

and individuals with lower income, education, and residing in rural areas had higher PIM prevalence compared with the individuals with higher income, education, and residing in urban areas.

Demographic and socioeconomic disparities in different aspects of healthcare have been reported in prior studies. For example, it has been reported that white women have an increase in death rates and a decline in life expectancies compared to white men.[33] The rise in death among white women are often linked to the rise in the use of prescription opioids.[34] According to the Beers Criteria, opioids are considered to be potentially inappropriate in older adults and are recommended to avoid with a history of fall or fracture.[28] It has been found that women are more likely than men to be diagnosed with depression and are more likely to take an antidepressant.[35-37] Moreover, whites have more access to psychiatric services than blacks and are more likely to take antidepressants.[36,37] Many antidepressants also are considered as inappropriate according to the Beers Criteria.[28] In our study, white females compared to white males had higher odds of receiving PIM prescription which is consistent with some of the prior studies focusing on gender-race inequality.

Prior studies demonstrated that racial disparities are most persistent, most difficult to address, and shapes other socioeconomic disparities.[38,39] It has been found that African-American patients have a less participatory relationship with their physicians than whites.[40] Oliver et al. found that white physicians spent more time with white patients than African-American patients for planning a treatment, evaluating health literacy, providing health education, and answering questions.[41] In our study, although whites received more medications than blacks, blacks were more likely than whites to receive more PIMs. It is

possible that blacks are being treated differently by the providers. However, further study is needed to know the providers' prescribing behavior.

In general, low income individuals across all races have comparatively poor health status than their higher income counterparts.[42] Additionally, people with lower income have inadequate healthcare coverage.[35] Lower income was associated with higher odds of receiving PIM prescription in our study which supports the findings of prior studies. The reasons mentioned above could also be the driving factors for higher PIM prescription in these lower income subgroups.

We also explored disparities across education and region of residence. Our study found the association between lower education and higher PIM use. Studies have shown that higher education is linked to better job, better income, and better health literacy and behavior.[43] Lower health literacy could be an influential factor for using more OTC PIMs. Moreover, individuals with lower income and education are more likely to live in poor neighborhoods which may lack resources for good health.[43] Disparities among individuals living in smaller geographic location has been described in many studies.[14,44] Individuals living in the rural areas lack timely access to healthcare providers and have limited availability of subspecialty physicians.[45] All these factors can interplay and contribute to inappropriate use of medications in the population with lower education and living in rural areas.

Similar factors also can contribute to the higher odds of DDIs in rural residents compared to the urban dwellers in our study. In our study, the total number of medications used by the participants remained a significant predictor of DDIs. We observed that higher the number of medications, higher the odds of DDIs. We also observed that whites

compared with blacks had higher odds of having DDIs and older age was a significant predictor of DDI for whites only. Prior studies have found that whites are more likely than blacks to receive more medications.[36,46-48] Moreover, older adults are often present with multiple chronic conditions that may require the use of multiple drugs concomitantly which in turn can increase the risk DDIs.[49] It has been found that patients taking two medications face a 13% risk of DDIs. This percentage rises up to 38% for patients taking four medications and rises up to 82% if seven or more medications are given concomitantly.[50] Our findings also support the conclusions derived from the prior studies.

The root causes of health inequality are very diverse, complex, and often difficult to understand.[35] One reason for health disparity is considered to be the implicit bias from the providers' perspective which is defined by John Dovidio as “unconscious discrimination”.[51] These biases may not be arbitrary and could be shaped by the racial stratification and societal norms.[35] Due to the implicit biases, physicians are found to treat patients differently based on their race, ethnicity, or gender rather than the actual underlying conditions.[52,53] Functional magnetic resonance imaging (MRI) of brains also revealed that white providers have implicit biases against African-Americans.[54] Experts often suggest for patient-provider concordance to overcome such biases.[53,55] Patient-provider concordance can happen in terms of gender, social class, age, ethnicity, race, language, sexual orientation, beliefs about health and illness, values, and health care decisions.[56] However, debate exists as to whether this concordance would help overcome health disparities.[56] Studies showed that patients prefer providers who treat them more respectfully rather than the providers of their own race or ethnicity.[57,58] Pharmacists also can play an important role in reducing health disparities in terms of PIM use. For example,

when they receive a new prescription for a drug which is potentially inappropriate for older patients, they can consider discussing it with the prescriber for a safer but equally efficacious alternative regardless of the race, gender, or other pertaining disparity parameters of the patient. While advising the patients about OTC drugs, pharmacists can recommend the drugs that are not considered as PIMs. Appropriate training programs for the pharmacists on the harmful effect of PIMs and the related disparities can help reduce this problem.

Our study has some limitations. First, we used the 2015 Beers Criteria to identify PIMs. There are other explicit criteria to identify PIMs which have shown differences in detecting PIMs in prior studies.[59,60] However, the Beers criteria was developed in the US and is the most widely used tool for PIM identification.[61] Since we are looking for disparities in PIM use in the US population, we believe that the Beers Criteria is an appropriate tool for PIM identification for our study. Still, it is possible to have some misclassification bias. Second, participants were asked to provide information regarding their medication use within the past two weeks by the trained EMSI personnel. There is a chance of recall bias and it is possible that we did not have full information regarding the participants' medication use patterns. Additionally, although the trained personnel did perform rigorous pill bottle assessment, medication doses were not recorded. As a result, we could not establish a dose-response relationship. Another limitation of the study is the high ORs obtained across the total number of medication use and race interactions. ORs such big are usually driven by small cell size and are unstable and may overestimate the study interpretation.[62] Furthermore, we did not have information regarding the provider's characteristics. In future studies, it would be helpful to know the pattern of the prescribers

and their prescribing behavior. And finally, some of the data may be as old as 15 years and Beers Criteria has evolved over time, thereby potentially changing therapeutic interpretation.

To the best of our knowledge, this is the first attempt to evaluate disparities in the appropriateness of medication use. Our study found significant demographic and socioeconomic disparities in PIM use. Although medication prescription is a process measure, an inappropriate prescription can lead to poor outcomes especially in older adults. Future studies should seek to better understand factors contributing to the disparities in order to guide development of interventions.

References

1. US healthcare spending compared to others. Peterson-Kaiser Health System Tracker. http://www.healthsystemtracker.org/chart-collection/health-spending-u-s-compare-countries/?_sf_s=health+spending#item-start. Accessed July 7, 2017.
2. Squires DA. The U.S. health system in perspective: a comparison of twelve industrialized nations. Issues in International Health Policy. 2011. http://www.commonwealthfund.org/~/media/Files/Publications/Issue%20Brief/2011/Jul/1532_Squires_US_hlt_sys_comparison_12_nations_intl_brief_v2.pdf. Accessed July 7, 2017.
3. FAMILIESUSA. Measuring Health Care Quality: An Overview of Quality Measures. 2014. http://familiesusa.org/sites/default/files/product_documents/HSI%20Quality%20Measurement_Brief_final_web.pdf. Accessed October 24, 2017.
4. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med.* 2003;348(26):2635-2645.
5. AHRQ. 2015 National Healthcare Quality and Disparities Report. http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/nhqrdr/nhqdr15/2015nhqdr.pdf. Accessed on September 1, 2016.
6. Gary Claxton CC, Selena Gonzales, Rabah Kamal, Larry Levitt. Measuring the quality of healthcare in the U.S. https://www.healthsystemtracker.org/brief/measuring-the-quality-of-healthcare-in-the-u-s/#item-start. Accessed April 22, 2018. 2015.
7. Howard G. Ancel Keys Lecture: Adventures (and misadventures) in understanding (and reducing) disparities in stroke mortality. *Stroke.* 2013;44(11):3254-3259.
8. RURAL AND URBAN HEALTH. Georgetown University. Health Policy Institute. https://hpi.georgetown.edu/agingsociety/pubhtml/rural/rural.html. Accessed August 5, 2018.
9. Agency for Healthcare Research and Quality, 2014. Health care coverage analyses of the National Healthcare Quality and Disparities Reports: 2000-2008 trends. https://www.medicaid.gov/medicaid/quality-of-care/downloads/health-coverage-analyses-of-nhqr-2000-2008-trends.pdf. Accessed July 8, 2017.
10. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation.* 2013;127(1):e6-e245.
11. Ayala C, Greenlund KJ, Croft JB, et al. Racial/ethnic disparities in mortality by stroke subtype in the United States, 1995-1998. *Am J Epidemiol.* 2001;154(11):1057-1063.
12. American Diabetes Association. Health Disparities. http://www.diabetes.org/advocacy/advocacy-priorities/health-disparities.html?referrer=https://www.google.com/. Accessed February 2, 2018.
13. Robbins AS, Chen AY, Stewart AK, Staley CA, Virgo KS, Ward EM. Insurance status and survival disparities among nonelderly rectal cancer patients in the National Cancer Data Base. *Cancer.* 2010;116(17):4178-4186.
14. Kulkarni SC, Levin-Rector A, Ezzati M, Murray CJ. Falling behind: life expectancy in US counties from 2000 to 2007 in an international context. *Popul Health Metr.* 2011;9(1):16.
15. Epstein D, Reibel M, Unger JB, et al. The effect of neighborhood and individual characteristics on pediatric critical illness. *J Community Health.* 2014;39(4):753-759.
16. Signorello LB, Cohen SS, Williams DR, Munro HM, Hargreaves MK, Blot WJ. Socioeconomic status, race, and mortality: a prospective cohort study. *Am J Public Health.* 2014;104(12):e98-e107.
17. NCQA. The essential guide to healthcare quality. https://www.ncqa.org/Portals/0/Publications/Resource%20Library/NCQA_Primer_web.pdf. Accessed October 24, 2017.

18. Institute of Medicine Committee on Quality of Health Care in A. In: Kohn LT, Corrigan JM, Donaldson MS, eds. *To Err is Human: Building a Safer Health System*. Washington (DC): National Academies Press (US)

 2000.
19. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.
20. Chen LL, Tangiisuran B, Shafie AA, Hassali MA. Evaluation of potentially inappropriate medications among older residents of Malaysian nursing homes. *Int J Clin Pharm.* 2012;34(4):596-603.
21. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. *J Clin Pharm Ther.* 2007;32(2):113-121.
22. Ament PW, Bertolino JG, Liszewski JL. Clinically significant drug interactions. *Am Fam Physician.* 2000;61(6):1745-1754.
23. Goren Z, M JD, Akpinar Acet G, Cali S, Gulcebi Idriz Oglu M. Potential drug-drug interactions among prescriptionsfor elderly patients in primary health care. *Turk J Med Sci.* 2017;47(1):47-54.
24. Vieira de Lima TJ, Garbin CA, Garbin AJ, Sumida DH, Saliba O. Potentially inappropriate medications used by the elderly: prevalence and risk factors in Brazilian care homes. *BMC Geriatr.* 2013;13:52.
25. Felton M, Hanlon JT, Perera S, Thorpe JM, Marcum ZA. Racial differences in anticholinergic use among community-dwelling elders. *Consult Pharm.* 2015;30(4):240-245.
26. Healthy people 2020. Disparities Overview by Income. https://www.healthypeople.gov/2020/data/disparities/summary/Chart/4155/6.1. Accessed on April 25, 2017.*,.*
27. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology.* 2005;25(3):135-143.
28. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.
29. Hansen RA, Khodneva Y, Glasser SP, Qian J, Redmond N, Safford MM. Antidepressant Medication Use and Its Association With Cardiovascular Disease and All-Cause Mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Ann Pharmacother.* 2016;50(4):253-261.
30. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med.* 1991;10(4):585-598.
31. Barzi F, Woodward M. Imputations of missing values in practice: results from imputations of serum cholesterol in 28 cohort studies. *Am J Epidemiol.* 2004;160(1):34-45.
32. Thacker EL, Gillett SR, Wadley VG, et al. The American Heart Association Life's Simple 7 and incident cognitive impairment: The REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *J Am Heart Assoc.* 2014;3(3):e000635.
33. Arias E. Changes in Life Expectancy by Race and Hispanic Origin in the United States, 2013-2014. *NCHS Data Brief.* 2016(244):1-8.
34. Nan Marie Astone SM, Laudan Y. Aron. Death Rates for US Women Ages 15 to 54. https://www.urban.org/research/publication/death-rates-us-women-ages-15-54. Accessed August 27, 2018. 2015.
35. National Academies of Sciences E, Medicine. *Communities in Action: Pathways to Health Equity.* Washington, DC: The National Academies Press; 2017.
36. Mundell EJ. U.S. Antidepressant Use Jumps 65 Percent in 15 Years. https://consumer.healthday.com/mental-health-information-25/antidepressants-news-723/u-s-antidepressant-use-jumps-65-percent-in-15-years-725586.html. Accessed August 27, 2018. 2017.

37. Laura A. Pratt DJB, Qiuping Gu. Antidepressant Use Among Persons Aged 12 and Over: United States, 2011–2014. https://www.cdc.gov/nchs/products/databriefs/db283.htm. Accessed August 27, 2018. 2017.
38. Williams DR, Mohammed SA. Discrimination and racial disparities in health: evidence and needed research. *J Behav Med.* 2009;32(1):20-47.
39. Farmer MM, Ferraro KF. Are racial disparities in health conditional on socioeconomic status? *Soc Sci Med.* 2005;60(1):191-204.
40. Cooper-Patrick L, Gallo JJ, Gonzales JJ, et al. Race, gender, and partnership in the patient-physician relationship. *JAMA.* 1999;282(6):583-589.
41. Oliver MN, Goodwin MA, Gotler RS, Gregory PM, Stange KC. Time use in clinical encounters: are African-American patients treated differently? *J Natl Med Assoc.* 2001;93(10):380-385.
42. Braveman PA, Cubbin C, Egerter S, Williams DR, Pamuk E. Socioeconomic disparities in health in the United States: what the patterns tell us. *Am J Public Health.* 2010;100 Suppl 1:S186-196.
43. Health VCfSa. Why Education Matters to Health: Exploring the Causes. https://societyhealth.vcu.edu/work/the-projects/why-education-matters-to-health-exploring-the-causes.html#healthBenefits. Accessed August 27, 2018. 2015.
44. Emily Zimmerman SHW. Understanding the Relationship Between Education and Health. IOM Roundtable on Population Health Improvement. https://nam.edu/wp-content/uploads/2015/06/BPH-UnderstandingTheRelationship1.pdf. Accessed August 27, 2018. 2014.
45. Wong ST, Regan S. Patient perspectives on primary health care in rural communities: effects of geography on access, continuity and efficiency. *Rural Remote Health.* 2009;9(1):1142.
46. Khandker RK, Simoni-Wastila LJ. Differences in prescription drug utilization and expenditures between Blacks and Whites in the Georgia Medicaid population. *Inquiry.* 1998;35(1):78-87.
47. Wang J, Zuckerman IH, Miller NA, Shaya FT, Noel JM, Mullins CD. Utilizing New Prescription Drugs: Disparities among Non-Hispanic Whites, Non-Hispanic Blacks, and Hispanic Whites. *Health Serv Res.* 2007;42(4):1499-1519.
48. Singhal A, Tien YY, Hsia RY. Racial-Ethnic Disparities in Opioid Prescriptions at Emergency Department Visits for Conditions Commonly Associated with Prescription Drug Abuse. *PLoS One.* 2016;11(8):e0159224.
49. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother.* 2007;5(4):345-351.
50. Goldberg RM, Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. *Am J Emerg Med.* 1996;14(5):447-450.
51. Dovidio JF, Gaertner SL, Kawakami K, Hodson G. Why can't we just get along? Interpersonal biases and interracial distrust. *Cultur Divers Ethnic Minor Psychol.* 2002;8(2):88-102.
52. Institute of Medicine Committee on U, Eliminating R, Ethnic Disparities in Health C. In: Smedley BD, Stith AY, Nelson AR, eds. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*. Washington (DC): National Academies Press (US)

53. Zestcott CA, Blair IV, Stone J. Examining the Presence, Consequences, and Reduction of Implicit Bias in Health Care: A Narrative Review. *Group Process Intergroup Relat.* 2016;19(4):528-542.
54. Hall WJ, Chapman MV, Lee KM, et al. Implicit Racial/Ethnic Bias Among Health Care Professionals and Its Influence on Health Care Outcomes: A Systematic Review. *Am J Public Health.* 2015;105(12):e60-76.
55. Betancourt JR, Corbett J, Bondaryk MR. Addressing disparities and achieving equity: cultural competence, ethics, and health-care transformation. *Chest.* 2014;145(1):143-148.

56. Cooper LA and Powe RN. 2004. Disparities in Patient Experiences, Health Care Processes, and Outcomes: The Role of Patient-Provider Racial, Ethnic, and Language Concordance. http://www.commonwealthfund.org/~/media/files/publications/fund-report/2004/jul/disparities-in-patient-experiences--health-care-processes--and-outcomes--the-role-of-patient-provide/cooper_disparities_in_patient_experiences_753-pdf.pdf. Accessed February 28, 2018.
57. Dale HE, Polivka BJ, Chaudry RV, Simmonds GC. What young African American women want in a health care provider. *Qual Health Res.* 2010;20(11):1484-1490.
58. Volandes AE, Paasche-Orlow M, Gillick MR, et al. Health literacy not race predicts end-of-life care preferences. *J Palliat Med.* 2008;11(5):754-762.
59. Mann E, Haastert B, Bohmdorfer B, et al. Prevalence and associations of potentially inappropriate prescriptions in Austrian nursing home residents: secondary analysis of a cross-sectional study. *Wien Klin Wochenschr.* 2013;125(7-8):180-188.
60. Oliveira MG, Amorim WW, de Jesus SR, Heine JM, Coqueiro HL, Passos LC. A comparison of the Beers and STOPP criteria for identifying the use of potentially inappropriate medications among elderly patients in primary care. *J Eval Clin Pract.* 2015;21(2):320-325.
61. O'Mahony D, Gallagher P, Ryan C, et al. STOPP & START criteria: A new approach to detecting potentially inappropriate prescribing in old age. *European Geriatric Medicine.*1(1):45-51.
62. Nemes S, Jonasson JM, Genell A, Steineck G. Bias in odds ratios by logistic regression modelling and sample size. *BMC Med Res Methodol.* 2009;9:56.

Table 1. Baseline Characteristics of the Study Population by Use of PIM or DDI.

	PIM use (n = 13 623)			DDI (n = 26 798)		
Characteristic	Yes (n = 11 912)	No (n = 1711)	*P* Value	Yes (n = 1014)	No (n = 25 784)	*P* Value
Age, mean (SD), years	72.8 ± 5.9	72.3 ± 5.8	0.0002	67.4 ± 9.1	65.2 ± 9.4	<0.0001
Female, n (%)	6375 (53.5)	887 (51.8)	0.19	458 (45.2)	14 603 (56.6)	<0.0001
Black, n (%)	4492 (37.7)	692 (40.4)	0.03	238 (23.5)	10 697 (41.5)	<0.0001
Income, n (%)			0.01			0.47
Less than $20,000	2578 (21.6)	319 (18.6)		185 (18.2)	4727 (18.3)	
$20,000- $34,999	3404 (28.6)	473 (27.6)		270 (26.6)	6240 (24.2)	
$35,000- $74,999	3169 (26.6)	494 (28.9)		292 (28.8)	7590 (29.4)	
≥ $75,000	1040 (8.7)	173 (10.1)		147 (14.5)	4002 (15.5)	
Education, n (%)			0.0008			0.29
Less than high school	1998 (16.8)	246 (14.4)		109 (10.8)	3293 (12.8)	
High school	3231 (27.2)	433 (25.3)		266 (26.3)	6734 (26.1)	
Some college	2967 (24.9)	422 (24.5)		278 (27.44)	6873 (26.7)	
College graduate and above	3702 (31.1)	609 (35.6)		360 (35.5)	8864 (34.4)	
Location of residence, n (%)			0.0079			0.0003
Isolated	262 (2.4)	27 (1.7)		18 (2.0)	525 (2.3)	
Small rural	656 (6.1)	82 (5.3)		78 (8.6)	1359 (5.8)	
Large rural	1306 (12.1)	155 (9.9)		130 (14.3)	2727 (11.7)	
Urban	8576 (79.4)	1294 (83.1)		684 (75.2)	18 691 (80.2)	

PIM: Potentially Inappropriate Medication; for PIM use, the patients are of age >=65; DDI: Drug-Drug Interactions, for DDIs, the patients are of age >= 45 years;

Table 2. Descriptive statistics of PIM use across prescription vs. OTC drugs in different subgroups of the study population age >=65

Variables	PIM use across prescription only drugs*, n (%)**	PIM use across OTC drugs*, n (%)**
	Age ≥ 65	**Age ≥ 65**
Gender		
Male	4719 (79.4)	2709 (63.0)
Female	5815 (84.3)	2677 (52.2)
Race		
White	6416 (81.3)	3708 (58.1)
Black	4118 (83.3)	1678 (55.1)
Income		
≥$75,000	860 (76.4)	528 (60.5)
$35,000 - $74,999	2754 (79.8)	1493 (57.3)
$20,000 - 34,999	3033 (83.0)	1515 (56.2)
< $20,000	2347 (85.6)	1060 (56.5)
Education		
>College	3156 (78.6)	1774 (57.0)
Some college	2641 (82.8)	1319 (55.7)
High school	2897 (83.2)	1462 (57.5)
<High school	1827 (85.5)	824 (59.2)
Location of residence		
Urban	7640 (81.9)	3739 (56.4)
Large rural	1123 (82.0)	657 (60.9)
Small rural	559 (81.1)	345 (62.4)
Isolated	226 (81.9)	122 (52.6)

* The same person may have both prescription and OTC drugs and thus, may be counted more than once.
** % calculated as of the total corresponding population

Table 3. Disparities across PIM use and DDIs

Characteristic	PIM use across all drugs, OR (95% CI)	PIM use across prescription only drugs, OR (95% CI)	PIM use across OTC drugs, OR (95% CI)	DDIs, OR (95% CI)
Gender				
Male	Ref	Ref	Ref	Ref
Female	a	a	**0.61 (0.56 - 0.67)**	**0.55 (0.48 - 0.63)**
Race				
White	Ref	Ref	Ref	Ref
Black	a, b	a, b	c	d
Income				
≥ $75,000	Ref	Ref	Ref	Ref
Less than $20,000	1.16 (0.86 - 1.44)	**1.26 (1.01 - 1.57)**	c	1.22 (0.93 - 1.60)
$20,000- $34,999	1.06 (0.85 - 1.34)	**1.24 (1.02 - 1.51)**		1.11 (0.87 - 1.41)
$35,000- $74,999	0.96 (0.77 - 1.20)	1.11 (0.92 - 1.33)		1.02 (0.81 - 1.28)
Education				
College graduate and above	Ref	Ref	Ref	Ref
Less than high school	1.15 (0.94 - 1.41)	**1.31 (1.09 - 1.56)**	**1.16 (1.01 - 1.33)**	0.86 (0.66 - 1.11)
High school	1.08 (0.92 - 1.28)	**1.17 (1.01 - 1.34)**	1.12 (0.99 - 1.26)	0.96 (0.79 - 1.16)
Some college	1.09 (0.92 - 1.27)	**1.19 (1.04 - 1.37)**	1.00 (0.89 - 1.12)	0.97 (0.81 - 1.16)
Location of residence				
Urban	Ref	Ref	Ref	Ref
Isolated	1.45 (0.94 - 2.24)	1.09 (0.77 - 1.54)	0.84 (0.64 - 1.09)	0.76 (0.47 - 1.24)
Small rural	1.24 (0.96 - 1.62)	0.93 (0.75 - 1.15)	**1.29 (1.07 - 1.54)**	**1.37 (1.07 - 1.76)**
Large rural	1.20 (0.99 - 1.46)	0.96 (0.82 - 1.13)	**1.18 (1.03 - 1.35)**	1.07 (0.88 - 1.31)
Total number of medications				
First quartile	Ref	Ref	Ref	Ref
Second quartile	b	b	**1.42 (1.20 - 1.68)**	**9.22 (4.28 - 19.84)**
Third quartile			**1.73 (1.46 - 2.04)**	**28.86 (13.59 - 61.29)**
Fourth quartile			**1.78 (1.50 - 2.10)**	**76.01 (35.97 - 160.61)**
Age group, years				
< 60	-	-	-	Ref
60-64	-	-	-	d

65-75	-	-	-	
≥ 75	-	-	-	
Significant interactions				
Gender-Race [a]				
Female vs. Male; Race = Black	0.86 (0.73 - 1.01)	0.93 (0.81 - 1.07)	-	-
Female vs. Male; Race = White	**0.84 (0.74 - 0.96)**	**1.33 (1.20 - 1.48)**	-	-
Black vs. White; Gender = Female	1.12 (0.97 - 1.29)	1.12 (0.99 - 1.26)	-	-
Black vs. White; Gender = Male	1.06 (0.91 - 1.24)	**1.60 (1.41 - 1.82)**	-	-
Total number of medications-Race [b]				
Second vs. first quartile; Race = Black	**5.06 (4.28 - 5.97)**	**3.22 (2.74 - 3.77)**	-	-
Third vs. first quartile; Race = Black	**26.19 (19.61 - 34.97)**[*]	**11.32 (9.18 - 13.97)**[*]	-	-
Fourth vs. first quartile; Race = Black	**65.53 (40.79 - 105.29)**[*]	**31.45 (22.72 - 43.53)**[*]	-	-
Second vs. first quartile; Race = White	**4.62 (3.99 - 5.34)**	**2.50 (2.18 - 2.87)**	-	-
Third vs. first quartile; Race = White	**12.48 (10.36 - 15.04)**[*]	**5.96 (5.12 - 6.93)**[*]	-	-
Fourth vs. first quartile; Race = White	**38.13 (28.97 - 50.18)**[*]	**16.98 (14.03 - 20.52)**[*]	-	-
Income-Race [c]				
Less than $20,000 vs. ≥ $75,000; race = Black	-	-	1.40 (0.94 - 2.08)	-
$20,000- $34,999 vs. ≥ $75,000; race = Black	-	-	1.00 (0.67 - 1.47)	-
$35,000- $74,999 vs. ≥ $75,000; race = Black	-	-	1.06 (0.71 - 1.58)	-
Less than $20,000 vs. ≥ $75,000; race = White	-	-	0.76 (0.51 - 1.01)	-
$20,000- $34,999 vs. ≥ $75,000; race = White	-	-	0.87 (0.72 - 1.06)	-
$35,000- $74,999 vs. ≥ $75,000; race = White	-	-	0.83 (0.69 – 1.00)	-
Black vs. White; income = Less than $20,000	-	-	**1.32 (1.08 - 1.61)**	-
Black vs. White; income = $20,000- $34,999	-	-	0.81 (0.61 - 1.02)	-
Black vs. White; income = $35,000- $74,999	-	-	0.91 (0.75 - 1.10)	-
Black vs. White; income = ≥ $75,000	-	-	0.71 (0.48 - 1.06)	-
Age group-Race [d]				
60-64 vs. < 60; race = Black	-	-	-	1.16 (0.79 - 1.71)
65-75 vs. < 60; race = Black	-	-	-	0.89 (0.63 - 1.26)
≥ 75 vs. < 60; race = Black	-	-	-	0.74 (0.46 - 1.20)
60-64 vs. < 60; race = White	-	-	-	1.12 (0.86 - 1.45)
65-75 vs. < 60; race = White	-	-	-	1.05 (0.84 - 1.32)

≥ 75 vs. < 60; race = White	-	-	-	**1.48 (1.16 - 1.90)**
Black vs. White; age = < 60	-	-	-	**0.60 (0.43 - 0.83)**
Black vs. White; age = 60-64	-	-	-	**0.63 (0.45 - 0.88)**
Black vs. White; age = 65-75	-	-	-	**0.51 (0.39 - 0.66)**
Black vs. White; age ≥ 75	-	-	-	**0.30 (0.19 - 0.46)**

[a] Significant gender-race interaction; [b] Significant total number of medications-race interaction; [c] Significant income-race interaction; [d] Significant age group-race interaction; PIM: Potentially inappropriate medication; DDI: Drug-drug interaction; OTC: Over the counter.

[*] ORs such big are usually driven by small cell size and are unstable and may overestimate the study interpretation.[63]

Table 4. Effect of different disparity parameters on total medication count

Characteristic	PIM use across all drugs, PR (95% CI)	PIM use across prescription only drugs, PR (95% CI)	PIM use across OTC drugs, PR (95% CI)
Gender			
Male	Ref	Ref	Ref
Female	**1.11 (1.09 - 1.12)**	**1.09 (1.08 - 1.11)**	**1.12 (1.10 - 1.14)**
Race			
White	Ref	Ref	Ref
Black	**0.86 (0.85 - 0.88)**	**0.86 (0.85 - 0.87)**	**0.89 (0.87 - 0.91)**
Income			
≥ $75,000	Ref	Ref	Ref
Less than $20,000	**1.03 (1.01 - 1.07)**	**1.04 (1.01 - 1.08)**	0.99 (0.96 - 1.02)
$20,000- $34,999	1.01 (0.98 - 1.04)	1.02 (0.99 - 1.05)	0.99 (0.96 - 1.02)
$35,000- $74,999	1.00 (0.97 - 1.03)	1.00 (0.98 - 1.03)	1.00 (0.97 - 1.03)
Education			
College graduate and above	Ref	Ref	Ref
Less than high school	**1.04 (1.01 - 1.06)**	**1.03 (1.01 - 1.05)**	**1.04 (1.01 - 1.07)**
High school	1.00 (0.98 - 1.02)	0.99 (0.97 - 1.01)	0.99 (0.97 - 1.01)
Some college	**1.03 (1.01 - 1.05)**	**1.02 (1.01 - 1.04)**	**1.03 (1.01 - 1.05)**
Location of residence			
Urban	Ref	Ref	Ref
Isolated	1.01 (0.97 - 1.06)	1.02 (0.97 - 1.06)	0.98 (0.93 - 0.99)
Small rural	0.99 (0.96 - 1.02)	0.99 (0.96 - 1.02)	0.96 (0.93 - 1.00)
Large rural	**1.03 (1.01 - 1.05)**	**1.03 (1.01 - 1.05)**	1.01 (0.99 - 1.04)

* No significant interaction; PR: Prevalence ratio

Table 5. Effect of different disparity parameters on total PIM count

Characteristic	PIM use across all drugs, PR (95% CI)	PIM use across prescription only drugs, PR (95% CI)	PIM use across OTC drugs, PR (95% CI)
Gender			
Male	Ref	Ref	Ref
Female	**1.03 (1.01 - 1.06)**	**1.03 (1.01 - 1.06)**	1.02 (0.99 - 1.05)
Race			
White	Ref	Ref	Ref
Black	**1.04 (1.02 - 1.07)**	**1.04 (1.01 - 1.06)**	**1.06 (1.03 - 1.09)**
Income			
≥ $75,000	Ref	Ref	Ref
Less than $20,000	**1.11 (1.06 - 1.17)**	**1.12 (1.06 - 1.18)**	**1.14 (1.07 - 1.21)**
$20,000- $34,999	**1.07 (1.02 - 1.13)**	**1.07 (1.02 - 1.13)**	**1.09 (1.03 - 1.16)**
$35,000- $74,999	1.05 (1.00 - 1.10)	1.04 (0.99 - 1.09)	**1.07 (1.01 - 1.13)**
Education			
College graduate and above	Ref	Ref	Ref
Less than high school	**1.14 (1.09 - 1.18)**	**1.13 (1.09 - 1.18)**	**1.15 (1.09 - 1.20)**
High school	**1.08 (1.04 - 1.11)**	**1.07 (1.04 - 1.11)**	**1.07 (1.03 - 1.11)**
Some college	**1.06 (1.03 - 1.09)**	**1.06 (1.03 - 1.10)**	**1.07 (1.03 - 1.11)**
Location of residence			
Urban	Ref	Ref	Ref
Isolated	0.95 (0.88 **-** 1.03)	0.95 (0.88 - 1.03)	0.95 (0.87 - 1.04)
Small rural	1.05 (1.00 **-** 1.10)	1.04 (0.99 - 1.09)	1.05 (0.99 - 1.11)
Large rural	**1.05 (1.01 - 1.09)**	**1.05 (1.01 - 1.08)**	**1.06 (1.01 - 1.10)**
Total number of medications			
First quartile	Ref	Ref	Ref
Second quartile	**2.43 (2.28 - 2.59)**	**2.36 (2.21 - 2.53)**	**2.24 (2.04 - 2.47)**
Third quartile	**3.91 (3.68 - 4.16)**	**3.73 (3.49 - 3.99)**	**3.59 (3.28 - 3.94)**
Fourth quartile	**6.22 (5.87 - 6.61)**	**5.89 (5.52 - 6.29)**	**5.92 (5.41 - 6.48)**

* No significant interaction; PR: Prevalence ratio

Aim 2

Abstract

Background: Prior work has identified disparities in the quality and outcomes of healthcare across socioeconomic subgroups. Mortality with inappropriate medication use may be subject to similar disparities.

Objective: To assess the association between inappropriate medication use and all-cause mortality and the effect of disparity parameters (gender, age, race, income, education, and rural or urban areas) on this relationship.

Methods: The analyses included 26,399 black and white US adults aged ≥ 45 years from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, of which 13,475 participants were of age ≥ 65 years (recruited 2003-2007). The appropriateness of medication use was measured at baseline by the presence of drug-drug interactions (DDIs) and use of potentially inappropriate medications (PIMs) in older adults. Cox proportional hazards time-to-event analysis followed the participants until their death (all-cause) on or before March 31, 2016, iteratively adjusting for disparity parameters and other covariates. Sensitivity analysis by stratifying censored follow-up time intervals intended to seek the predictive capability of baseline PIM use to assess mortality. The full models included interaction terms between PIM/DDI use and other covariates.

Results: Approximately 87% of the participants aged ≥ 65 years used at least one drug listed in the Beers criteria, and 3.8% of all participants used two or more drugs with DDIs. The fully adjusted model, censored at all years, found that among whites, PIM use

increased the risk of all-cause mortality (hazard ratio [HR]=1.27, 95% CI 1.10-1.47). DDIs were found to increase the risk of mortality only among females in the fully adjusted model censored at 2 years (HR=1.77, 95% CI 1.11-2.80). Higher medication use was a significant predictor of mortality across all the fully adjusted models (P<0.01).

Conclusion: In the fully adjusted models, PIM use was associated with higher risk of mortal events. Further research is needed to better understand the contributing factors of such disparities in order to develop appropriate interventions.

Key words: REGARDS, potentially inappropriate medication, drug-drug interaction, socioeconomic disparity, mortality

Introduction

Although the United States (US) spends almost twice as much in health care than other high-income countries,[1] health-related quality indicators lag behind many other countries.[2] A low quality score is often attributed to inequalities among subpopulations within the US.[3] These inequalities, or health disparities, are defined as the systematic differences among certain population groups in incidence, prevalence, mortality, and burden of diseases or other adverse events.[4,5] The subpopulations affected can be defined by different domains of health disparities, including: 1) socioeconomic status; 2) location of residence (e.g., rural vs urban setting); and 3) obstacles related to race or ethnicity.[6]

The measures to evaluate healthcare quality can broadly be classified into three standardized categories: structure, process, and outcomes as suggested by Avedis Donabedian, a pioneering scientist in the field of quality measurement (widely known as the Donabedian framework).[7-9] According to the Donabedian model, any change in the structure of care results in a change in the clinical processes which ultimately alters patients' outcomes.[9] Previous research has explored the relationship between health disparities and various quality indicators reflecting health care structure, process, and outcome measures. For structure measures, for example, blacks and people with low income had more limited access to care compared with whites and high-income individuals.[10] Individuals residing in the rural areas also have limited access to care due to the lack of providers.[11] It has been reported that there is a lack of physicians in the areas with higher proportions of minorities.[12]

For process measures, for example, African-American patients compared with white patients were found to have a less participatory relationship with their physicians.[13] Disparities in health service utilization were documented in previous studies as well. It was found that blacks were less likely than whites to receive eye examination after diabetes diagnosis, post hospitalization mental illness follow-up, and flu vaccination.[14-16] McBean et al. found that blacks compared with whites had 72% and 68% lower rates of coronary artery bypass grafting and angioplasty, respectively.[17]

For outcome measures, numerous health disparities have been documented in terms of disease-specific outcomes, morbidity, and mortality. For example, blacks and American-Indians or Alaska natives had higher prevalence of diabetes, asthma, and cardiovascular diseases compared with the whites.[18] Blacks demonstrated higher hemorrhage mortality with stroke among adults aged between 25 to 44 years.[19,20] Blacks and American-Indians or Alaska natives have higher infant mortality rates compared with whites,[18] and black males had the lowest life expectancy compared with other population subgroups.[21] However, low income individuals across all races had comparatively poor health status than their higher income counterparts.[22]

One important quality measure involves the study of the appropriateness of medication prescribing and use. Although some studies focused on health disparities in terms of the appropriateness of medication prescribing and the quality of population-based medication use, systematic assessment of the appropriateness of medication use across health disparities defined on the basis of socioeconomic factors, rural vs. urban residence, and race has never been done before. Understanding the concept of

appropriate medication use and following clinical guidelines while prescribing are important aspects of healthcare quality.

Potentially inappropriate medications (PIMs) are defined as the use of medications where risks outweigh benefits when safer and equally effective alternatives exist.[23,24] PIM prescription can take place in persons of all ages; however, older adults (age ≥ 65 years) are more susceptible to experiencing adverse drug events (ADEs) in the presence of PIMs.[25,26] In older adults, PIM prescribing can contribute to an increased risk of ADEs, prolonged hospital stay, re-hospitalization, mortality, and increased overall healthcare costs.[27] Older adults often have multiple chronic conditions and require multiple medications to manage their condition which can increase the risk of drug-drug interaction (DDIs).[28] DDIs also can increase the risk of ADEs, hospitalization, morbidity and mortality in older adults.[25,29] Each year, more than 30 medications are introduced into the market and it is quite impossible for physicians and pharmacists to memorize all the possible DDIs[30] and thus putting patients more at risk. Hence, identifying clinically significant DDIs is an important healthcare quality indicator.

Medication prescription is a process measure and inappropriate prescription can lead to poor outcomes especially in older adults. The harmful effects of PIMs and DDIs, and disparities in all-cause mortality are well documented. However, disparities in PIM and DDI use and the associated mortality have never been studied before. The purpose of this study is to evaluate the association between baseline PIM/DDI use and all-cause mortality and whether there are any disparities in this relationship. Studying health disparities requires access to unique data that can identify disparities and measure

longitudinal outcomes. One useful study is the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

Methods

Data source

Data for this study was obtained from the REGARDS study which is a national, population-based, longitudinal study initially designed to assess health disparities in stroke treatment and outcomes in the Southeastern US ("Stroke Belt") compared to the other parts of the US.[31] Participants in this study were randomly selected via mail and telephone contacts from a commercially available list purchased through Genesys Inc.. Potential participants were introduced to the study via mailed letter and study brochure.

Baseline data were obtained via telephone interview, self-administered questionnaires, and an in-home visit. Demographic and socioeconomic characteristics, health behaviors, health status, and self-reported comorbid conditions were obtained via computer-assisted telephone interviewing (CATI). Information regarding both prescription and nonprescription medications taken within the past two weeks were obtained through in-home examinations provided by the trained technicians of the Examination Management Services, Inc. (EMSI). EMSI technicians also obtained blood pressure measurements, blood and urine samples, and electrocardiograms (ECG) during the in-home visit. Patients' written informed consents were collected at that time. Participants were followed-up every 6 months after the baseline data collection to obtain information regarding stroke, coronary heart disease, and all-cause mortality. Full study design and

the methodological details of the REGARDS study is published elsewhere.[31] The REGARDS study was approved by the Institutional Review Boards of all the participating institutions.

Study participants

30,239 US adults age ≥ 45 years (42% black, 55% women) were enrolled in the study from January 2003 to October 2007. Individuals other than blacks or whites, actively receiving cancer treatment, unable to communicate in English, and nursing home residents or on a waiting list were excluded from the study.

Measures

PIM and DDI exposure

PIM use was identified using the American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (described as "Beers Criteria" from here forward). This includes a list of medications that are considered to be potentially harmful for older adults.[32] PIM use was coded as binary variables (yes/no) by matching the patients' medication list with the Beers Criteria. The total number of medications used per patient and the total number of PIMs used per patient also were calculated. Both prescription and non-prescription PIMs were included in our study.

DDIs were coded as binary variables (yes/no) using the known clinically significant drug interactions list published by Ament et al (**Appendix A**).[30] The clean and coded medication list data was merged with the patients' sociodemographic and complete medical record based on a unique patient identifier for further analyses.

Study outcome

The primary outcome for these analyses was all-cause mortality. For participants that died, the last follow-up date was their death date. The rest of the participants were followed until March 31, 2016.

Disparity parameters

The disparity parameters for this study were defined as gender (male/female), race (black/white), annual income (stratified as less than $20,000, $20,000- $34,999, $35,000- $74,999, and ≥ $75,000), education (stratified as less than high school, high school or some college, and greater than college), and location of residence (stratified as isolated, small rural, large rural, and urban).

Analyses of disparities parameters was restricted to the patients aged ≥ 65 years since Beers Criteria is only applicable for this patient age group. For the study of DDIs, we used the full cohort of patients aged ≥ 45 years. For this purpose, age was stratified as less than 60 years, 60-64 years, 65-75 years, and greater than 75 years.

Other Covariates

Other than the disparity variables, patients' medical condition, physiologic risk factors, total number of medications, and total PIM use were considered as covariates. Medical conditions included diabetes (self-reported), atrial fibrillation, Afib (defined as self-reported history or evidence on an ECG performed during the in-home assessment), chronic kidney disease, CKD (defined as estimated glomerular filtration rate (eGFR) ***<60 ml/min/ 1.73 m²***,[33] history of stroke (self-reported), and history of cardiovascular

diseases, CVD (defined by self-reported myocardial infarction (MI), coronary artery bypass grafting (CABG), bypass, angioplasty, or stenting or evidence of MI via ECG).

Physiologic risk factors included dyslipidemia (defined as total cholesterol (TC) ≥ 240 mg/dL or low-density lipoprotein (LDL) ≥ 160 mg/dL or high-density lipoprotein (HDL) ≤ 40 mg/dL or on any cholesterol lowering medication), atherosclerosis risk in communities (ARIC) study stroke risk score,[34] total cholesterol, and urinary creatinine levels.

Diabetes, Afib, CKD, history of stroke, CVD, and dyslipidemia were coded as binary variables (yes/no), whereas the total cholesterol, ARIC stroke risk scores, urinary creatinine levels, total number of medications, and total PIM use were converted into quartiles for further analyses.

Statistical analysis

Descriptive statistics were obtained for PIM use and DDIs by using chi-square statistics for categorical characteristics and Student *t* tests for continuous characteristics. Time-to-event analyses were performed for all-cause mortality where the participants were followed-up until the event of interest through March 31, 2016.

The association of all-cause mortality with PIM use and DDIs were studied by sequentially adjusted Cox proportional Hazard models. The resultant hazard ratio (HR) and corresponding 95% confidence intervals (CI) were reported as a measure of significance of association. Proportional hazard assumptions were tested via Schoenfeld Residuals method.[35,36] Model 1 was the unadjusted Cox proportional hazard model that

accounted for only the PIM exposure. Model 2 was adjusted for demographics and socioeconomic characteristics. Model 3 adjusted for all the model 2 covariates plus patients' medical conditions, physiologic risk factors, total number of medications used, and total PIM use. Same model adjustment techniques were used for the analyses of DDIs except for the model 3 where we adjusted for the model 2 covariates plus patients' medical conditions, physiologic risk factors, and total number of medications used. All the covariates had less than 5% missing values except for location of residence (about 9% missing values), income (about 12% missing values), and ARIC stroke risk scores (about 13% missing values). According to Schafer, missing values less than 5% are insignificant[37] and according to Bennet, an statistical analysis may be potentially biased if more than 10% data are missing.[38] In our study, missing data in covariates were replaced by multivariable multiple imputation technique using chain equations in 10 datasets with sample bootstrapping.[39,40] Prior studies recommended multiple imputation in case of data where 10 to 60% of values are missing.[41,42]

Due to the cross-sectional nature of the PIM exposure, we conducted a series of predictive models as a measure of sensitivity analysis to test the impact of censoring follow-up intervals.[39] Apart from the full follow-up time, that is, follow-up time up to March 31, 2016 (method 1), we stratified the follow-up time intervals as 0-2 years (method 2), 0-4 years (method 3), and 0-6 years (method 4). Further, to study the effect of disparity parameters on the relationship of PIM use and all-cause mortality, interaction variables were created to test for interaction between PIM use and all the disparity variables. We also tested the interaction between PIM use and other covariates. Interactions were

considered significant at an alpha= 0.1 level.[43] Similar analyses were performed for the study of DDIs and all-cause mortality.

Finally, Kaplan-Meier survival curves and log-rank tests were performed to test the effect of PIM use, DDIs, total number of medication use, and total number of PIM use per person on the survival probability. We also studied the impact of disparity variables on survival probability among participants with PIM use and DDIs using the Kaplan-Meier estimator. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

A total of 3,441 participants out of 30,239 US adults were excluded due to missing drug information, and an additional 399 patients also were excluded due to missing death indicators. So, a total of 26,399 participants were included in the study out of which 13,475 were of age ≥ 65 years.

Of the participants aged ≥ 65 years (n = 13,475), 87.5% (n= 11,784) used at least one drug listed in the Beers criteria, and 3.8% (n= 996) of all the participants (n=26,399), used two or more drugs with DDIs. On average, each participant aged 65 and over used 6.5 medications which ranged from 1 to 20. The mean number of PIMs used per person aged ≥ 65 years was 2.4, which ranged from 0 to 14. Characteristics of the PIM and DDI users and non-users are shown in Table 1.

Significant differences between PIM users and non-users were observed (Table 1). For instance, PIM users compared to the non-users were older (mean age 72.8 vs

72.3 years) and more likely whites (62.5% vs 59.8%). Compared with non-users, PIM users had lower income, education, and mainly resided in rural areas. We also observed significant differences between PIM users and non-users across medical conditions and physiologic risk factors. For example, compared with non-users, PIM users were more likely to have diabetes (27% vs 14.6%) and dyslipidemia (64.3% vs 55.1%). Similar differences were observed for DDI users and non-users. For example, people with DDI, were older (mean age 67.4 vs 65.2 years), more likely male (54.9% vs 43.4%), whites (76.7% vs 58.8%), and resided in rural areas. Similarly, individuals having DDIs had significantly different medical conditions and more physiologic risk factors.

An increased risk of mortality among PIM users was observed in the Kaplan-Meier survival plots in Figure 1 (panel A log-rank P <0.0001). Similarly, an increased risk mortality was observed for individuals with DDIs compared with those with no DDIs (panel B, log-rank P <0.0001). We also tested the impact of total medication use and the number of PIM use on survival probability. We observed that individuals with more PIM use (panel C log-rank P<0.0001) and more medication use (panel D log-rank P<0.0001) had lower survival probabilities.

We also tested the survival probability of PIM users across different disparity parameters (Figure 2). We observed that males compared with females (panel A log-rank P<0.0001), blacks compared with whites (panel B log-rank P=0.0068), individuals with lower income (panel C log-rank P<0.0001), and lower education (panel D log-rank P<0.0001) had higher risks of mortality with PIM use. Survival curves of participants with DDIs across different disparity parameters (Figure 3) also revealed that males compared with females (panel A log-rank P<0.0001), blacks compared with whites (panel B log-rank

P=0.0194), individuals with lower income (panel C log-rank P<0.0001), and included with lower education (panel D log-rank P<0.0001) had higher risks of mortality with DDIs. For both PIMs and DDIs, the location of residence did not satisfy the proportionality of hazard assumption (**Figure in Appendix C**) and thus was excluded from further analyses.

Consistent with our survival plots, for follow-up time censored across all years (Table 2), the unadjusted HR (model 1) indicated an increased risk of all-cause mortality with PIM use. Males had higher risks of mortality compared with females (model 3, female vs. male: HR = 0.56, 95% CI 0.52 – 0.60). Individuals with lower income and education had an increased risk or mortality compared to their higher income and educated counterparts (in both the models 2 and 3). For example, in the fully adjusted model (model 3), income less than $20,000 vs. ≥ $75,000: HR = 2.67, 95% CI 2.30 – 3.10 and education level less than high school vs. college graduate and above: HR = 1.44, 95% CI 1.29 – 1.60. A significant Race-PIM interaction illustrated that the impact of PIM differs by race (in the fully adjusted model, PIM use Yes vs. No among whites: HR = 1.27, 95% CI 1.10 – 1.47). Additionally, stroke (HR = 1.63, 95% CI 1.49 – 1.80) and Afib (HR = 1.50, 95% CI 1.40 – 1.64) were significantly associated with higher risks of mortality with PIM use.

We found similar results in the sensitivity analyses across all the censored follow-up time intervals. The unadjusted HR (model 1) in all the censored follow-up time intervals indicated an increased risk of all-cause mortality with PIM use. However, the magnitude of the HRs decreased gradually as the censoring time interval increased. Males compared with females, and individuals with lower income and education had higher risks of all-cause mortality compared to their higher income and educated counterparts. Detail on these analyses can be found in **appendix D**.

Additionally, the total number of medication use was an independent predictor of mortality across all the censored follow-up time intervals (**appendix D**) except for the full censored time (table 2). We observed that higher number of medication use was related to higher risk of mortality. Likewise, higher PIM use also was significantly associated with the higher risk of mortality across all the censored follow-up time intervals.

Similar to the PIM analyses, the unadjusted model (model 1) suggested that individuals with DDIs had an increased risk of all-cause mortality (table 3). Although DDIs were significantly associated with higher risks of mortality in adjusted model 2, they were not found to be a significant predictor of mortality in the fully adjusted model. No interaction terms were found to be significant. Older age, males compared with females, blacks compared with whites, and individuals with lower income and education had significantly higher risks of mortality compared with individuals with higher income and education. Individuals with higher medication use also had higher risks of mortality. Sensitivity analyses across all the censored follow-up time intervals also demonstrated similar conclusions. Detail on these analyses can be found in **appendix E**.

Discussion

Prior studies have found a significant association between PIM use identified through the Beers Criteria and poor patient outcomes such as ADEs, hospitalization, and mortality.[27,44] Health disparities are frequently observed in populations with negative health outcomes.[45,46] For example, an increased mortality rates, disability, and poor quality of life has been observed among patients who receive disparate medical care and

treatment. Our study assessed how the baseline PIM use and DDIs can be related to all-cause mortality and whether there are any disparities in this relationship. High PIM prevalence (about 87% of the participants) among older adults was observed in our analyses. The unadjusted HRs across all the models demonstrated significantly higher risks of mortality with PIM use and DDIs. However, in our iterative model building approach, we observed interesting differences in HRs across different censored follow-up time intervals. We observed that potential PIM/DDI related all-cause mortality can partly be explained by the disparity parameters and partly by other medical or physiologic risk factors. For example, for the full follow-up time, medical conditions like stroke and Afib were significant predictors of mortality only among the individuals with PIM use. We also observed similar trends in other censored follow-up time intervals. This suggests that while PIM use may not be a direct cause of mortality, it is related to other factors that can increase the risk of mortality. This is, in fact, consistent with prior studies. For example, Afib is known to be associated with an increased risk of all-cause mortality.[47,48] Amiodarone, an antiarrhythmic drug, is considered to be a PIM for older adults according to the Beers Criteria and is recommended to be avoided as the first-line therapy in patients with Afib due to its greater toxicity than other antiarrhythmic agents.[32] Careful consideration in medication prescription and choosing safer alternatives can improve such outcomes.

We also observed disparities across income and education in mortality outcomes where individuals with lower income and education had higher risks of mortality compared to their higher income and educated counterparts. Prior studies have explored disparities in all-cause mortality and found that low income could be a driving force in this regard.[49,50]

Education level, which often shapes employment and income, also is considered to be one of the strongest predictors of life expectancy.[51] Individuals with lower income and education tend to reside in the neighborhoods with fewer healthcare facilities.[52] These groups of patients often have limited availability to subspecialty physicians.[51-53] All these factors are often intertwined and can contribute to inappropriate prescription, and ultimate higher risk of mortality.

Racial disparities also were observed in our analyses. We found that whites compared with blacks had a higher risk of mortality with PIM use. However, blacks demonstrated higher risk of mortality even without the PIM use. This is consistent with past research that suggests that blacks have higher risks of all-cause mortality.[46,54] Additionally, past studies also found that whites are more likely than blacks to receive more medications.[55,56] Polypharmacy can lead to more PIM use and in turn increase the risk of mortality.[24]

Similar to our survival plots, higher medication use and higher PIM use were associated with higher risks of mortality. Older adults have multiple chronic conditions and require multiple medications to treat them.[28] In our study, the average medication use among older adults was 6.5. This supports past research that polypharmacy increases the risk of mortality.[57,58] Nascimento et al. found that the risk of all-cause mortality was 44% higher among users of at least one PIM which rises up to 84% with the use of two or more PIMs compared to the non-PIM users.[59] This supports our interpretation that higher PIM use can increase the risk mortality. However, it is possible that participants with higher medication use are sicker and have higher likelihoods of mortality. Moreover, more medication use can be associated with more PIM use. So, it is also possible that

PIM use is a marker of more medication use and individuals with more PIM use can be sicker. All these factors can be interlinked and contribute to higher risk of mortality. This could be a sign of endogeneity.[60] Further research is needed to assess this phenomenon which is beyond the scope of this research project.

Although the REGARDS study is very rigorously designed and a rich data source due to its longitudinal follow-up, patient diversity, and measurement of covariates, our study may still be limited by some unmeasured confounders. The biggest limitation of this study is the cross-sectional baseline measurement of PIM exposure. It is possible that patients have switched or stopped the medication, yet we classified them as exposed. Our exposure measurement may be subject to misclassification bias since we did not have a longitudinal measurement of PIM use. However, baseline PIM use has been employed to predict longitudinal outcomes in prior studies.[61,62] A recent study by Karuturi et al. used baseline PIM measurement to predict all-cause mortality, emergency room visit, hospitalization or composite endpoint of all the aforementioned outcomes in patients with colorectal and breast cancer.[61] Cross et al. also used baseline PIM measurement to predict all-cause mortality in a 3-year follow-up period.[62] Hansen et al. used the REGARDS data to predict all-cause mortality and cardiovascular outcomes using baseline antidepressant use.[39] The authors anticipated that the baseline antidepressant users might still be on their medications after two-years of follow-up. We also stratified our censored follow-up time period to see how far in the process the baseline PIM use can predict mortality. Our consistent findings across all the censored follow-up time intervals are indicative of probable method validity. Still, there is a high likelihood of misclassification bias.

The Beers Criteria provides a list of various PIMs across a variety of therapeutic classes.[32] All the medications may not have the same exposure window. A class specific analyses could have given a better exposure definition. However, that was beyond the scope of our study since we wanted to explore disparities across all-cause mortality with PIM use as a whole. Additionally, we did not have information regarding the dose of the medications. Hence, we could not establish any dose-response relationship. And finally, use of the Beers Criteria as a sole measure of PIM identification can also be problematic since there are other tools to identify PIMs which showed differences in detecting PIMs.[63,64] However, since the Beers Criteria was developed in the US and most widely used tool for PIM identification,[24,65] we consider this to be the most appropriate tool for our study.

This is the first attempt to evaluate disparities across all-cause mortality with PIM use. Our study, to some extent, found significant disparities in all-cause mortality with PIM use. Although interpretations across different censored time intervals are slightly different, it is quite apparent that the use of PIMs can influence some other drivers of all-cause mortality. Proper awareness and training programs tailored towards healthcare providers can help reduce adverse events with PIM prescription and associated disparities. Although due to the cross-sectional nature of the PIM measurement we could not establish any causal relationship, this study opens a new dimension in disparity research which will instigate further research to better understand the contributing factors of such disparities in order to develop appropriate intervention techniques.

References

1. Papanicolas I, Woskie LR, Jha AK. Health care spending in the united states and other high-income countries. *JAMA.* 2018;319(10):1024-1039.
2. Squires DA. The U.S. health system in perspective: a comparison of twelve industrialized nations. Issues in International Health Policy. 2011. http://www.commonwealthfund.org/~/media/Files/Publications/Issue%20Brief/2011/Jul/1532_Squires_US_hlt_sys_comparison_12_nations_intl_brief_v2.pdf. Accessed July 7, 2017.
3. Gary Claxton CC, Selena Gonzales, Rabah Kamal, Larry Levitt. Measuring the quality of healthcare in the U.S. https://www.healthsystemtracker.org/brief/measuring-the-quality-of-healthcare-in-the-u-s/#item-start. Accessed April 22, 2018. 2015.
4. NIH. NIH announces Institute on Minority Health and Health Disparities. Transition from center to institute highlights expanded responsibilities. https://www.nih.gov/news-events/news-releases/nih-announces-institute-minority-health-health-disparities. Accessed September 01, 2018. 2010.
5. Graham H. Social determinants and their unequal distribution: clarifying policy understandings. *Milbank Q.* 2004;82(1):101-124.
6. Howard G. Ancel Keys Lecture: Adventures (and misadventures) in understanding (and reducing) disparities in stroke mortality. *Stroke.* 2013;44(11):3254-3259.
7. AHRQ. Understanding quality measurement. https://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/chtoolbx/understand/index.html. Accessed October 24, 2017.
8. FAMILIESUSA. Measuring Health Care Quality: An Overview of Quality Measures. 2014. http://familiesusa.org/sites/default/files/product_documents/HSI%20Quality%20Measurement_Brief_final_web.pdf. Accessed October 24, 2017.
9. Donabedian A. The quality of care: How can it be assessed? *JAMA.* 1988;260(12):1743-1748.
10. AHRQ. 2015 National Healthcare Quality and Disparities Report. http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/nhqrdr/nhqdr15/2015nhqdr.pdf. Accessed on September 1, 2016.
11. RURAL AND URBAN HEALTH. Georgetown University. Health Policy Institute. https://hpi.georgetown.edu/agingsociety/pubhtml/rural/rural.html. Accessed August 5, 2018.
12. Komaromy M, Grumbach K, Drake M, et al. The role of black and Hispanic physicians in providing health care for underserved populations. *N Engl J Med.* 1996;334(20):1305-1310.
13. Cooper-Patrick L, Gallo JJ, Gonzales JJ, et al. Race, gender, and partnership in the patient-physician relationship. *JAMA.* 1999;282(6):583-589.
14. Trivedi AN, Zaslavsky AM, Schneider EC, Ayanian JZ. Trends in the quality of care and racial disparities in Medicare managed care. *N Engl J Med.* 2005;353(7):692-700.
15. Schneider EC, Zaslavsky AM, Epstein AM. Racial disparities in the quality of care for enrollees in medicare managed care. *JAMA.* 2002;287(10):1288-1294.
16. Virnig BA, Lurie N, Huang Z, Musgrave D, McBean AM, Dowd B. Racial variation in quality of care among Medicare+Choice enrollees. *Health Aff (Millwood).* 2002;21(6):224-230.
17. Saha S, Taggart SH, Komaromy M, Bindman AB. Do patients choose physicians of their own race? *Health Aff (Millwood).* 2000;19(4):76-83.
18. Disparities in Health and Health Care: Five Key Questions and Answers. http://kff.org/disparities-policy/issue-brief/disparities-in-health-and-health-care-five-key-questions-and-answers/#endnote_link_195310-4. Accessed April 25, 2017.

19. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation.* 2013;127(1):e6-e245.
20. Ayala C, Greenlund KJ, Croft JB, et al. Racial/ethnic disparities in mortality by stroke subtype in the United States, 1995-1998. *Am J Epidemiol.* 2001;154(11):1057-1063.
21. Elizabeth Arias. United States Life Tables, 2011. National Vital Statistics Reports 64(11). 2015. https://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_11.pdf. Accessed December 21, 2017.
22. Braveman PA, Cubbin C, Egerter S, Williams DR, Pamuk E. Socioeconomic disparities in health in the United States: what the patterns tell us. *Am J Public Health.* 2010;100 Suppl 1:S186-196.
23. Chen LL, Tangiisuran B, Shafie AA, Hassali MA. Evaluation of potentially inappropriate medications among older residents of Malaysian nursing homes. *Int J Clin Pharm.* 2012;34(4):596-603.
24. Al Odhayani A, Tourkmani A, Alshehri M, Alqahtani H, Mishriky A. Potentially inappropriate medications prescribed for elderly patients through family physicians. *Saudi Journal of Biological Sciences.* 2017;24(1):200-207.
25. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.
26. Laroche ML, Charmes JP, Nouaille Y, Picard N, Merle L. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? *Br J Clin Pharmacol.* 2007;63(2):177-186.
27. Page RL, 2nd, Linnebur SA, Bryant LL, Ruscin JM. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. *Clin Interv Aging.* 2010;5:75-87.
28. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother.* 2007;5(4):345-351.
29. Goren Z, M JD, Akpinar Acet G, Cali S, Gulcebi Idriz Oglu M. Potential drug-drug interactions among prescriptionsfor elderly patients in primary health care. *Turk J Med Sci.* 2017;47(1):47-54.
30. Ament PW, Bertolino JG, Liszewski JL. Clinically significant drug interactions. *Am Fam Physician.* 2000;61(6):1745-1754.
31. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology.* 2005;25(3):135-143.
32. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.
33. Fedewa SA, McClellan WM, Judd S, Gutierrez OM, Crews DC. The association between race and income on risk of mortality in patients with moderate chronic kidney disease. *BMC Nephrol.* 2014;15:136.
34. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol.* 1989;129(4):687-702.
35. INTRODUCTION TO SURVIVAL ANALYSIS IN SAS. https://stats.idre.ucla.edu/sas/seminars/sas-survival/. Accessed March 3, 2018.
36. Xue X, Xie X, Gunter M, et al. Testing the proportional hazards assumption in case-cohort analysis. *BMC Medical Research Methodology.* 2013;13(1):88.
37. Schafer JL. Multiple imputation: a primer. *Statistical Methods in Medical Research.* 1999;8(1):3-15.
38. Bennett DA. How can I deal with missing data in my study? *Aust N Z J Public Health.* 2001;25(5):464-469.
39. Hansen RA, Khodneva Y, Glasser SP, Qian J, Redmond N, Safford MM. Antidepressant Medication Use and Its Association With Cardiovascular Disease and All-Cause Mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Ann Pharmacother.* 2016;50(4):253-261.

40. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med.* 1991;10(4):585-598.
41. Barzi F, Woodward M. Imputations of missing values in practice: results from imputations of serum cholesterol in 28 cohort studies. *Am J Epidemiol.* 2004;160(1):34-45.
42. Thacker EL, Gillett SR, Wadley VG, et al. The American Heart Association Life's Simple 7 and incident cognitive impairment: The REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *J Am Heart Assoc.* 2014;3(3):e000635.
43. SAS_user_guide. Survival analysis. Modeling with categorical predictors. http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_phreg_sect034.htm. Accessed September 03, 2018.
44. Jano E, Aparasu RR. Healthcare outcomes associated with beers' criteria: a systematic review. *Ann Pharmacother.* 2007;41(3):438-447.
45. Hall-Lipsy EA, Chisholm-Burns MA. Pharmacotherapeutic disparities: racial, ethnic, and sex variations in medication treatment. *Am J Health Syst Pharm.* 2010;67(6):462-468.
46. Beydoun MA, Beydoun HA, Mode N, et al. Racial disparities in adult all-cause and cause-specific mortality among us adults: mediating and moderating factors. *BMC Public Health.* 2016;16:1113.
47. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: A systematic review and meta-analysis. *European Journal of Preventive Cardiology.* 2017;24(14):1555-1566.
48. Healey JS, Oldgren J, Ezekowitz M, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet.* 2016;388(10050):1161-1169.
49. Rehkopf DH, Berkman LF, Coull B, Krieger N. The non-linear risk of mortality by income level in a healthy population: US National Health and Nutrition Examination Survey mortality follow-up cohort, 1988–2001. *BMC Public Health.* 2008;8(1):383.
50. Sabanayagam C, Shankar A. Income Is a Stronger Predictor of Mortality than Education in a National Sample of US Adults. *Journal of Health, Population, and Nutrition.* 2012;30(1):82-86.
51. Olshansky SJ, Antonucci T, Berkman L, et al. Differences in life expectancy due to race and educational differences are widening, and many may not catch up. *Health Aff (Millwood).* 2012;31(8):1803-1813.
52. VCU_Center_for_Society_and_Health. Why Education Matters to Health: Exploring the Causes. https://societyhealth.vcu.edu/work/the-projects/why-education-matters-to-health-exploring-the-causes.html#healthBenefits. Accessed August 27, 2018. 2015.
53. Wong ST, Regan S. Patient perspectives on primary health care in rural communities: effects of geography on access, continuity and efficiency. *Rural Remote Health.* 2009;9(1):1142.
54. Borrell LN, Dallo FJ, Nguyen N. Racial/Ethnic Disparities in All-Cause Mortality in U.S. Adults: The Effect of Allostatic Load. *Public Health Reports.* 2010;125(6):810-816.
55. Wang J, Zuckerman IH, Miller NA, Shaya FT, Noel JM, Mullins CD. Utilizing New Prescription Drugs: Disparities among Non-Hispanic Whites, Non-Hispanic Blacks, and Hispanic Whites. *Health Serv Res.* 2007;42(4):1499-1519.
56. Singhal A, Tien YY, Hsia RY. Racial-Ethnic Disparities in Opioid Prescriptions at Emergency Department Visits for Conditions Commonly Associated with Prescription Drug Abuse. *PLoS One.* 2016;11(8):e0159224.
57. Gomez C, Vega-Quiroga S, Bermejo-Pareja F, Medrano MJ, Louis ED, Benito-Leon J. Polypharmacy in the Elderly: A Marker of Increased Risk of Mortality in a Population-Based Prospective Study (NEDICES). *Gerontology.* 2015;61(4):301-309.
58. Leelakanok N, Holcombe AL, Lund BC, Gu X, Schweizer ML. Association between polypharmacy and death: A systematic review and meta-analysis. *J Am Pharm Assoc (2003).* 2017;57(6):729-738.e710.

59. do Nascimento MM, Mambrini JV, Lima-Costa MF, Firmo JO, Peixoto SW, de Loyola Filho AI. Potentially inappropriate medications: predictor for mortality in a cohort of community-dwelling older adults. *Eur J Clin Pharmacol.* 2017;73(5):615-621.
60. Avery G. Endogeneity in Logistic Regression Models. *Emerg Infect Dis.* 2005;11(3):503-505.
61. Karuturi MS, Holmes HM, Lei X, et al. Potentially inappropriate medication use in older patients with breast and colorectal cancer. *Cancer.* 2018;124(14):3000-3007.
62. Cross AJ, George J, Woodward MC, et al. Potentially Inappropriate Medication, Anticholinergic Burden, and Mortality in People Attending Memory Clinics. *J Alzheimers Dis.* 2017;60(2):349-358.
63. Mann E, Haastert B, Bohmdorfer B, et al. Prevalence and associations of potentially inappropriate prescriptions in Austrian nursing home residents: secondary analysis of a cross-sectional study. *Wien Klin Wochenschr.* 2013;125(7-8):180-188.
64. Oliveira MG, Amorim WW, de Jesus SR, Heine JM, Coqueiro HL, Passos LC. A comparison of the Beers and STOPP criteria for identifying the use of potentially inappropriate medications among elderly patients in primary care. *J Eval Clin Pract.* 2015;21(2):320-325.
65. O'Mahony D, Gallagher P, Ryan C, et al. STOPP & START criteria: A new approach to detecting potentially inappropriate prescribing in old age. *European Geriatric Medicine.*1(1):45-51.

Table 1. Baseline Characteristics of the Study Population by Use of PIM or DDI.

	PIM use (n = 13 475)			DDI (n = 26 399)		
Characteristic	Yes (n = 11 784)	No (n = 1691)	*P* Value	Yes (n = 996)	No (n = 25 403)	*P* Value
Demographic and Socioeconomic factors						
Age, mean (SD), years	72.8 ± 5.9	72.3 ± 5.8	0.0002	67.4 ± 9.1	65.2 ± 9.4	<0.0001
Female, n (%)	6302 (53.5)	872 (51.6)	0.14	449 (45.1)	14 382 (56.6)	<0.0001
Black, n (%)	4423 (37.5)	680 (40.2)	0.03	232 (23.3)	10 469 (41.2)	<0.0001
Income, n (%)			0.01			0.42
Less than $20,000	2543 (21.6)	313 (18.5)		179 (18.0)	3173 (12.5)	
$20,000- $34,999	3366 (28.6)	470 (27.8)		266 (26.7)	6141 (24.2)	
$35,000- $74,999	3149 (26.7)	488 (28.9)		290 (29.1)	7505 (29.5)	
≥ $75,000	1030 (8.7)	171 (10.1)		143 (14.4)	3960 (15.6)	
Education, n (%)			0.0003			0.13
Less than high school	1968 (16.7)	241 (14.3)		105 (10.5)	3228 (12.7)	
High school or some college	6132 (52.1)	845 (50.0)		537 (53.9)	13 394 (52.8)	
College graduate and above	3671 (31.2)	604 (35.7)		354 (35.5)	8762 (34.5)	
Location of residence, n (%)			0.0086			0.0006
Isolated	261 (2.4)	27 (1.8)		18 (2.0)	522 (2.3)	
Small rural	651 (6.1)	82 (5.3)		76 (8.5)	1341 (5.8)	
Large rural	1295 (12.1)	153 (9.9)		127 (14.2)	2696 (11.7)	
Urban	8474 (79.3)	1277 (82.9)		675 (75.3)	18 397 (80.1)	
Medical conditions						
Diabetes, n (%)	3171 (27.0)	246 (14.6)	<0.0001	336 (33.9)	6010 (23.7)	<0.0001
Atrial fibrillation, n (%)	1380 (12.0)	75 (4.5)	<0.0001	274 (28.2)	2104 (8.7)	<0.0001
CKD, n (%)	2688 (22.8)	205 (12.1)	<0.0001	251 (25.2)	3956 (15.6)	<0.0001
History of stroke, n (%)	1079 (9.2)	46 (2.7)	<0.0001	155 (15.7)	1622 (6.4)	<0.0001
History of cardiovascular disease, n (%)	3023 (26.2)	219 (13.1)	<0.0001	432 (44.4)	4466 (17.9)	<0.0001
Physiological risk factors						
Dyslipidemia, n (%)	7313 (64.3)	898 (55.1)	<0.0001	744 (77.1)	14 722 (60.1)	<0.0001
Total cholesterol, mean (SD), mg/dL	186.3 ± 39.7	196.5 ± 40.1	0.0054	175.4 ± 43.2	191.7 ± 39.8	<0.0001
ARIC stroke risk score, median (25th-75th percentile)	9.3 [4.5-18.9]	6.5 [3.6-12.5]	<0.0001	8.2 [3.1-17.9]	4.6 [2.0-11.0]	<0.0001
Urinary creatinine, median (25th-75th percentile), mg/dL	116 [74-163]	118 [75-167]	0.34	115 [72-163]	121 [77-174]	0.03

PIM: Potentially Inappropriate Medication; for PIM use, the patients are of age >=65; DDI: Drug-Drug Interactions, for DDIs, the patients are of age >= 45 years; CKD: Chronic Kidney disease; ARIC: atherosclerosis risk in communities study.

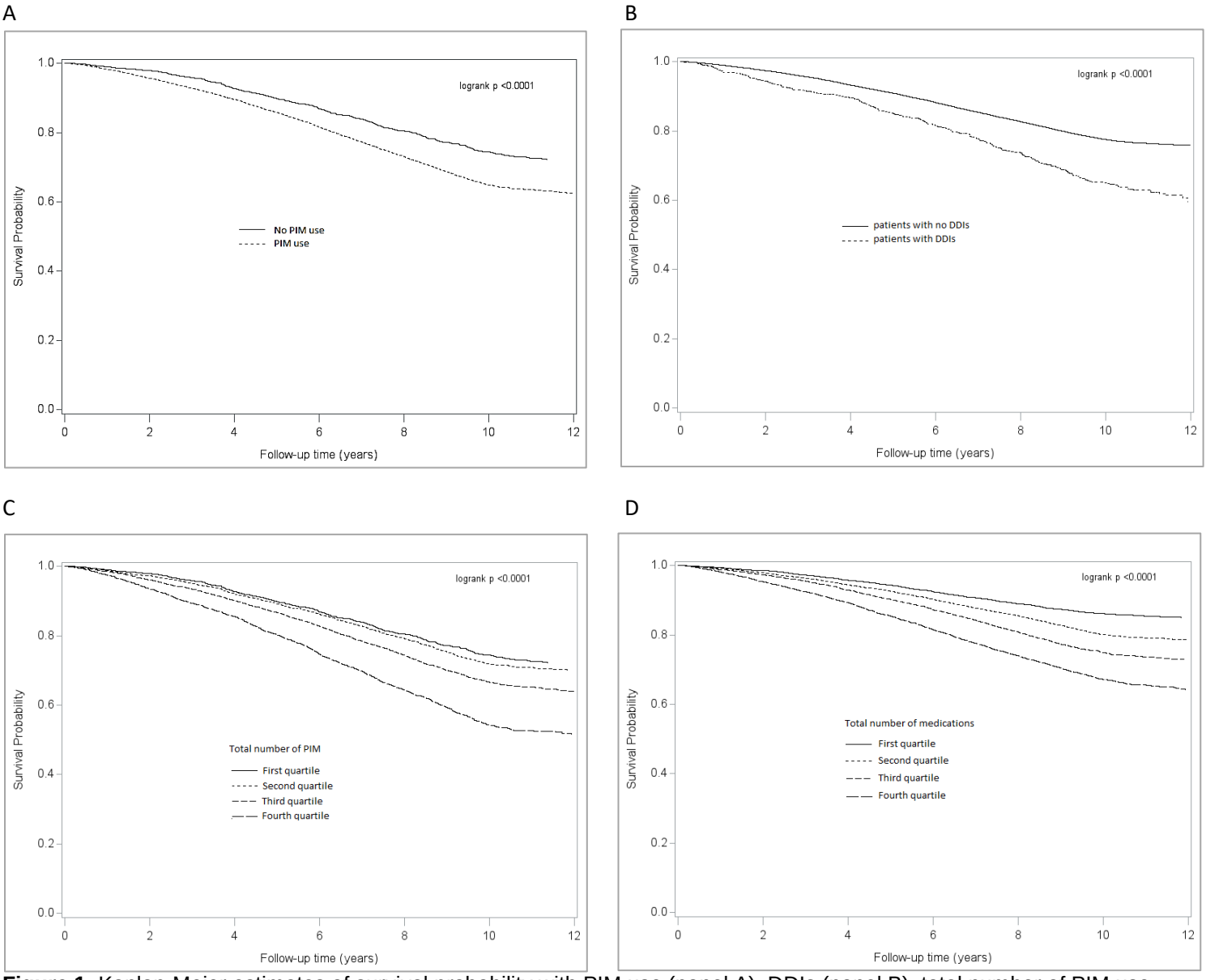

Figure 1. Kaplan-Meier estimates of survival probability with PIM use (panel A), DDIs (panel B), total number of PIM use (panel C), and total number of medication use (panel D).

Death was calculated on or before 3/31/2016; PIM: potentially inappropriate medication

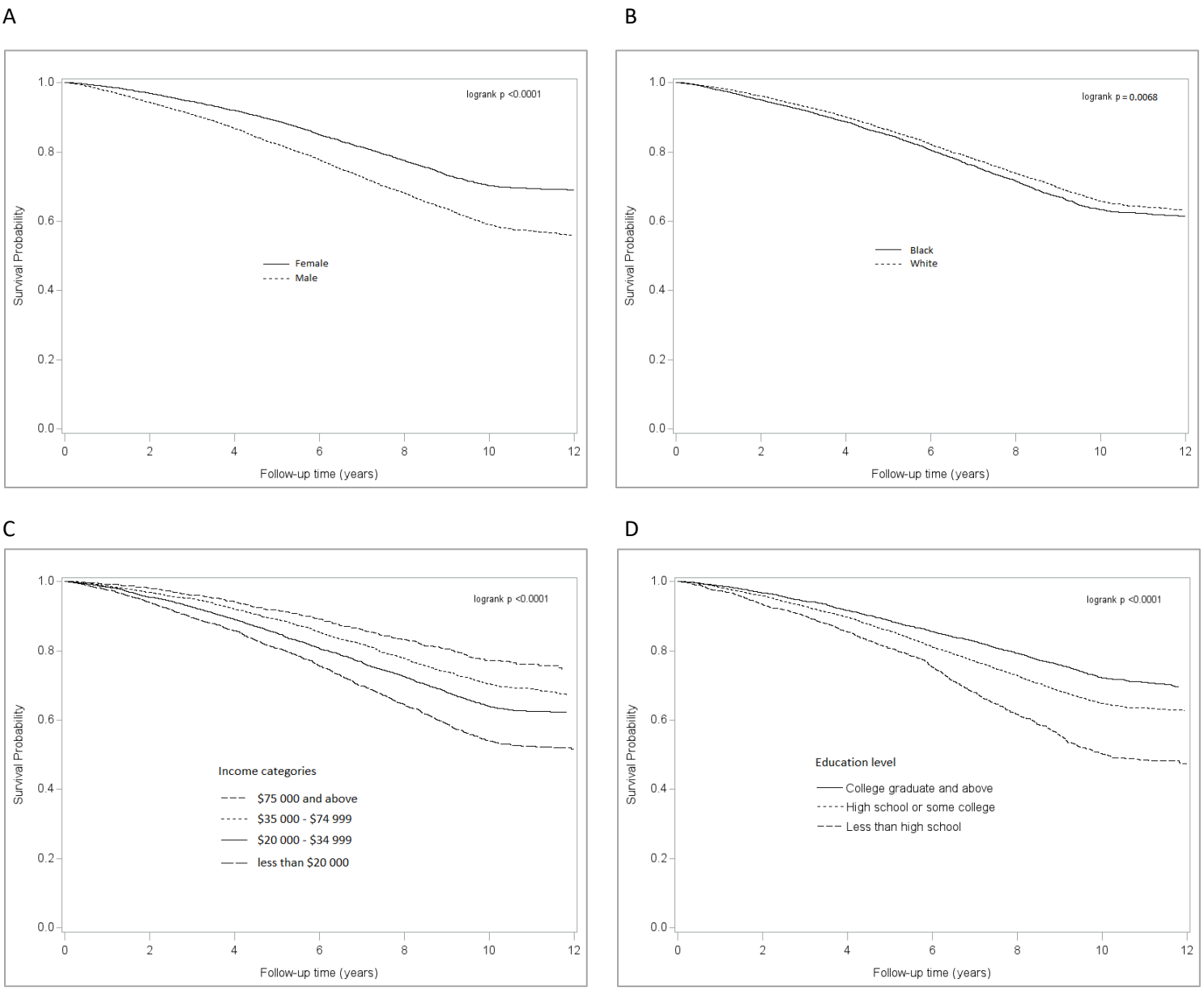

Figure 2. Survival probability of PIM users across different disparity parameters which include gender (panel A), race (panel B), income (panel C), and education (panel D).

Death was calculated on or before 3/31/2016; PIM: potentially inappropriate medication

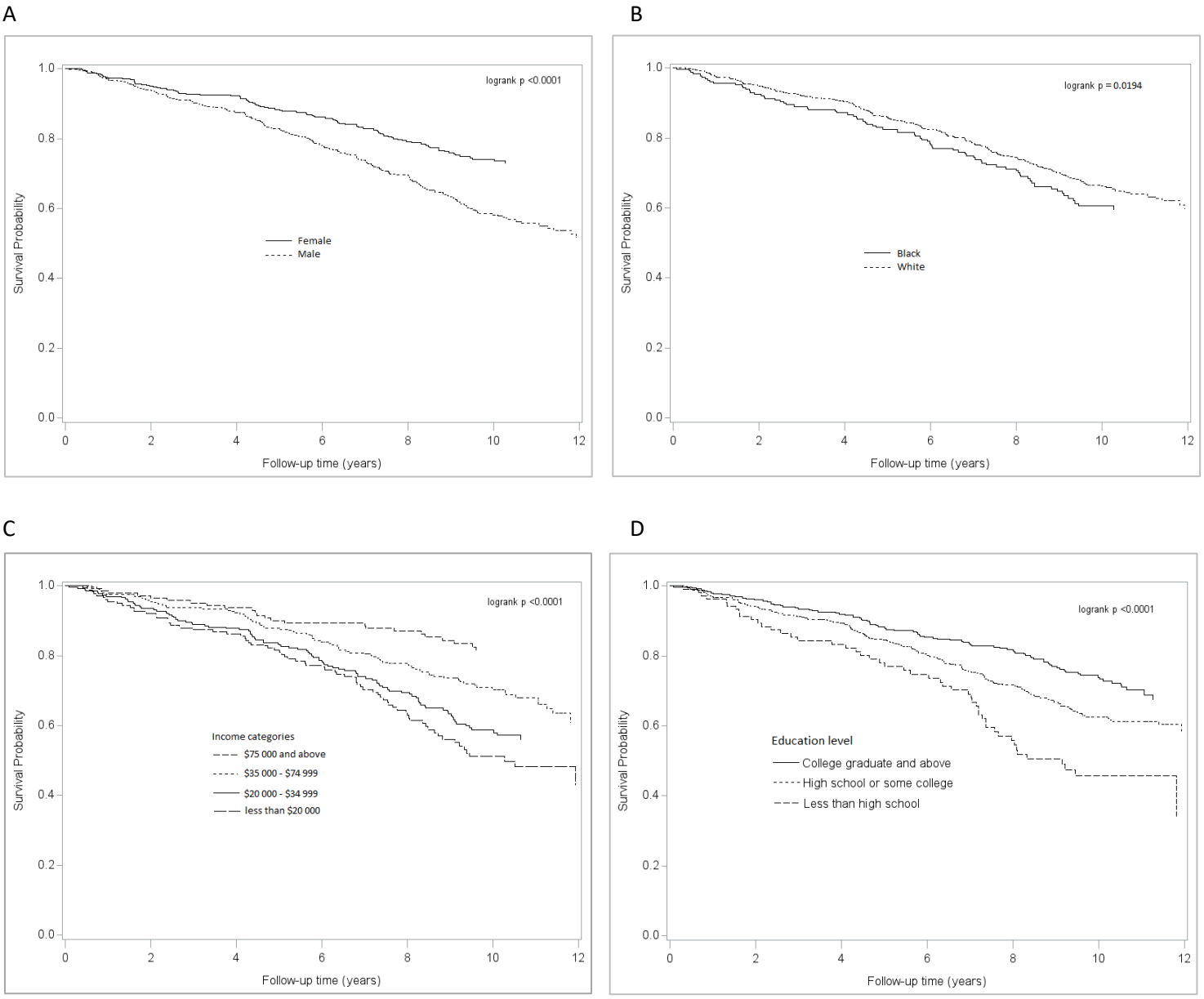

Figure 3. Survival probability of participants with DDIs across different disparity parameters which include gender (panel A), race (panel B), income (panel C), and education (panel D).

Death was calculated on or before 3/31/2016; DDI: drug-drug interaction

Table 2. Association between PIM use and all-cause mortality and the effect of health disparities on this relationship

Characteristics	**Full follow-up time up to 3/31/2016 (method 1), HR (95% CI)**		
	Model 1	Model 2	Model 3 ¶
PIM use			
No	Ref	Ref	Ref
Yes	**1.45 (1.30 - 1.61)**	a	a, b, c
Gender			
Male	-	Ref	Ref
Female	-	**0.53 (0.50 - 0.56)**	**0.56 (0.52 - 0.60)**
Race			
White	-	Ref	Ref
Black	-	a	a
Income			
≥ $75,000	-	Ref	Ref
Less than $20,000	-	**2.56 (2.20 - 2.99)**	**2.67 (2.30 - 3.10)**
$20,000- $34,999	-	**1.86 (1.61 - 2.15)**	**1.93 (1.67 - 2.23)**
$35,000- $74,999	-	**1.41 (1.22 - 1.62)**	**1.33 (1.25 - 1.67)**
Education			
College graduate and above	-	Ref	Ref
Less than high school	-	**1.60 (1.45 - 1.78)**	**1.44 (1.29 - 1.60)**
High school or some college	-	**1.18 (1.09 - 1.28)**	**1.15 (1.06 - 1.24)**
Total number of medications use			
First quartile	-	-	Ref
Second quartile	-	-	1.03 (0.87-1.21)
Third quartile	-	-	1.05 (0.88-1.25)
Fourth quartile	-	-	1.13 (0.94-1.36)
Total PIM use			
First quartile	-	-	Ref
Second quartile	-	-	1.04 (0.92-1.18)
Third quartile	-	-	**1.21 (1.07-1.37)**
Fourth quartile	-	-	**1.66 (1.45-1.91)**
Significant interactions			
Race-PIM [a]			

PIM Yes vs. No; Race = Black	-	**1.22 (1.04 - 1.42)**	0.99 (0.84 - 1.16)
PIM Yes vs. No; Race = White	-	**1.61 (1.40 - 1.86)**	**1.27 (1.10 - 1.47)**
Black vs. White; PIM = Yes	-	1.03 (0.96 - 1.10)	1.04 (0.97 - 1.12)
Black vs. White; PIM = No	-	**1.36 (1.11 - 1.66)**	**1.34 (1.09 - 1.65)**
Stroke-PIM [b]			
Stroke: Yes vs. No; PIM = No	-	-	1.50 (0.92-2.40)
Stroke: Yes vs. No; PIM = Yes	-	-	**1.63 (1.49-1.80)**
Afib-PIM [c]			
Afib: Yes vs. No; PIM = No	-	-	1.41 (0.93-2.13)
Afib: Yes vs. No; PIM = Yes	-	-	**1.50 (1.40-1.64)**

PIM: potentially inappropriate medication, HR: hazard ratio; CVD: history of cardiovascular diseases; CKD: chronic kidney disease; Afib: atrial fibrillation;

Model 1 was the unadjusted Cox proportional hazard model that accounted for only the PIM exposure. Model 2 was adjusted for demographics and socioeconomic characteristics. Model 3 adjusted for all the model 2 covariates plus patients' medical conditions, physiologic risk factors, total number of medications used, and total PIM use

[a] Significant race-PIM interaction; [b] Significant stroke-PIM interaction; [c] Significant Afib-PIM interaction; Bold refers to P <0.05.
[¶] Significant covariates include: CVD (HR = 1.45, 95% CI 1.35 – 1.56), diabetes (HR = 1.32, 95% CI 1.23 – 1.41), and CKD (HR = 1.89, 95% CI 1.76 – 2.03).

Table 3. Association between DDIs and all-cause mortality and the effect of health disparities on this relationship

Characteristics	**Full follow-up time up to 3/31/2016 (method 1), HR (95% CI)**		
	Model 1	Model 2	Model 3 ¶
DDI use			
No	Ref	Ref	Ref
Yes	**1.72 (1.54 - 1.93)**	**1.50 (1.34 - 1.68)**	1.07 (0.95 - 1.21)
Age group, years			
< 60	-	Ref	Ref
60-64	-	**1.51 (1.35 - 1.69)**	**1.40 (1.25 - 1.58)**
65-75	-	**2.56 (2.33 - 2.82)**	**2.28 (2.07 - 2.51)**
≥ 75	-	**6.16 (5.59 - 6.79)**	**5.04 (4.56 - 5.58)**
Gender			
Male	-	Ref	Ref
Female	-	**0.54 (0.51 - 0.57)**	**0.58 (0.54 - 0.61)**
Race			
White	-	Ref	Ref
Black	-	**1.13 (1.06 - 1.20)**	**1.11 (1.05 - 1.18)**
Income			
≥ $75,000	-	Ref	Ref
Less than $20,000	-	**2.57 (2.27 - 2.92)**	**2.24 (1.97 - 2.55)**
$20,000- $34,999	-	**1.83 (1.62 - 2.06)**	**1.70 (1.51 - 1.92)**
$35,000- $74,999	-	**1.37 (1.22 - 1.54)**	**1.33 (1.18 - 1.50)**
Education			
College graduate and above	-	Ref	Ref
Less than high school	-	**1.65 (1.51 - 1.81)**	**1.46 (1.33 - 1.61)**
High school or some college	-	**1.29 (1.21 - 1.39)**	**1.23 (1.14 - 1.32)**
Total number of medications use			
First quartile	-	-	Ref
Second quartile	-	-	**1.44 (1.31 - 1.58)**
Third quartile	-	-	**1.91 (1.74 - 2.10)**
Fourth quartile	-	-	**2.72 (2.48 - 2.98)**

DDI: drug-drug interaction. Bold refers to P <0.05.

Model 1 was the unadjusted Cox proportional hazard model that accounted for only the DDI exposure. Model 2 was adjusted for demographics and socioeconomic characteristics. Model 3 adjusted for all the model 2 covariates plus patients' medical conditions, physiologic risk factors, and total number of medications used.

¶ Significant covariates included: CVD (HR = 1.50, 95% CI 1.41 – 1.60), stroke (HR = 1.70, 95% CI 1.57 – 1.85), diabetes (HR = 1.49, 95% CI 1.40 – 1.58), CKD (HR = 1.80, 95% CI 1.69 – 1.91), and Afib (HR = 1.45, 95% CI 1.34 – 1.58).

Aim 3

ABSTRACT

Background: Anticholinergic drug (ACH) use is linked with cognitive dysfunction and is often considered to be potentially inappropriate in older adults. Health disparities in cognitive status with ACH use may exist.

Objective: To evaluate the association between ACH use and cognitive impairment and the effect of disparity parameters (gender, race, income, education, and rural or urban areas) on this relationship.

Methods: The analyses included 13,623 black and white US adults aged ≥ 65 years from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study (recruited 2003-2007). The ACH use was defined by the 2015 Beers Criteria and cognitive impairment was measured by the Six-Item Cognitive Screener (SIS). Multivariable logistic regression models assessed disparities in cognitive impairment with ACH use, iteratively adjusting for disparity parameters and other covariates. The full models included interaction terms between ACH use and other covariates. A similar approach was used for class specific ACH exposure and cognitive impairment analyses.

Results: Approximately 14% of the participants used at least one ACH listed in the Beers criteria. Antidepressants were the most frequently prescribed ACH class. A significant gender-race interaction illustrated that females compared with males (in blacks: odds ratio [OR]=1.28, 95% CI 1.10–1.49 and in whites: OR=1.96, 95% CI 1.74–2.20), and especially white females (black vs. white females: OR=0.71, 95% CI 0.64–0.80) were more likely to receive ACHs. The fully adjusted model suggested that ACH users than non-users

(OR=1.27, 95% CI 1.01–1.59), males compared with females (female vs. male: OR=0.77, 95% CI 0.63 – 0.95), blacks compared with whites (OR=1.78, 95% CI 1.47–2.15), and individuals with lower education (<high school vs. >college: OR=1.59, 95% CI 1.22–2.07) had higher odds of using ACHs. Only antidepressant users (OR=1.44, 95% CI 1.01–2.04) showed significant association with cognitive impairment in the fully adjusted model.

Conclusion: We observed demographic and socioeconomic disparities in ACH use and in cognitive impairment, individually. Further research is needed to better understand the contributing factors of such disparities in order to develop appropriate interventions.

Key words: REGARDS, anticholinergic drugs, socioeconomic disparity, cognitive impairment

Introduction

Older adults often suffer from multiple chronic conditions, require multiple prescription and over-the-counter (OTC) medications to manage them, and are at an increased risk of developing dementia.[1-3] These factors often expose them to drugs with anticholinergic properties.[4,5] Anticholinergic drugs (ACHs), or simply anticholinergics, are routinely used for the treatment of depression, psychosis, Parkinson's disease, muscle spasms, allergy, intestinal motility disorders, and urinary incontinence.[4,5] Older adults are more sensitive to CNS AEs due to the reduction in cholinergic neurons in the brain, decreased hepatic metabolism and renal drug excretion, and increased permeability of the blood-brain barrier.[6] For these reasons, many ACHs are considered potentially inappropriate in older adults.[7] These drugs are particularly problematic for older adults with pre-existing cognitive impairments.[2,6] Hence, the study of appropriateness of ACH use in older adults is an important aspect of the quality of medication use.

Although the United States (US) spends more per capita on healthcare than any other nation,[8] health-related quality indicators lag behind many other countries.[9] These low quality indicators differentially affect subpopulations within the US.[10] These inequalities, or health disparities, are defined as the systematic differences among certain population groups in incidence, prevalence, mortality, and burden of diseases or other adverse events.[11,12] Populations affected by health disparities are frequently defined by socioeconomic status, urban-rural residence, and race/ethnicity.[13] Avedis Donabedian broadly classified the healthcare quality measures into three categories: structure, process, and outcomes.[14-16] According to the Donabedian framework, changes in the structure of care can change the clinical processes which ultimately changes the patients'

outcomes.[16] Inappropriate ACH prescription is a process measure which can lead to a poor clinical outcome such as cognitive impairment in older adults.

Felton et al. studied racial differences in ACH use among community dwelling elders and found that whites used more ACH drugs from blacks.[17] However, no prior studies systematically assessed ACH use across health disparities defined on the basis of socioeconomic factors, rural vs. urban residence, and race. The purpose of this study is to evaluate the association between ACH use and cognitive impairment and whether there are disparities in this relationship. Studying health disparities requires access to unique data that can identify disparities and measure outcomes in a diverse population controlling for clinically relevant covariates. One such useful study is the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. We leveraged REGARDS' infrastructure to quantify health disparities on ACH use and resulting association of ACH use with cognitive impairments.

Methods

Study participants

We used the data from the REGARDS study which is a national, population-based, longitudinal study initially designed to assess health disparities in stroke treatment and outcomes in the Southeastern US ("Stroke Belt") compared to the other parts of the US.[18] REGARDS included 30,239 US adults age ≥ 45 years (42% black, 55% women) enrolled from January 2003 to October 2007. Individuals other than blacks or whites, actively receiving cancer treatment, unable to communicate in English, and nursing home

residents or on a waiting list were excluded from the study. The study sample includes 21% of participants from the Stroke Buckle (coastal plain region of North Carolina, South Carolina, and Georgia), 35% from the Stroke Belt states (remainder of North Carolina, South Carolina, and Georgia, plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana), and rest of the 44% from the other 40 neighboring states which are referred to as non-Belt.[18,19]

Data collection

Participants for this study were recruited via mail and telephone contacts from commercially available lists of US residents. Baseline data were obtained via telephone interview, self-administered questionnaires, and an in-home visit. Demographic and socioeconomic characteristics, health behaviors, health status, and self-reported comorbid conditions were obtained via computer-assisted telephone interviewing (CATI). Information regarding both prescription and nonprescription medications taken within the past two weeks were obtained through in-home examinations provided by the trained technicians of the Examination Management Services, Inc. (EMSI). EMSI technicians also obtained blood pressure measurements, blood and urine samples, and electrocardiograms (ECG) during the in-home visit. Written informed consent was obtained during that time. Full study design and the methodological details of the REGARDS study is published elsewhere.[18] The REGARDS study was approved by the Institutional Review Boards of all the participating institutions, and the analyses were approved by the Auburn University IRB.

Measures

ACH exposure

ACH use was classified according to the American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (described as “Beers Criteria” from here forward). This includes a list of medications that are considered to be potentially harmful for older adults.[7] ACHs are the largest subset of inappropriate medications listed in the Beers Criteria. ACH medications included several classes, including antihistamines, antidepressants, antimuscarinics, antiparkinsonian agents, antipsychotics, antispasmodics, skeletal muscle relaxants, antiarrhythmics, and antiemetics. ACH use for each of these classes was coded as binary variables (yes/no) by matching the patients’ medication list with the ACH component of the Beers Criteria. A full list of medications studied are given in **Appendix B.**

Study outcome

The outcome measure for our study was the cognitive status, measured by the Six-Item Cognitive Screener (SIS). The SIS was added to the REGARDS baseline data on December 18, 2003. The SIS is a test of global cognitive function derived from the Mini-Mental State Exam (MMSE).[20,21] SIS scores range from 0 to 6, with lower scores reflecting poorer cognitive function. A score ≤ 4 denoted cognitive impairment.[21,22]

Disparity parameters

The disparity parameters for this study were defined as gender (male/female), race (black/white), annual income (stratified as less than $20,000, $20,000- $34,999, $35,000- $74,999, and ≥ $75,000), education (stratified as less than high school, high school or

some college, and greater than college), and location of residence (stratified as isolated, small rural, large rural, and urban).

Other Covariates

Other than the disparity variables, patients' medical condition, physiologic risk factors, health behaviors, and markers of mental health were considered as covariates. Medical conditions included diabetes (self-reported) and chronic kidney disease, CKD (defined as estimated glomerular filtration rate (eGFR) <60 ml/min/ 1.73 m^2.[23] Physiologic risk factors included the atherosclerosis risk in communities (ARIC) study stroke risk score and urinary creatinine levels. Measures of health behaviors included alcohol use (defined as none; moderate: 1-7 for women, 1-14 for men; and heavy: ≥7 drinks/week for women, ≥14 drinks/week for men) and exercise (defined as none; 1 to 3 times; and 4 or more times/week). Finally, markers of mental health were assessed by the mental component scores (MCS) of the Short Form-12 (SF-12), presence of depressive symptoms (defined as a score ≥4 of the Centers for Epidemiologic Study Depressive Scale [CES-D]), and Cohen's Perceived Stress Scale(PSS) score.[19]

Prior studies showed that complete abstinence from alcohol, lack of exercise, and depression were associated with cognitive impairment.[21,24] Also, stress level was found to be associated with depression and depression can lead to cognitive impairment.[25] Similarly, higher creatinine levels were found to be associated with CKD[23], and CKD was associated with cognitive impairment.[26] Diabetes and stroke increases the permeability of the blood-brain barrier and increase the penetration of anticholinergic drugs[27,28] which in turn can increase the risk of cognitive impairment.[21,26,29] All of these factors contributed to the selection of these covariates for this study.

In our study, diabetes, CKD, and depressive symptoms were coded as binary variables (yes/no) whereas the ARIC stroke risk scores, urinary creatinine levels, MCS, and PSS scores were converted into quartiles for further analyses.

Statistical analysis

Descriptive statistics were obtained for ACH uses by using chi-square statistics for categorical characteristics and Student t tests for continuous characteristics.

The association between cognitive impairment and ACH use were studied by sequentially adjusted multivariable logistic regression models. The resultant odds ratio (OR) and corresponding 95% confidence intervals (CI) were reported as a measure of significance of association. Model 1 reflects the unadjusted logistic regression model that accounted for only the ACH exposure. Model 2 was adjusted for demographics and socioeconomic characteristics. Model 3 adjusted for all the model 2 covariates plus patients' medical condition and physiologic risk factors. Model 4 was adjusted for model 3 covariates plus measures of health behaviors. And finally, model 5 was adjusted for all the model 4 covariates plus markers of mental health. All the covariates had less than 5% missing values except for location of residence (about 9% missing values), income (about 12% missing values), and ARIC stroke risk scores (about 13% missing values). According to Schafer, missing values less than 5% are insignificant[30] and according to Bennet, an statistical analysis may be potentially biased if more than 10% data are missing.[31] In our study, missing data in covariates were replaced by multivariable multiple imputation technique using chain equations in 10 datasets with sample bootstrapping.[19,32] Prior studies recommended multiple imputation in case of data where 10 to 60% of values are missing.[33,34]

To study the effect of disparity parameters on the relationship of ACH exposure and cognitive impairment, interaction variables were created to test for interaction between ACH use and all the disparity variables and covariates. The interaction of race with other disparity variables also was considered to study disparities across ACH use only. Interactions were considered significant at an alpha= 0.1 level. A similar approach was used for class specific ACH exposure and cognitive impairment analyses. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Out of 30,239 US adults age ≥ 45 years, a total of 3,441 participants were excluded due to missing drug information. Since we only included patients aged ≥ 65 years, only 13,623 of these older adults were included. However, an additional 2,820 subjects were excluded due to missing cognitive impairment information. So, a total of 10,803 older adults were included to study the association between ACH use and cognitive impairment.

Of these, approximately 14% (n= 1,912) of the participants aged ≥ 65 years (n = 13,623) used at least one ACH listed in the Beers criteria. Significant differences between ACH users and non-users were observed (Table 1). For instance, ACH users compared to the non-users were more likely females (65.7% vs. 51.3%), had lower income (P<0.0001), lower education (P<0.0001), and mainly resided in rural areas (P=0.01). We also observed significant differences between ACH users and non-users across medical conditions, physiologic risk factors, health behaviors, and markers of mental health. For

example, ACH users compared with non-users were more likely diabetic (30.5% vs 24.7%) and had more depressive symptoms (13.8% vs 8.3%). Similar differences were observed across the cohort for the study of cognitive status. The most widely used ACH classes among the study participants were antidepressants (n= 631), antihistamines (n= 625), and antimuscarinics (n= 497). Amitriptyline (n= 569), paroxetine (n= 466), and diphenhydramine (n= 447) were the most frequently used ACH drugs in our study (Table 2).

Significant gender-race interactions were observed among the antimuscarinic users and ACH users as a whole (Table 3). Females compared with males in both blacks and whites had higher odds of having antimuscarinics (female vs. male in blacks: OR=1.41, 95% CI 1.07 – 1.85; female vs. male in whites: OR=2.44, 95% CI 1.95 – 3.07) and ACH (female vs. male in blacks: OR=1.28, 95% CI 1.10 – 1.49; female vs. male in whites: OR=1.96, 95% CI 1.74 – 2.20) as a whole. White females compared with black females had higher odds of having ACHs (black vs. white females: OR=0.71, 95% CI 0.64 – 0.80), whereas black males had higher odds of using antimuscarinics (OR=1.45, 95% CI 1.08 – 1.96) compared with white males. Gender was an independent predictor of different classes of ACH use. For example, females compared with males had higher odds of using antihistamines (OR=1.26, 95% CI 1.05 – 1.52), skeletal muscle relaxants (OR=1.59, 95% CI 1.08 – 2.34) antidepressants (OR=1.72, 95% CI 1.42 – 2.07), and antispasmodics (OR=1.88, 95% CI 1.27 – 2.79). Individuals with lower income were more likely than their higher income counterparts to receive antihistamines (<$20,000 vs. ≥$75,000: OR=1.72, 95% CI 1.12 – 2.66), antidepressants (<$20,000 vs. ≥$75,000: OR=1.59, 95% CI 1.04 – 2.42), and ACHs as a whole (<$20,000 vs. ≥$75,000: OR=1.71,

95% CI 1.32 – 2.21). Lower education was a significant predictor of skeletal muscle relaxant (some college vs. ≥college graduate: OR=1.67, 95% CI 1.01 – 2.76) and antidepressant use (<high school vs. ≥college graduate: OR=1.55, 95% CI 1.17 – 2.06). Residing in rural areas was a significant predictor of antihistamine use (small rural vs. urban: OR=1.49, 95% CI 1.09 – 2.04). Racial disparity was observed only among the antidepressant users where whites compared with blacks had higher odds of receiving antidepressants (black vs. white OR=0.63, 95% CI 0.52 – 0.77).

We studied disparities in cognitive impairment with ACH use by using sequentially adjusted logistic regression models (Table 4). No ACH-covariate interactions were found significant. However, ACH use was independently associated with higher odds of cognitive impairment across all of the adjusted models (Model 1: OR=1,.29, 95% CI 1.10 – 1.52; Model 5: OR=1.27, 95% CI 1.101 – 1.59). Males compared with females (female vs. male OR, 95% CI in the fully adjusted model: 0.77 [0.63 – 0.95]), blacks compared with whites (OR, 95% CI in the fully adjusted model: 1.78 [1.47 – 2.15]) and individuals with less than high school degree compared to college graduates and above also had higher odds of cognitive impairment (OR, 95% CI in the fully adjusted model: 1.59 [1.22 – 2.07]). Income level did not show any significant association with cognitive impairment in the fully adjusted model (model 5). Additionally, in the full adjusted model, depressive symptoms (OR=1.70, 95% CI 1.30 – 2.24) and ARIC stroke risk score (third vs first quartile: OR=1.40, 95% CI 1.06 – 1.86; fourth vs. first quartile: OR=1.80, 95% CI 1.33 – 2.45) were significantly associated with a higher likelihood of cognitive impairments.

Our class level analyses of disparities across ACH use and cognitive impairment (Table 5) illustrated that only antidepressant use was significantly associated with a

higher likelihood of cognitive impairment across all the adjusted models (in the fully adjusted model: OR=1.44, 95% CI 1.01 – 2.04). Similar to the prior analyses, we did not find any significant ACH class-covariate interactions. For antidepressant users, the fully adjusted model also illustrated that gender (female vs. male: OR=0.71, 95% CI 0.56 – 0.89), race (black vs. white: OR=1.82, 95% CI 1.49 – 2.22), education (<high school vs. >college: OR=1.57, 95% CI 1.20 – 2.05), depressive symptoms (OR=1.70, 95% CI 1.30 – 2.23), and ARIC stroke risk score (fourth vs. first quartile: OR=1.65, 95% CI 1.01 – 2.73) were independently associated with cognitive impairments. All of these covariates also were significant predictors of cognitive impairments across all other ACH class level analyses.

Discussion

Our study found that antidepressants were the most widely used ACH, and of these, amitriptyline and paroxetine were the most frequently prescribed antidepressants among older adults. Our findings suggest that females across both the races were more likely than males to receive ACHs. White females were the most likely to receive an ACH. For users, we observed disparities across all of the domains of health disparities except for rurality. Females compared with males, whites compared with blacks, and individuals with lower income and education had higher odds of receiving antidepressants. While we did not find any significant ACH-covariate interaction, suggesting the association between ACH and cognitive decline is relatively consistent across subpopulations. For class specific ACH use, only antidepressants were associated with cognitive impairments in the fully adjusted model. Similar to the analyses of ACH use as a whole, we found that males

compared with females, blacks compared with whites, and individuals with lower income and education were more likely to have cognitive impairment. Additionally, depressive symptoms and ARIC stroke risk scores were significantly associated with cognitive impairment across all of the analyses.

Prior studies have found that women are more likely than men to be diagnosed with depression and are more likely to take antidepressants.[35-37] Moreover, whites have better access to psychiatric services than blacks and also more likely to take antidepressants.[36,37] All of these factors support our findings that whites, especially white females, are being exposed to more ACHs and particularly to antidepressants. However, unlike our study, none of these studies focused exclusively on older adults. Due to the altered pharmacokinetics associated with advanced age, extra care should be taken in prescribing antidepressants, specially the tricyclic antidepressants (TCAs), in older adults.[38] Amitriptyline, a TCA, which is the most frequently prescribed antidepressant in our study adds more concern in this regard. A recent case-control study among older adults (age 65-99) by Richardson et al. found that antidepressants, antiparkinsonian agents, and drugs to treat urinary incontinence were associated with an increased risk of dementia.[39] The five most common ACHs according to the researchers were amitriptyline, dosulepin, paroxetine, oxybutynin, and tolterodine which were consistently associated with incident dementia .[39] In our study, all the aforementioned drugs except for dosulepin (which is not available in the US) were the most frequently prescribed antidepressants (amitriptyline and paroxetine) and antimuscarinics, that is, drugs to treat urinary incontinence (oxybutynin and tolterodine). Consistent with this study, we also found that antidepressants were significantly associated with cognitive impairments in older adults.

Although the antimuscarinics did not show significant association with cognitive impairment in the fully adjusted analyses, they were found to be significant when we adjusted for demographics and socioeconomic characteristics only (table 5, model 2). This is likely due to sample size. While in our study, females compared with males showed higher odds of using ACH across all the drug classes, males consistently demonstrated higher odds of cognitive impairment than females across all the adjusted models. This finding is consistent with some of the prior research in this area. McCarrey et al. found that men have a higher rate of age-related cognitive decline than women.[40] The authors concluded that societal changes, financial status, and brain structure and function could be associated with the better outcome among older women. Van Exel et al. also found that women had a better cognitive function than men.[41] Similar results also were obtained in a study that measured gender differences across the prevalence of mild cognitive impairment.[42] However, opposing results suggest that females have higher odds of cognitive impairment than males. For example, Sohn et al. found that females with Alzheimer's disease had a higher decline in cognitive score than males.[43] Lin et al. also found that women with mild cognitive impairments had a greater rate of cognitive and functional progression than men.[44] Due to the contrasting evidence, careful interpretation of the results and further research are needed prior to drawing any definitive conclusion.

Education and income were found to be linked with cognitive function in prior studies. These studies demonstrated lower education among blacks compared to whites.[35,45] More and better education accounts for better learning opportunities, improves health literacy, and improves overall job accomplishments and income.[45-47] All of these factors, in turn, can influence the assessment of cognitive status in older adults.[45-

[47] Stern et al. found that higher education and income can reduce the risk of Alzheimer's disease.[46] Prior research also found that individuals with lower income and education often live in poor neighborhoods with substandard healthcare facilities and have limited access to subspecialty physicians,[48,49] which can lead to inappropriate prescription. Our study findings that blacks and individuals with lower education had higher cognitive impairment support the notions proposed by the prior studies.

Our initial plan was to study disparities in cognitive impairment with the use of all the nine ACH classes listed in the Beers Criteria.[7] However, we could not conduct multivariable analyses on antiemetics, antipsychotics, antiparkinsonian agents, and antiarrhythmics due to limited sample size. Additionally, although our class specific analyses of ACH use did not find any significant association with cognitive impairment except for antidepressants, the OR point estimates continuously remained elevated even in the fully adjusted models (except for the skeletal muscle relaxants). Wider 95% confidence intervals across these ACH classes illustrate that this could be a function of small sample size. We should be cautious regarding the clinical interpretation of these findings.

Our study has some limitations. We used baseline ACH use to assess disparities in cognitive impairment in older adults. We did not have information regarding the duration of medication exposure which can confound the outcome of interest. We cannot establish causality due to the cross-sectional nature of the study. Additionally, although the trained REGARDS study personnel performed rigorous pill bottle assessment, medication doses were not recorded. Hence, we could not establish any dose-response relationship. And finally, the small sample size may be a driving factor for insignificant results in some ACH

class specific analyses of cognitive impairment. Small sample size also hindered us from conducting multivariable analyses for some ACH classes.

This is the first attempt to comprehensively evaluate disparities in cognitive impairment with ACH use across the three domains of health disparities. While we did not find disparities in cognitive impairment with ACH use, we did find demographic and socioeconomic disparities in ACH use and in cognitive impairment, individually. Future studies should seek to better understand factors contributing to the disparities to help develop interventions.

References

1. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med.* 2002;162(20):2269-2276.
2. Schubert CC, Boustani M, Callahan CM, et al. Comorbidity profile of dementia patients in primary care: are they sicker? *J Am Geriatr Soc.* 2006;54(1):104-109.
3. Boustani M, Peterson B, Harris R, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. *Screening for Dementia*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2003.
4. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging.* 2009;4:225-233.
5. Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis. *Br J Clin Pharmacol.* 2015;80(2):209-220.
6. Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry.* 2001;62 Suppl 21:11-14.
7. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.
8. US healthcare spending compared to others. Peterson-Kaiser Health System Tracker. http://www.healthsystemtracker.org/chart-collection/health-spending-u-s-compare-countries/?_sf_s=health+spending#item-start. Accessed July 7, 2017.
9. Squires DA. The U.S. health system in perspective: a comparison of twelve industrialized nations. Issues in International Health Policy. 2011. http://www.commonwealthfund.org/~/media/Files/Publications/Issue%20Brief/2011/Jul/1532_Squires_US_hlt_sys_comparison_12_nations_intl_brief_v2.pdf. Accessed July 7, 2017.
10. Gary Claxton CC, Selena Gonzales, Rabah Kamal, Larry Levitt. Measuring the quality of healthcare in the U.S. https://www.healthsystemtracker.org/brief/measuring-the-quality-of-healthcare-in-the-u-s/#item-start. Accessed April 22, 2018. 2015.
11. NIH. NIH announces Institute on Minority Health and Health Disparities. Transition from center to institute highlights expanded responsibilities. https://www.nih.gov/news-events/news-releases/nih-announces-institute-minority-health-health-disparities. Accessed September 01, 2018. 2010.
12. Graham H. Social determinants and their unequal distribution: clarifying policy understandings. *Milbank Q.* 2004;82(1):101-124.
13. Howard G. Ancel Keys Lecture: Adventures (and misadventures) in understanding (and reducing) disparities in stroke mortality. *Stroke.* 2013;44(11):3254-3259.
14. AHRQ. Understanding quality measurement. https://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/chtoolbx/understand/index.html. Accessed October 24, 2017.
15. FAMILIESUSA. Measuring Health Care Quality: An Overview of Quality Measures. 2014. http://familiesusa.org/sites/default/files/product_documents/HSI%20Quality%20Measurement_Brief_final_web.pdf. Accessed October 24, 2017.
16. Donabedian A. The quality of care: How can it be assessed? *JAMA.* 1988;260(12):1743-1748.
17. Felton M, Hanlon JT, Perera S, Thorpe JM, Marcum ZA. Racial differences in anticholinergic use among community-dwelling elders. *Consult Pharm.* 2015;30(4):240-245.
18. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology.* 2005;25(3):135-143.

19. Hansen RA, Khodneva Y, Glasser SP, Qian J, Redmond N, Safford MM. Antidepressant Medication Use and Its Association With Cardiovascular Disease and All-Cause Mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Ann Pharmacother.* 2016;50(4):253-261.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.
21. Wadley VG, McClure LA, Howard VJ, et al. Cognitive status, stroke symptom reports, and modifiable risk factors among individuals with no diagnosis of stroke or transient ischemic attack in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Stroke.* 2007;38(4):1143-1147.
22. Wilber ST, Lofgren SD, Mager TG, Blanda M, Gerson LW. An evaluation of two screening tools for cognitive impairment in older emergency department patients. *Acad Emerg Med.* 2005;12(7):612-616.
23. Fedewa SA, McClellan WM, Judd S, Gutierrez OM, Crews DC. The association between race and income on risk of mortality in patients with moderate chronic kidney disease. *BMC Nephrol.* 2014;15:136.
24. Espeland MA, Gu L, Masaki KH, et al. Association between reported alcohol intake and cognition: results from the Women's Health Initiative Memory Study. *Am J Epidemiol.* 2005;161(3):228-238.
25. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science.* 2003;301(5631):386-389.
26. Wadley VG, Unverzagt FW, McGuire LC, et al. Incident cognitive impairment is elevated in the stroke belt: the REGARDS study. *Ann Neurol.* 2011;70(2):229-236.
27. Lampela P, Paajanen T, Hartikainen S, Huupponen R. Central Anticholinergic Adverse Effects and Their Measurement. *Drugs Aging.* 2015;32(12):963-974.
28. Weiss N, Miller F, Cazaubon S, Couraud PO. The blood-brain barrier in brain homeostasis and neurological diseases. *Biochim Biophys Acta.* 2009;1788(4):842-857.
29. Pullicino PM, Wadley VG, McClure LA, et al. Factors contributing to global cognitive impairment in heart failure: results from a population-based cohort. *J Card Fail.* 2008;14(4):290-295.
30. Schafer JL. Multiple imputation: a primer. *Statistical Methods in Medical Research.* 1999;8(1):3-15.
31. Bennett DA. How can I deal with missing data in my study? *Aust N Z J Public Health.* 2001;25(5):464-469.
32. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med.* 1991;10(4):585-598.
33. Barzi F, Woodward M. Imputations of missing values in practice: results from imputations of serum cholesterol in 28 cohort studies. *Am J Epidemiol.* 2004;160(1):34-45.
34. Thacker EL, Gillett SR, Wadley VG, et al. The American Heart Association Life's Simple 7 and incident cognitive impairment: The REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *J Am Heart Assoc.* 2014;3(3):e000635.
35. National Academies of Sciences E, Medicine. *Communities in Action: Pathways to Health Equity.* Washington, DC: The National Academies Press; 2017.
36. Mundell EJ. U.S. Antidepressant Use Jumps 65 Percent in 15 Years. https://consumer.healthday.com/mental-health-information-25/antidepressants-news-723/u-s-antidepressant-use-jumps-65-percent-in-15-years-725586.html. Accessed August 27, 2018. 2017.
37. Laura A. Pratt DJB, Qiuping Gu. Antidepressant Use Among Persons Aged 12 and Over: United States, 2011–2014. https://www.cdc.gov/nchs/products/databriefs/db283.htm. Accessed August 27, 2018. 2017.

38. Page RL, 2nd, Linnebur SA, Bryant LL, Ruscin JM. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. *Clin Interv Aging.* 2010;5:75-87.
39. Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *Bmj.* 2018;361:k1315.
40. McCarrey AC, An Y, Kitner-Triolo MH, Ferrucci L, Resnick SM. Sex differences in cognitive trajectories in clinically normal older adults. *Psychol Aging.* 2016;31(2):166-175.
41. van Exel E, Gussekloo J, de Craen AJM, et al. Cognitive function in the oldest old: women perform better than men. *Journal of Neurology, Neurosurgery & Psychiatry.* 2001;71(1):29.
42. Neurology AAo. MEN MORE LIKELY TO HAVE PROBLEMS WITH MEMORY AND THINKING SKILLS. https://www.aan.com/PressRoom/Home/PressRelease/596. Accessed September 12, 2018. 2008.
43. Sohn D, Shpanskaya K, Lucas JE, et al. Sex Differences in Cognitive Decline in Subjects with High Likelihood of Mild Cognitive Impairment due to Alzheimer's disease. *Scientific Reports.* 2018;8(1):7490.
44. Lin KA, Choudhury KR, Rathakrishnan BG, Marks DM, Petrella JR, Doraiswamy PM. Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimers Dement (N Y).* 2015;1(2):103-110.
45. Zahodne LB, Manly JJ, Azar M, Brickman AM, Glymour MM. Racial Disparities in Cognitive Performance in Mid- and Late Adulthood: Analyses of Two Cohort Studies. *J Am Geriatr Soc.* 2016;64(5):959-964.
46. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA.* 1994;271(13):1004-1010.
47. Manly JJ, Jacobs DM, Touradji P, Small SA, Stern Y. Reading level attenuates differences in neuropsychological test performance between African American and White elders. *J Int Neuropsychol Soc.* 2002;8(3):341-348.
48. Wong ST, Regan S. Patient perspectives on primary health care in rural communities: effects of geography on access, continuity and efficiency. *Rural Remote Health.* 2009;9(1):1142.
49. VCU_Center_for_Society_and_Health. Why Education Matters to Health: Exploring the Causes. https://societyhealth.vcu.edu/work/the-projects/why-education-matters-to-health-exploring-the-causes.html#healthBenefits. Accessed August 27, 2018. 2015.

Table 1. Baseline Characteristics of the Study Population by Anticholinergic Drug Use

	ACH use (n = 13 623)			ACH use ¶ (n = 10 803)		
Characteristic	Yes (n = 1912)	No (n = 11 711)	*P* Value	Yes (n = 1549)	No (n = 9254)	*P* Value
Demographics						
Age, mean (SD), years	72.9 ± 5.9	72.7 ± 5.9	0.22	73.0 ± 5.9	72.7 ± 5.9	0.03
Female, n (%)	1257 (65.7)	6005 (51.3)	<0.0001	1070 (69.1)	5187 (56.1)	<0.0001
Black, n (%)	713 (37.3)	4471 (38.2)	0.46	577 (37.3)	3515 (38.0)	0.58
Income, n (%)			<0.0001			<0.0001
Less than $20,000	510 (26.7)	2387 (20.4)		387 (25.0)	1838 (19.9)	
$20,000- $34,999	555 (29.0)	3322 (28.4)		443 (28.6)	2594 (28.0)	
$35,000- $74,999	416 (21.8)	3247 (27.7)		339 (21.9)	2547 (27.5)	
≥ $75,000	109 (5.7)	1104 (9.4)		91 (5.9)	891 (9.6)	
Education, n (%)			<0.0001			<0.0001
Less than high school	362 (19.0)	1882 (16.1)		282 (18.3)	1403 (15.2)	
High school	557 (29.2)	3107 (26.6)		467 (30.2)	2501 (27.1)	
Some college	486 (25.5)	2903 (24.8)		385 (24.9)	2348 (25.4)	
College graduate and above	503 (26.4)	3803 (32.6)		411 (26.6)	2994 (32.4)	
Location of residence, n (%)			0.01			0.03
Isolated	30 (1.8)	259 (2.4)		26 (1.9)	202 (2.4)	
Small rural	125 (7.3)	613 (5.8)		101 (7.3)	506 (6.1)	
Large rural	219 (12.8)	1242 (11.7)		189 (13.7)	989 (11.8)	
Urban	1225 (78.1)	8535 (80.2)		1068 (77.2)	6666 (79.7)	
Medical conditions						
Diabetes, n (%)	580 (30.5)	2881 (24.7)	<0.0001	469 (30.5)	2270 (24.6)	<0.0001
CKD, n (%)	515 (26.9)	2415 (20.6)	<0.0001	410 (26.5)	1886 (20.4)	<0.0001
Physiological risk factors						
ARIC stroke risk score, median (25th-75th percentile)	8.4 [3.9-18.0]	8.8 [4.4-18.0]	0.31	8.2 [3.8-17.6]	8.3 [4.1-17.2]	0.92
Urinary creatinine, median (25th-75th percentile), mg/dL	107 [70-155]	117 [75-165]	<0.0001	106 [69-153]	116 [74-163]	<0.0001
Markers of mental health						
Mental component score of SF-12, mean (SD)	53.9 ± 9.1	55.4 ± 7.3	<0.0001	54.1 ± 8.9	55.4 ± 7.3	<0.0001
Perceived stress (PSS score), mean (SD)	3.5 (3.0)	2.9 (2.8)	<0.0001	3.5 (3.0)	2.9 (2.8)	<0.0001
Depressive symptoms (CES-D ≥ 4), n (%)	263 (13.8)	976 (8.3)	<0.0001	211 (13.6)	793 (8.6)	<0.0001
Health behaviors						
Alcohol use (drinks per week), n (%)			<0.0001			<0.0001
None	1381 (73.6)	7487 (65.3)		1113 (73.3)	5954 (65.6)	
Moderate	443 (23.6)	3552 (31.0)		364 (24.0)	2801 (30.9)	
Heavy	53 (2.8)	422 (3.7)		42 (2.8)	321 (3.5)	
Exercise per week, n (%)			<0.0001			<0.0001
None	856 (45.7)	4126 (35.9)		728 (47.9)	3364 (37.0)	
1 to 3 times	559 (29.8)	3839 (33.4)		439 (28.9)	2999 (33.0)	
4 or more	459 (24.5)	3535 (30.7)		354 (23.3)	2720 (30.0)	

¶ Excluding the patients with missing cognitive status. ACH: Anticholinergic drugs; CKD: Chronic Kidney Disease; CES-D: Center for Epidemiological Studies Depression scale

Table 2. Top 10 anticholinergic drugs used by the study participants

Serial Num	Drug type	n (%)
1	Amitriptyline	569 (13.3)
2	Paroxetine	466 (10.9)
3	Diphenhydramine	447 (10.5)
4	Cyclobenzaprine	396 (9.3)
5	Tolterodine	389 (9.1)
6	Oxybutynin	298 (7.0)
7	Meclizine	257(6.0)
8	Hydroxyzine	175 (4.1)
9	Nortriptyline	103 (2.4)
10	Promethazine	103 (2.4)

Table 3. Effects of different disparity parameters on different anticholinergic drug use

Characteristic	ACH use, OR (95% CI)	Antimuscarinic use, OR (95% CI)	Antihistamine use, OR (95% CI)	Skeletal muscle relaxant use, OR (95% CI)	Antidepressant use, OR (95% CI)	Antispasmodic use, OR (95% CI)
Gender						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	¶	¶	**1.26 (1.05 - 1.52)**	**1.59 (1.08 - 2.34)**	**1.72 (1.42 - 2.07)**	**1.88 (1.27 - 2.79)**
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	¶	¶	0.94 (0.77 - 1.13)	0.93 (0.64 - 1.36)	**0.63 (0.52 - 0.77)**	0.76 (0.51 - 1.13)
Income						
≥ $75,000	Ref	Ref	Ref	Ref	Ref	Ref
Less than $20,000	**1.71 (1.32 - 2.21)**	1.43 (0.88 - 2.33)	**1.72 (1.12 - 2.66)**	2.28 (0.91 - 5.75)	**1.59 (1.04 - 2.42)**	0.97 (0.45 - 2.09)
$20,000- $34,999	**1.51 (1.18 - 1.91)**	1.56 (0.99 - 2.46)	**1.55 (1.03 - 2.34)**	1.30 (0.53 - 3.21)	1.30 (0.87 - 1.95)	0.75 (0.37 - 1.55)
$35,000- $74,999	**1.27 (1.01 - 1.62)**	1.41 (0.89 - 2.21)	1.28 (0.85 - 1.93)	1.17 (0.47 - 2.89)	1.24 (0.83 - 1.85)	0.81 (0.40 - 1.63)
Education						
College graduate and above	Ref	Ref	Ref	Ref	Ref	Ref
Less than high school	1.16 (0.97 - 1.38)	0.83 (0.60 - 1.15)	1.14 (0.85 - 1.53)	1.43 (0.79 - 2.58)	**1.55 (1.17 - 2.06)**	1.32 (0.71 - 2.45)
High school	1.06 (0.92 - 1.23)	0.85 (0.65 - 1.11)	1.23 (0.96 - 1.56)	1.03 (0.60 - 1.78)	1.18 (0.92 - 1.51)	1.41 (0.85 - 2.33)
Some college	1.08 (0.94 - 1.25)	1.01 (0.78 - 1.30)	1.09 (0.85 - 1.40)	**1.67 (1.01 - 2.76)**	1.13 (0.88 - 1.44)	1.14 (0.68 - 1.92)
Location of residence						
Urban	Ref	Ref	Ref	Ref	Ref	Ref
Isolated	0.69 (0.47 - 1.02)	0.29 (0.09 - 1.01)	0.96 (0.53 - 1.73)	1.30 (0.47 - 3.58)	0.64 (0.33 - 1.25)	0.32 (0.06 - 2.33)
Small rural	1.22 (0.99 - 1.50)	0.83 (0.54 - 1.27)	**1.49 (1.09 - 2.04)**	0.46 (0.17 - 1.26)	1.33 (0.97 - 1.83)	1.02 (0.49 - 2.12)
Large rural	1.10 (0.94 - 1.28)	1.04 (0.77 - 1.39)	1.23 (0.95 - 1.58)	0.67 (0.36 - 1.25)	1.14 (0.89 - 1.47)	1.24 (0.75 - 2.05)
Significant interactions ¶						
Gender-race						
Female vs. Male; Race = Black	**1.28 (1.10 - 1.49)**	**1.41 (1.07 - 1.85)**	-	-	-	-
Female vs. Male; Race = White	**1.96 (1.74 - 2.20)**	**2.44 (1.95 - 3.07)**	-	-	-	-
Black vs. White; Gender = Female	**0.71 (0.64 - 0.80)**	0.84 (0.68 - 1.02)	-	-	-	-
Black vs. White; Gender = Male	1.09 (0.93 - 1.27)	**1.45 (1.08 - 1.96)**	-	-	-	-

¶ Significant gender-race interaction; ACH: Anticholinergic drug use. Bold refers to P<0.05.

We could not conduct multivariable analyses for antiemetics, antipsychotics, antiparkinsonian agents, and antiarrhythmics due to the lack of sample size.

Table 4. Association between anticholinergic drug use and cognitive impairment and the effect of health disparities on this relationship

Characteristics	**Model 1, OR (95% CI)**	**Model 2, OR (95% CI)**	**Model 3, OR (95% CI)**	**Model 4, OR (95% CI)**	**Model 5, OR (95% CI)**
ACH use					
No	Ref	Ref	Ref	Ref	Ref
Yes	**1.29 (1.10 - 1.52)**	**1.35 (1.13 - 1.61)**	**1.30 (1.06 - 1.60)**	**1.35 (1.09 - 1.67)**	**1.27 (1.01 - 1.59)**
Gender					
Male	-	Ref	Ref	Ref	Ref
Female	-	**0.65 (0.57 - 0.75)**	**0.80 (0.66 - 0.96)**	**0.79 (0.65 - 0.96)**	**0.77 (0.63 - 0.95)**
Race					
White	-	Ref	Ref	Ref	Ref
Black	-	**2.00 (1.74 - 2.31)**	**1.75 (1.47 - 2.08)**	**1.78 (1.48 - 2.13)**	**1.78 (1.47 - 2.15)**
Income					
≥ $75,000	-	Ref	Ref	Ref	Ref
Less than $20,000	-	**1.61 (1.15 - 2.25)**	**1.48 (1.02 - 2.15)**	**1.47 (1.08 - 2.16)**	1.34 (0.90 - 2.01)
$20,000- $34,999	-	**1.55 (1.13 - 2.13)**	**1.44 (1.01 - 2.03)**	**1.47 (1.03 - 2.11)**	1.42 (0.98 - 2.05)
$35,000- $74,999	-	1.11 (0.81 - 1.52)	1.09 (0.77 - 1.53)	1.12 (0.78 - 1.60)	1.08 (0.75 - 1.55)
Education					
College graduate and above	-	Ref	Ref	Ref	Ref
Less than high school	-	**2.13 (1.73 - 2.63)**	**1.66 (1.30 - 2.12)**	**1.58 (1.23 - 2.03)**	**1.59 (1.22 - 2.07)**
High school	-	**1.31 (1.08 - 1.59)**	1.21 (0.97 - 1.50)	1.13 (0.91 - 1.41)	1.13 (0.90 - 1.43)
Some college		1.02 (0.83 - 1.25)	0.85 (0.67 - 1.06)	0.82 (0.65 - 1.04)	0.82 (0.64 - 1.05)
Location of residence					
Urban	-	Ref	Ref	Ref	Ref
Isolated	-	0.93 (0.58 - 1.50)	0.92 (0.54 - 1.55)	0.91 (0.53 - 1.57)	0.99 (0.57 - 1.72)
Small rural	-	1.23 (0.94 - 1.61)	1.35 (1.00 - 1.83)	1.34 (0.98 - 1.82)	1.25 (0.90 - 1.75)
Large rural	-	0.96 (0.77 - 1.19)	0.93 (0.73 - 1.19)	0.93 (0.72 - 1.20)	0.95 (0.73 - 1.24)

ACH: Anticholinergic drugs; Outcome of interest: Cognitive impairment; Odds ratios (OR) are for drug users vs. non-users; Bold refers to P<0.05.

Model 1 reflects the unadjusted logistic regression model that accounted for only the ACH exposure. Model 2 was adjusted for demographics and socioeconomic characteristics. Model 3 adjusted for all the model 2 covariates plus patients' medical condition and physiologic risk factors. Model 4 was adjusted for model 3 covariates plus measures of health behaviors. Model 5 was adjusted for all the model 4 covariates plus markers of mental health.

Medical conditions included diabetes (self-reported) and chronic kidney disease, CKD (defined as estimated glomerular filtration rate (eGFR) <60 ml/min/ 1.73 m^2. Physiologic risk factors included the atherosclerosis risk in communities (ARIC) study stroke risk score and urinary creatinine levels. Measures of health behaviors included alcohol use (defined as none; moderate: 1-7 for women, 1-14 for men; and heavy: ≥7 drinks/week for women, ≥14 drinks/week for men) and exercise (defined as none; 1 to 3 times; and 4 or more times/week). Markers of mental health were assessed by the mental component scores (MCS) of the Short Form-12 (SF-12), presence of depressive symptoms (defined as a score ≥4 of the Centers for Epidemiologic Study Depressive Scale [CES-D]), and Cohen's Perceived Stress Scale(PSS) score.

Table 5. Association between different classes of anticholinergic drug use and cognitive impairment and the effect of health disparities on this relationship

ACH drug classes	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)	Model 4, OR (95% CI)	Model 5, OR (95% CI)
Antidepressants	**1.40 (1.08 - 1.82)**	**1.56 (1.18 - 2.05)**	**1.55 (1.13 - 2.14)**	**1.63 (1.18 - 2.25)**	**1.44 (1.01 - 2.04)**
Antihistamines	1.22 (0.93 - 1.60)	1.20 (0.89 - 1.61)	1.22 (0.86 - 1.72)	1.23 (0.86 - 1.75)	1.14 (0.78 - 1.67)
Skeletal muscle relaxants	0.93 (0.51 - 1.69)	0.70 (0.35 - 1.40)	0.55 (0.22 - 1.37)	0.56 (0.23 - 1.41)	0.52 (0.19 - 1.43)
Antimuscarinics	**1.35 (1.01 - 1.80)**	**1.44 (1.06 - 1.97)**	1.22 (0.83 - 1.81)	1.29 (0.87 - 1.91)	1.19 (0.78 - 1.82)
Antispasmodics	1.20 (0.68 - 2.11)	1.26 (0.67 - 2.35)	1.21 (0.57 - 2.55)	1.25 (0.59 - 2.65)	1.44 (0.67 - 3.08)

ACH: Anticholinergic drugs; Odds ratios (OR) are for drug users vs. non-users; Bold refers to P<0.05.

Model 1 reflects the unadjusted logistic regression model that accounted for only the ACH exposure. Model 2 was adjusted for demographics and socioeconomic characteristics. Model 3 adjusted for all the model 2 covariates plus patients' medical condition and physiologic risk factors. Model 4 was adjusted for model 3 covariates plus measures of health behaviors. Model 5 was adjusted for all the model 4 covariates plus markers of mental health.

Medical conditions included diabetes (self-reported) and chronic kidney disease, CKD (defined as estimated glomerular filtration rate (eGFR) <60 ml/min/ 1.73 m^2. Physiologic risk factors included the atherosclerosis risk in communities (ARIC) study stroke risk score and urinary creatinine levels. Measures of health behaviors included alcohol use (defined as none; moderate: 1-7 for women, 1-14 for men; and heavy: ≥7 drinks/week for women, ≥14 drinks/week for men) and exercise (defined as none; 1 to 3 times; and 4 or more times/week). Markers of mental health were assessed by the mental component scores (MCS) of the Short Form-12 (SF-12), presence of depressive symptoms (defined as a score ≥4 of the Centers for Epidemiologic Study Depressive Scale [CES-D]), and Cohen's Perceived Stress Scale(PSS) score.

Chapter Five | Discussion

The overall objectives of this study were to assess the association between 1) potentially inappropriate medication (PIM) use and different disparity parameters (gender, age, race, income, education, and rural or urban areas), 2) PIM use and all-cause mortality and the effect of disparity parameters on this relationship, and 3) anticholinergic drug use and cognitive impairment and the effect of disparity parameters on this relationship. This chapter summarizes the overall research findings and its implications as well as directions for future research.

5.1 Findings and Implications for Aim 1

At first, we investigated the association between demographic factors and socioeconomic status (gender, age, race, income, education, and rural or urban areas) and appropriateness of medication use. We further stratified the PIM use across prescription-only and over-the-counter (OTC) drugs. We observed significant differences in PIM use across gender, race, income, education, and location of residence. White females compared with white males and black males compared with white males had higher odds of receiving prescription-only PIMs. Prior research has found that there is a rise in the use of prescription opioids among white females.[184] Additionally, white women are more likely than men to be diagnosed with depression and are more likely to take

antidepressants.[96,185,186] Opioids and many antidepressants are considered as potentially inappropriate in older adults.[9] Our findings are consistent with some of these studies focusing on gender-race inequality. Lower income and education also were significant predictors of PIM prescription. Males compared with females, individuals with lower education, and residing in rural areas also demonstrated higher odds of using OTC PIMs. We consistently observed that individuals with higher medication use had higher odds of using PIMs in both blacks and whites. Past studies found that lower income individuals have limited access to care and have inadequate health coverages.[30,96,187] Studies have shown that higher education is linked to better job, better income, and better health literacy and behavior.[188] Lower health literacy could be an influential factor for using more OTC PIMs. Moreover, individuals with lower income and education are more likely to live in poor neighborhoods which may lack resources for good health.[188] Similarly, individuals living in the rural areas lack timely access to healthcare providers and have limited availability of subspecialty physicians.[85] All these factors can interplay and contribute to inappropriate use of medications in the population with lower income, education, and living in rural areas.

Another measure of PIM use is the use of clinically significant drug-drug interactions (DDIs). We observed that whites compared with blacks, males compared with females and individuals living in the rural areas had higher odds of having DDIs. Older age and total number of medication use also were significant predictors of having DDIs. Prior studies found that older adults often require multiple medications to manage their multiple chronic conditions which can increase the likelihood of DDIs.[108] Moreover, whites

are more likely than blacks to receive more medications.[185,189-191] Our results are consistent with the findings of the prior studies.

Finally, we conducted a sensitivity analysis to assess the effect of different disparity parameters on total number of medications and total number of PIMs use. We observed that females compared with males, blacks compared with whites, individuals with lower income, education, and residing in rural areas had higher medication use and PIM prevalence than the individuals with higher income, education, and residing in urban areas.

This is the first study to assess the relationship between health disparities and PIM use as a whole along with the specific subset of PIM in the Beers list. Also, this is the first study that used 2015 Beers Criteria to identify PIM use and assess its relationship with health disparities. Another measure of PIM use is based on known DDIs which is an indicator of inappropriate drug use. Additionally, this is the first study that assessed the relationship between health disparities and the use of interacting drugs together. This study has informed us about both prescription and nonprescription PIM use patterns in the minority population and will increase awareness among the prescribers, which we believe, has the potential to shift clinical practice paradigms.

The root cause of health disparities may be very complex and difficult to fully comprerhend.[96] There may be implicit bias from the provider's perspective. Experts often say that patient-provider concordance in terms of gender, social class, age, ethnicity, race, language, sexual orientation, beliefs about health and illness can help alleviate the problem.[6,192] However, debate exists as to whether this concordance would help

overcome health disparities.[193,194] Studies showed that patients prefer providers who treat them more respectfully rather than the providers of their own race or ethnicity.[195,196] Pharmacists also can play an important role in reducing health disparities in terms of PIM use. For example, when they receive a new prescription for a drug which is potentially inappropriate for older patients, they can consider discussing it with the prescriber for a safer but equally efficacious alternative regardless of the race, gender, or other pertaining disparity parameters of the patients. While advising the patients about OTC drugs, pharmacists can recommend the drugs that are not considered as PIMs. Appropriate training programs for the pharmacists on the harmful effect of PIMs and the related disparities can help reduce this problem.

5.2 Findings and Implications for Aim 2

Our study assessed how the baseline PIM use and DDIs can be related to all-cause mortality and whether there are any disparities in this relationship. The association of all-cause mortality with PIM use and DDIs were studied by sequentially adjusted Cox proportional Hazard models. Due to the cross-sectional nature of the PIM and DDI exposure, we conducted a series of predictive modelling to test the impact of censoring follow-up intervals. Apart from the full follow-up time, that is, follow-up time up to March 31, 2016, we stratified the follow-up time intervals as 0-2 years, 0-4 years, and 0-6 years.

The unadjusted hazard ratios (HRs) across all the models demonstrated significantly higher risks of mortality with PIM use and DDIs. However, in our iterative model building approach, we observed interesting differences in HRs across different

censored follow-up time intervals. We observed that potential PIM/DDI related all-cause mortality can partly be explained by the disparity parameters and partly by other medical or physiologic risk factors. For example, for the full follow-up time, medical conditions like stroke and atrial fibrillation (Afib) were significant predictors of mortality only among the individuals with PIM use. We also observed similar trends in other censored follow-up time intervals. This suggests that while PIM use may not be a direct cause of all-cause mortality, it is related to other factors that can increase the risk of mortality. This is, in fact, consistent with the prior studies. For example, Afib is known to be associated with an increased risk of all-cause mortality.[197,198] Amiodarone, an antiarrhythmic drug, is considered to be a PIM for older adults according to the Beers Criteria and are recommended to avoid as the first-line therapy in patients with Afib due to its greater toxicity than other antiarrhythmic agents.[9] Careful consideration in medication prescription and choosing safer alternatives can improve such outcomes.

Our study demonstrated that lower income and education were associated with higher risks of mortality with PIM use. Individuals with lower income and education tend to reside in the neighborhoods with low healthcare facilities.[199] These groups of patients often have limited availability of subspecialty physicians. All these factors can contribute to inappropriate prescription, and ultimately higher risk of mortality. We also found that, whites compared with blacks had a higher risk of mortality with PIM use. Additionally, past studies also found that whites are more likely than blacks to receive more medications.[190,191] Polypharmacy can lead to more PIM use and in turn increase the risk of mortality.[200] In our study, we also found that higher medication use and higher PIM use

was significantly associated with a higher risk of mortality. However, it is possible that participants with higher medication use are sicker and have higher likelihoods of mortality. Moreover, more medication use can be associated with more PIM use. So, it is also possible that PIM use is a marker of more medication use and individuals with more PIM use can be sicker. All these factors can be interlinked and contribute to higher risk of mortality. This could be a sign of endogeneity.[201] Further research is needed to assess this phenomenon which is beyond the scope of this research project.

This is the first attempt to evaluate disparities across all-cause mortality with PIM use. Our study, to some extent, found significant disparities in all-cause mortality with PIM use. Although interpretations across different censored time intervals are slightly different, it is quite apparent that the use of PIMs can influence some other drivers of all-cause mortality. Proper awareness and training programs tailored towards the healthcare providers can help reduce the adverse events with PIM prescription and associated disparities. Although due to the cross-sectional nature of the PIM measurement we could not establish any causal relationship, this study opens a new dimension in disparity research which will instigate further research to better understand the contributing factors of such disparities in order to develop appropriate intervention techniques.

5.3 Findings and Implications for Aim 3

At first, we studied the odds of anticholinergic drug (ACH) use across different population subgroups defined by gender, race, income, education, and location of residence. We also studied disparities across class specific ACH use. Further, we studied disparities in cognitive impairment with ACH use by sequentially adjusted multivariable

logistic regression models. Our findings suggest that females compared with males across both the races were more likely to receive ACHs among which white females showed the most likelihood of receiving ACHs. We found that antidepressants were the most frequently prescribed ACH and observed that females compared with males, whites compared with blacks, and individuals with lower income and education had higher odds of receiving antidepressants. While we did not find any significant ACH-covariate interaction, we did find that males compared with females, blacks compared with whites, and individuals with lower education had higher likelihoods of cognitive impairments. For class specific ACH use, only antidepressants were associated with cognitive impairments in the fully adjusted model. Similar to the analyses of ACH use as a whole, we found that males compared with females, blacks compared with whites, and individuals with lower income and education were more likely to have cognitive impairment. Additionally, depressive symptoms and ARIC stroke risk scores were significantly associated with cognitive impairment across all of the analyses.

Past studies have found that women are more likely than men to be diagnosed with depression and have more antidepressants.[96,185,186] Moreover, whites have more access to psychiatric services than blacks and also more likely to take antidepressants.[185,186] All of these support our findings that whites, especially white females, are being exposed to more ACHs and particularly to antidepressants. A recent study by Richardson et al. found that antidepressants, antiparkinsonian agents, and drugs to treat urinary incontinence were associated with an increased risk of dementia.[202] Our study also is in line with these findings. McCarrey et al. found that men than women have

a higher rate of age-related cognitive decline.[203] Van Exel et al. also found that women had a better cognitive function than men.[204] Similar results also were obtained in a study that measured gender differences across the prevalence of mild cognitive impairment.[205] Consistent with these findings, we observed that males compared with females had higher odds of cognitive impairment across all the adjusted models event though the females showed higher odds of using ACHs across all the drug classes. However, studies by Sohn et al. and Lin et al. demonstrated contradicting evidence where they found that females than males had a higher decline in cognitive function.[206,207] Thus, careful interpretation of the results and further research are needed prior to drawing any definitive conclusion .

Consistent with the prior research, our study demonstrated higher cognitive impairments in blacks and individuals with lower education in the fully adjusted analysis. Lower education levels were observed among blacks compared with whites in prior studies.[96,208] It has been found that more and better education accounts for better learning opportunities, improves health literacy, and improves overall job accomplishments and income.[208-210] All of these factors, in turn, can influence the performance of cognitive status in older adults.[208-210] Stern et al. also found that higher education and income can reduce the risk of Alzheimer's disease.[209]

This is the first attempt to comprehensively evaluate disparities in cognitive impairment with ACH use across the three domains of health disparities, including: 1) socioeconomic status; 2) location of residence (e.g., rural vs urban setting); and 3) obstacles related to race. While we did not find disparities in cognitive impairment with

ACH use, we did find demographic and socioeconomic disparities in ACH use and in cognitive impairment, individually. Awareness among both the physicians and pharmacists regarding the appropriate use of ACHs, especially in older adults, is essential to reduce the adverse events associated with ACHs. Appropriate training programs to overcome health disparities and strict maintenance of the evidence-based guidelines for prescribing can help improve the situation.

5.4. Limitations

This study has several limitations. We only used the 2015 Beers Criteria to identify PIMs. There are other explicit criteria to identify PIMs which have shown differences in detecting PIMs in prior studies.[211,212] However, the Beers criteria was developed in the US and is the most widely used tool for PIM identification.[124] Since we are looking for disparities in PIM use in the US population, we believe that the Beers Criteria is an appropriate tool for PIM identification for our study. Still, it is possible to have some misclassification bias. Moreover, defining all-cause PIM may be non-specific and lead to overestimation of PIM use. The 2015 Beers Criteria contains a list of PIMs for older adults along with the categorization of the quality of evidence (high, moderate, and low) and strength of recommendation (strong, weak, and insufficient).[9] We did not consider those while defining PIMs.

Information regarding the medications was obtained by the trained Examination Management Services, Inc. (EMSI) personnel where the participants were asked to provide information regarding their medication use within the past two weeks. There is a

chance of recall bias and it is possible that we did not have full information regarding the participants' medication use patterns. Additionally, although the trained personnel did perform rigorous pill bottle assessment, medication doses were not recorded. As a result, we could not establish a dose-response relationship. We also did not have information regarding the provider's characteristics. As a result, we do not know the pattern of the prescribers and their prescribing behavior. However, we did have information regarding the participants' residence status (rural/urban) which could help us to understand the nature of the surrounding healthcare facilities.

The biggest limitation of this study is the cross-sectional baseline measurement of PIM exposure. It is possible that patients have switched or stopped the medication, yet we classified them as exposed. Our exposure measurement may be subject to misclassification bias since we did not have a longitudinal measurement of PIM use. However, baseline PIM use has been employed to predict longitudinal outcomes in prior studies.[213,214] A recent study by Karuturi et al. used baseline PIM measurement to predict all-cause mortality, emergency room visit, hospitalization or composite endpoint of all the aforementioned outcomes in patients with colorectal and breast cancer.[213] Cross et al. also used baseline PIM measurement to predict all-cause mortality in 3-year follow-up period.[214] Hansen et al. used the REGARDS data to predict all-cause mortality and cardiovascular outcomes using the baseline antidepressant use.[164] The authors anticipated that the baseline antidepressant users might still be on their medications after two-years of follow-up. We also stratified our censored follow-up time period to see how far in the process the baseline PIM use can predict mortality. Our consistent findings

across all the censored follow-up time intervals are indicative of probable method validity. Still, there is a high likelihood of misclassification bias. The Beers Criteria provides a list of various PIMs across a variety of therapeutic classes.[9] All the medications may not have the same exposure window. A class specific analyses could have given a better exposure definition. However, that was beyond the scope of our study since we wanted to explore disparities across all-cause mortality with PIM use as a whole.

5.5 Future Research Directions

Our research findings and the limitations underscore the need for further research in this regard. Our study did find disparities in the appropriateness of medication use and future studies should primarily focus on overcoming such disparities. PIM use, although may not be a direct cause of mortality, can influence some other drivers of all-cause mortality. Medication prescription is a process measure and according to the Donabedian framework, this inappropriate clinical process could be the result of an inappropriate structure of care.[55,57] Initial focus of the future research, thus, should concentrate on improving the structure of the care.

Health disparities are often attributed to the implicit biases from the providers' perspective.[215] Due to the implicit biases, physicians are found to treat patients differently based on their race, ethnicity, or gender rather than the actual underlying conditions.[193,216] Experts often suggest for patient-provider concordance to overcome such biases.[193,194] However, debate exists as to whether this concordance would help overcome health disparities.[6] Studies showed that patients prefer providers who treat them more

respectfully rather than the providers of their own race or ethnicity.[195,196] However, none of these studies were conducted considering the disparities in PIM use or DDIs. Similar studies in the context of appropriate medication use would be interesting to look at. Additionally, research pertaining to behavioral intervention to overcome implicit bias may help understand the contributing factors to such disparities and alleviate the problem.[217]

One important issue in the disparity research revolves around the barriers to care. It can be studied from both the patients' and providers' perspective. Prior research suggested that more diversity among the physicians, that is, more physicians from the underrepresented groups can help improve access to care for minority populations and in turn lower health disparities.[77,218] We do know that this might improve patient-centeredness and improve communication;[192] however, we do not know whether this translates into good quality of care in terms of improved medication prescription. It also would be interesting to know what barriers the physicians are facing that prompts them to prescribe differently for different population subgroups. Research should pay special attention on the nature of the physicians, their socioeconomic and ethnic backgrounds, and their specialty of care.

Performance evaluation of the clinicians can help improve the situation. However, there is no standardized yardstick to measure clinical performance of the doctors.[219,220] Federal health programs can support research to develop such performance measures to guide evidence based decision making.[219] Additionally incentivizing the providers based on their performance can promote health equity.[219] However, a recent study by Roberts et al. found that Medicare pay-for-performance did not improve the quality of care

or reduce the healthcare cost.[221] Gupta et al. also found that incentivizing and penalizing physicians or hospitals based on arbitrary performance measures of hospital admission can increase the death rates among patients with heart failure.[222] All of these emphasize the fact that more research is needed from the policy standpoint to develop uniform standardized yardstick which can help improve healthcare quality and eliminate disparities in the long run. Additionally, the policymakers should focus on developing a low-cost and consumer-friendly insurance coverage that can help improve the overall health condition of the low-income individuals.

Regardless of disparities, PIM prevalence itself is a big problem. High PIM prevalence was observed in our study. Strict implementation of evidence-based guidelines while prescribing for older adults can improve the situation. More research on developing health information technologies that can flag the inappropriate prescriptions or DDIs in hospital and/or pharmacy settings is essential. Pharmacists also can play an important role in reducing health disparities in terms of PIM use. For example, when they receive a new prescription for a drug which is potentially inappropriate for older patients, they can consider discussing it with the prescriber for a safer but equally efficacious alternative regardless of the race, gender, or other pertaining disparity parameters of the patient. While advising the patients about OTC drugs, pharmacists can recommend the drugs that are not considered as PIMs. Appropriate training programs for the pharmacists on the harmful effect of PIMs and the related disparities and incentivizing them can help reduce this problem.

More federally funded training programs in cultural competence for both the physicians and pharmacists may help overcome health disparities.[219] Studies also can focus on training programs for both the physicians and pharmacists to help lower PIM prescriptions. Development of more care network and making physicians available in the rural or underserved areas can also improve the situation. As a whole, a good structure of care can lead to a good process of care which in turn will result in an improved outcome.

Additionally, considering our methodological limitations, the following research could also be conducted: we only used the Beers Criteria to identify PIMs. Another popular tool for this purpose is the Screening Tool of Older Persons (STOPP) and Screening Tool to Alert to Right Treatment (START) which are mainly used in European countries since many drugs in the Beers list are not available in the European market.[124] Prior studies showed differences between the two criteria in detecting PIM use.[211,212] Although both the tools agree on some PIMs, there are variabilities in their content. For example, all the tricyclic antidepressants are considered as potentially inappropriate in patients with a history of falls, fractures, syncope, and delirium according to the Beers Criteria[9] while the STOPP specifies them as PIM with dementia, glaucoma, arrhythmias, constipation, opioids, calcium channel blockers, benign prostate hypertrophy, and urinary retention.[124] Future studies should seek to comparatively analyze the different tools of PIM identification in the context of health disparities.

The Beers Criteria provides a list of various PIMs across a variety of therapeutic classes. We did not consider any class specific definition rather used all-cause PIMs while defining PIM exposure (except for the anticholinergic drug exposure in aim 3). All the

medications may not have the same exposure window. A class specific analyses could have given a better exposure definition. In future, studies should focus on disparities across different classes of PIMs. Additionally, future studies can focus on defining PIMs based on the quality of evidence and strength of recommendation and then comparatively study disparities across different definitions of PIMs.

We used the baseline medication information to predict mortality. Due to such cross-sectional design, we could not establish causality. In future, the studies should focus on using longitudinal PIM measurements and associated outcomes and whether there are any disparities in this relationship. Additionally, we studied the association between baseline PIM use and the baseline cognitive impairment. A longitudinal approach would have given us a more robust measurement. Moreover, we used Six-Item Cognitive Screener (SIS) to measure cognitive impairment. There are many other tools to measure cognitive function.[223] A comparative study among different tools in the context of health disparities would be very interesting to look at in future. Furthermore, rather than merely considering all-cause cognitive impairment, future studies also can focus on disease-specific cognitive impairments. We studied all-cause mortality and cognitive impairment with PIM use and the pertaining disparities. However, future studies should look at the impact of cognitive impairment, caused by PIM use, on survival probability and whether there are any disparities in this relationship.

Although we studied PIM prescription among older adults, inappropriate prescribing can occur in persons of all ages. Future studies can focus on disparities across inappropriate prescription among patients of all ages. While we studied disparities

in PIM prescription, we did not have information regarding the providers' characteristics. In the future, it would be helpful to know the pattern of the prescribers and their prescribing behavior to understand the contributing factors to such disparities. As a whole, future studies should seek to better understand factors contributing to the disparities in order to help develop interventions.

References

1. Centers for Disease Control and prevention. NCHS Data Brief. Number 42. Prescription drug use continues to increase: U.S. prescription drug data for 2007- 2008. September 2010. http://www.cdc.gov/nchs/data/databriefs/db42.htm. Accessed March 21, 2017.
2. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.
3. Laroche ML, Charmes JP, Nouaille Y, Picard N, Merle L. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? *Br J Clin Pharmacol.* 2007;63(2):177-186.
4. NIH | Misuse of Prescription Drugs | Older adults. https://www.drugabuse.gov/publications/research-reports/prescription-drugs/trends-in-prescription-drug-abuse/older-adults. Accessed March 21, 2017.
5. Page RL, 2nd, Linnebur SA, Bryant LL, Ruscin JM. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. *Clin Interv Aging.* 2010;5:75-87.
6. Edwards RF, Harrison TM, Davis SM. Potentially inappropriate prescribing for geriatric inpatients: an acute care of the elderly unit compared to a general medicine service. *Consult Pharm.* 2003;18(1):37-42, 47-39.
7. Jennifer Lucado KP, Anne Elixhauser. Medication-Related Adverse Outcomes in U.S. Hospitals and Emergency Departments, 2008. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb109.pdf. Accessed April 4, 2017. 2011.
8. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA.* 2008;300(24):2867-2878.
9. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.
10. Ament PW, Bertolino JG, Liszewski JL. Clinically significant drug interactions. *Am Fam Physician.* 2000;61(6):1745-1754.
11. Koberlein J, Gottschall M, Czarnecki K, Thomas A, Bergmann A, Voigt K. General practitioners' views on polypharmacy and its consequences for patient health care. *BMC Fam Pract.* 2013;14:119.
12. Tulner LR, Kuper IM, Frankfort SV, et al. Discrepancies in reported drug use in geriatric outpatients: relevance to adverse events and drug-drug interactions. *Am J Geriatr Pharmacother.* 2009;7(2):93-104.
13. Goren Z, M JD, Akpinar Acet G, Cali S, Gulcebi Idriz Oglu M. Potential drug-drug interactions among prescriptionsfor elderly patients in primary health care. *Turk J Med Sci.* 2017;47(1):47-54.
14. Ferret L, Ficheur G, Delaviez E, et al. Inappropriate anticholinergic drugs prescriptions in older patients: analysing a hospital database. *Int J Clin Pharm.* 2017.
15. Niznik J, Zhao X, Jiang T, et al. Anticholinergic Prescribing in Medicare Part D Beneficiaries Residing in Nursing Homes: Results from a Retrospective Cross-Sectional Analysis of Medicare Data. *Drugs Aging.* 2017;34(12):925-939.
16. Vieira de Lima TJ, Garbin CA, Garbin AJ, Sumida DH, Saliba O. Potentially inappropriate medications used by the elderly: prevalence and risk factors in Brazilian care homes. *BMC Geriatr.* 2013;13:52.

17. Felton M, Hanlon JT, Perera S, Thorpe JM, Marcum ZA. Racial differences in anticholinergic use among community-dwelling elders. *Consult Pharm.* 2015;30(4):240-245.
18. Healthy people 2020. Disparities Overview by Income. https://www.healthypeople.gov/2020/data/disparities/summary/Chart/4155/6.1. Accessed on April 25, 2017.,.
19. Disparities in Health and Health Care: Five Key Questions and Answers. http://kff.org/disparities-policy/issue-brief/disparities-in-health-and-health-care-five-key-questions-and-answers/#endnote_link_195310-4. Accessed April 25, 2017.
20. Hall-Lipsy EA, Chisholm-Burns MA. Pharmacotherapeutic disparities: racial, ethnic, and sex variations in medication treatment. *Am J Health Syst Pharm.* 2010;67(6):462-468.
21. Thomas LaVeist DG, and Patrick Richard. The Economic Burden of Health Inequalities in the United States. http://www.hhnmag.com/ext/resources/inc-hhn/pdfs/resources/Burden_Of_Health_FINAL_0.pdf. Accessed April 25, 2017. 2009.
22. Healthy People. https://www.healthypeople.gov/2020/About-Healthy-People. Accessed April 25, 2017.
23. Healthy People 2020. https://www.healthypeople.gov/sites/default/files/HP2020_brochure_with_LHI_508_FNL.pdf. Accessed April 25, 2017.
24. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology.* 2005;25(3):135-143.
25. Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Med Care.* 2002;40(9):771-781.
26. US healthcare spending compared to others. Peterson-Kaiser Health System Tracker. http://www.healthsystemtracker.org/chart-collection/health-spending-u-s-compare-countries/?_sf_s=health+spending#item-start. Accessed July 7, 2017.
27. Squires DA. The U.S. health system in perspective: a comparison of twelve industrialized nations. Issues in International Health Policy. 2011. http://www.commonwealthfund.org/~/media/Files/Publications/Issue%20Brief/2011/Jul/1532_Squires_US_hlt_sys_comparison_12_nations_intl_brief_v2.pdf. Accessed July 7, 2017.
28. Gary Claxton CC, Selena Gonzales, Rabah Kamal, Larry Levitt. Measuring the quality of healthcare in the U.S. https://www.healthsystemtracker.org/brief/measuring-the-quality-of-healthcare-in-the-u-s/#item-start. Accessed April 22, 2018. 2015.
29. Howard G. Ancel Keys Lecture: Adventures (and misadventures) in understanding (and reducing) disparities in stroke mortality. *Stroke.* 2013;44(11):3254-3259.
30. AHRQ. 2015 National Healthcare Quality and Disparities Report. http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/nhqrdr/nhqdr15/2015nhqdr.pdf. Accessed on September 1, 2016.
31. Niwata S, Yamada Y, Ikegami N. Prevalence of inappropriate medication using Beers criteria in Japanese long-term care facilities. *BMC Geriatr.* 2006;6:1.
32. Chen LL, Tangiisuran B, Shafie AA, Hassali MA. Evaluation of potentially inappropriate medications among older residents of Malaysian nursing homes. *Int J Clin Pharm.* 2012;34(4):596-603.
33. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. *J Clin Pharm Ther.* 2007;32(2):113-121.
34. Agency for Healthcare Research and Quality, 2014. Health care coverage analyses of the National Healthcare Quality and Disparities Reports: 2000-2008 trends.

https://www.medicaid.gov/medicaid/quality-of-care/downloads/health-coverage-analyses-of-nhqr-2000-2008-trends.pdf. Accessed July 8, 2017.
35. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation.* 2013;127(1):e6-e245.
36. Ayala C, Greenlund KJ, Croft JB, et al. Racial/ethnic disparities in mortality by stroke subtype in the United States, 1995-1998. *Am J Epidemiol.* 2001;154(11):1057-1063.
37. American Diabetes Association. Health Disparities. http://www.diabetes.org/advocacy/advocacy-priorities/health-disparities.html?referrer=https://www.google.com/. Accessed February 2, 2018.
38. Espey DK, Wu XC, Swan J, et al. Annual report to the nation on the status of cancer, 1975-2004, featuring cancer in American Indians and Alaska Natives. *Cancer.* 2007;110(10):2119-2152.
39. Robbins AS, Chen AY, Stewart AK, Staley CA, Virgo KS, Ward EM. Insurance status and survival disparities among nonelderly rectal cancer patients in the National Cancer Data Base. *Cancer.* 2010;116(17):4178-4186.
40. Kulkarni SC, Levin-Rector A, Ezzati M, Murray CJ. Falling behind: life expectancy in US counties from 2000 to 2007 in an international context. *Popul Health Metr.* 2011;9(1):16.
41. Epstein D, Reibel M, Unger JB, et al. The effect of neighborhood and individual characteristics on pediatric critical illness. *J Community Health.* 2014;39(4):753-759.
42. Signorello LB, Cohen SS, Williams DR, Munro HM, Hargreaves MK, Blot WJ. Socioeconomic status, race, and mortality: a prospective cohort study. *Am J Public Health.* 2014;104(12):e98-e107.
43. AHRQ. Understanding quality measurement. https://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/chtoolbx/understand/index.html. Accessed October 24, 2017.
44. AHRQ. A quick look at quality. https://archive.ahrq.gov/consumer/qnt/qntqlook.htm. Accessed October 24, 2017.
45. LabCE. Six domains of healthcare quality. https://www.labce.com/spg354501_six_domains_of_health_care_quality_as_defined_by_t.aspx. Accessed October 24, 2017.
46. DesHarnais SI. The Outcome Model of Quality. http://samples.jbpub.com/9780763781545/Chapter5.pdf. Accessed February 26, 2018
47. FAMILIESUSA. Measuring Health Care Quality: An Overview of Quality Measures. 2014. http://familiesusa.org/sites/default/files/product_documents/HSI%20Quality%20Measurement_Brief_final_web.pdf. Accessed October 24, 2017.
48. NCQA. The essential guide to healthcare quality. https://www.ncqa.org/Portals/0/Publications/Resource%20Library/NCQA_Primer_web.pdf. Accessed October 24, 2017.
49. HEDIS® & Performance Measurement. http://www.ncqa.org/hedis-quality-measurement. Accessed February 26, 2018.
50. HEDIS 2018. http://www.ncqa.org/hedis-quality-measurement/hedis-measures/hedis-2018. Accessed February 26, 2018.
51. CAHPS. https://www.ahrq.gov/cahps/about-cahps/cahps-program/cahps_brief.html. Accessed February 26, 2018.
52. Lee KY, Loeb JM, Nadzam DM, Hanold LS. Special Report: An Overview of the Joint Commission's ORYX Initiative and Proposed Statistical Methods. *Health Services and Outcomes Research Methodology.* 2000;1(1):63-73.

53. ORYX. https://www.ahrq.gov/professionals/quality-patient-safety/talkingquality/create/hospitals/measurementsets.html. Accessed February 26, 2018.
54. Health Outcomes Survey (HOS). https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/HOS/. Accessed February 26, 2018.
55. Donabedian A. The quality of care: How can it be assessed? *JAMA.* 1988;260(12):1743-1748.
56. Boston University School of Public Health. Linking Quality, Cost, and Outcomes | Quality. http://sphweb.bumc.bu.edu/otlt/MPH-Modules/HPM/AmericanHealthCare_Quality-Cost-Outcomes/AmericanHealthCare_Quality-Cost-Outcomes3.html. Accessed October 26, 2017.
57. Moore L, Lavoie A, Bourgeois G, Lapointe J. Donabedian's structure-process-outcome quality of care model: Validation in an integrated trauma system. *J Trauma Acute Care Surg.* 2015;78(6):1168-1175.
58. Jerry Cromwell MT, Gregory Pope, Janet Mitchell, and Leslie Greenwald. Pay for Performance in Health Care: Methods and Approaches. https://www.rti.org/sites/default/files/resources/bk-0002-1103-mitchell.pdf. Accessed October 26, 2017. 2011.
59. American Diabetes Association. Glycemic targets. Sec. 6. In Standards of Medical Care in Diabetesd2017. Diabetes Care 2017;40(Suppl. 1):S48–S56. http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf. Accessed February 27, 2018.
60. Lipska KJ, Krumholz HM. Is Hemoglobin A1c the Right Outcome for Studies of Diabetes? *JAMA.* 2017;317(10):1017-1018.
61. Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, 2008. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf. Accessed February 27, 2018.
62. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013;369(14):1317-1326.
63. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2015;373(3):232-242.
64. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311-322.
65. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.* 2016;375(19):1834-1844.
66. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015;373(22):2117-2128.
67. Lee CJ, Hwang J, Oh J, et al. Relation Between Blood Pressure and Clinical Outcome in Hypertensive Subjects With Previous Stroke. *J Am Heart Assoc.* 2017;6(12).
68. Wang X, Arima H, Heeley E, et al. Magnitude of blood pressure reduction and clinical outcomes in acute intracerebral hemorrhage: intensive blood pressure reduction in acute cerebral hemorrhage trial study. *Hypertension.* 2015;65(5):1026-1032.
69. Grossman E. Blood Pressure: The Lower, the Better: The con side. *Diabetes Care.* 2011;34(Suppl 2):S308-312.
70. Antonakoudis G, Poulimenos I, Kifnidis K, Zouras C, Antonakoudis H. Blood pressure control and cardiovascular risk reduction. *Hippokratia.* 2007;11(3):114-119.
71. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *Bmj.* 2009;338:b1665.

72. Patient-Centered Outcomes Research Definition Revision. https://www.pcori.org/assets/PCOR-Definition-Revised-Draft-and-Responses-to-Input.pdf. Accessed February 27, 2018.
73. The Eight Principles of Patient-Centered Care. http://www.oneviewhealthcare.com/the-eight-principles-of-patient-centered-care/. Accessed February 27, 2018.
74. Aligning Forces for Quality, Good for Health Good for Business: The Case for Measuring Patient Experience of Care. AHRQ @ the George Washington University Medical Center School of Public Health and Health Services. http://forces4quality.org/af4q/download-document/3212/Resource-Case%20for%20Patient%20Experience_branded2.pdf. Accessed December 19, 2017.
75. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med.* 2003;348(26):2635-2645.
76. Cook BL, McGuire TG, Zaslavsky AM. Measuring racial/ethnic disparities in health care: methods and practical issues. *Health Serv Res.* 2012;47(3 Pt 2):1232-1254.
77. Nelson A. Unequal treatment: confronting racial and ethnic disparities in health care. *J Natl Med Assoc.* 2002;94(8):666-668.
78. Baicker K, Chandra A, Skinner JS. Geographic variation in health care and the problem of measuring racial disparities. *Perspect Biol Med.* 2005;48(1 Suppl):S42-53.
79. Trivedi AN, Zaslavsky AM, Schneider EC, Ayanian JZ. Trends in the quality of care and racial disparities in Medicare managed care. *N Engl J Med.* 2005;353(7):692-700.
80. Gornick ME. A Decade of Research on Disparities in Medicare Utilization: Lessons for the Health and Health Care of Vulnerable Men. *Am J Public Health.* 2003;93(5):753-759.
81. Trivedi AN, Zaslavsky AM, Schneider EC, Ayanian JZ. Relationship between quality of care and racial disparities in Medicare health plans. *JAMA.* 2006;296(16):1998-2004.
82. Groeneveld PW, Laufer SB, Garber AM. Technology diffusion, hospital variation, and racial disparities among elderly Medicare beneficiaries: 1989-2000. *Med Care.* 2005;43(4):320-329.
83. Komaromy M, Grumbach K, Drake M, et al. The role of black and Hispanic physicians in providing health care for underserved populations. *N Engl J Med.* 1996;334(20):1305-1310.
84. VCU_Center_for_Society_and_Health. Why Education Matters to Health: Exploring the Causes. https://societyhealth.vcu.edu/work/the-projects/why-education-matters-to-health-exploringthe-causes.html#healthBenefits. Accessed September 13, 2018. .
85. Wong ST, Regan S. Patient perspectives on primary health care in rural communities: effects of geography on access, continuity and efficiency. *Rural Remote Health.* 2009;9(1):1142.
86. Kelvin Pollard LAJ. The Appalachian region: A data overview from the 2010–2014 American Community Survey chartbook. Appalachian Regional Commission and Population Reference Bureau. https://www.arc.gov/assets/research_reports/DataOverviewfrom2008-2012ACS.pdf. Accessed September 13, 2018. 2014.
87. Yao N, Matthews SA, Hillemeier MM. White infant mortality in Appalachian states, 1976-1980 and 1996-2000: changing patterns and persistent disparities. *J Rural Health.* 2012;28(2):174-182.
88. KFF. Gender Differences in Health Care, Status, and Use: Spotlight on Men's Health. https://www.kff.org/womens-health-policy/fact-sheet/gender-differences-in-health-care-status-and-use-spotlight-on-mens-health/. Accessed Septemnber 13, 2018. 2015.
89. Cooper-Patrick L, Gallo JJ, Gonzales JJ, et al. Race, gender, and partnership in the patient-physician relationship. *JAMA.* 1999;282(6):583-589.
90. Oliver MN, Goodwin MA, Gotler RS, Gregory PM, Stange KC. Time use in clinical encounters: are African-American patients treated differently? *J Natl Med Assoc.* 2001;93(10):380-385.
91. Schneider EC, Zaslavsky AM, Epstein AM. Racial disparities in the quality of care for enrollees in medicare managed care. *JAMA.* 2002;287(10):1288-1294.

92. Virnig BA, Lurie N, Huang Z, Musgrave D, McBean AM, Dowd B. Racial variation in quality of care among Medicare+Choice enrollees. *Health Aff (Millwood).* 2002;21(6):224-230.
93. Rosenheck R, Fontana A, Cottrol C. Effect of clinician-veteran racial pairing in the treatment of posttraumatic stress disorder. *Am J Psychiatry.* 1995;152(4):555-563.
94. Chen J, Rathore SS, Radford MJ, Wang Y, Krumholz HM. Racial differences in the use of cardiac catheterization after acute myocardial infarction. *N Engl J Med.* 2001;344(19):1443-1449.
95. McBean AM, Gornick M. Differences by race in the rates of procedures performed in hospitals for Medicare beneficiaries. *Health Care Financ Rev.* 1994;15(4):77-90.
96. National Academies of Sciences E, Medicine. *Communities in Action: Pathways to Health Equity.* Washington, DC: The National Academies Press; 2017.
97. Kaiser Family Foundation, Key Facts on Health and Health Care by Race and Ethnicity. 2016. http://files.kff.org/attachment/Chartpack-Key-Facts-on-Health-and-Health-Care-by-Race-and-Ethnicity. Accessed December 21, 2017.
98. Elizabeth Arias. United States Life Tables, 2011. National Vital Statistics Reports 64(11). 2015. https://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_11.pdf. Accessed December 21, 2017.
99. Braveman PA, Cubbin C, Egerter S, Williams DR, Pamuk E. Socioeconomic disparities in health in the United States: what the patterns tell us. *Am J Public Health.* 2010;100 Suppl 1:S186-196.
100. Richard A. Crosby MLW, Robin C. Vanderpool, Baretta R. Casey. Rural Populations and Health: Determinants, Disparities, and Solutions. *Preventing Chronic Disease.* 2012;10:E104.
101. Institute of Medicine Committee on Quality of Health Care in A. In: Kohn LT, Corrigan JM, Donaldson MS, eds. *To Err is Human: Building a Safer Health System*. Washington (DC): National Academies Press (US)

102. Hajjar ER, Hanlon JT, Sloane RJ, et al. Unnecessary drug use in frail older people at hospital discharge. *J Am Geriatr Soc.* 2005;53(9):1518-1523.
103. Coleman EA, Smith JD, Raha D, Min SJ. Posthospital medication discrepancies: prevalence and contributing factors. *Arch Intern Med.* 2005;165(16):1842-1847.
104. Bates DW, Miller EB, Cullen DJ, et al. Patient risk factors for adverse drug events in hospitalized patients. ADE Prevention Study Group. *Arch Intern Med.* 1999;159(21):2553-2560.
105. Carey IM, De Wilde S, Harris T, et al. What factors predict potentially inappropriate primary care prescribing in older people? Analysis of UK primary care patient record database. *Drugs Aging.* 2008;25(8):693-706.
106. Evans RS, Lloyd JF, Stoddard GJ, Nebeker JR, Samore MH. Risk factors for adverse drug events: a 10-year analysis. *Ann Pharmacother.* 2005;39(7-8):1161-1168.
107. Kanjanarat P, Winterstein AG, Johns TE, Hatton RC, Gonzalez-Rothi R, Segal R. Nature of preventable adverse drug events in hospitals: a literature review. *Am J Health Syst Pharm.* 2003;60(17):1750-1759.
108. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother.* 2007;5(4):345-351.
109. Goldberg RM, Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. *Am J Emerg Med.* 1996;14(5):447-450.
110. Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med.* 1990;150(4):841-845.
111. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med.* 2009;360(3):225-235.

112. Gill SS, Bronskill SE, Normand SL, et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med.* 2007;146(11):775-786.
113. Rochon PA, Normand SL, Gomes T, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. *Arch Intern Med.* 2008;168(10):1090-1096.
114. Menehan K. Partnership for Solutions: Better Lives for People with Chronic Conditions. Robert Wood Johnson Foundation. 2006. https://www.rwjf.org/en/library/research/2006/07/partnership-for-solutions.html. Accessed December 22, 2017.
115. Merrill CT, Elixhauser A. Hospitalization in the United States, 2002. Rockville, MD: Agency for Healthcare Research and Quality, 2005. HCUP Fact Book No. 6. AHRQ Publication No. 05-0056. ISBN 1-58763-217-9. https://archive.ahrq.gov/data/hcup/factbk6/factbk6.pdf. Accessed December 22, 2017.
116. Page RL, Hogan C, Strongin K, Mills R, Lindenfeld J. Abstract 5921: Medicare Beneficiaries with Mild to Severe Heart Failure See 15–23 Different Providers Annually. *Circulation.* 2008;118(Suppl 18):S_1030.
117. Kinirons MT, Crome P. Clinical pharmacokinetic considerations in the elderly. An update. *Clin Pharmacokinet.* 1997;33(4):302-312.
118. ElDesoky ES. Pharmacokinetic-pharmacodynamic crisis in the elderly. *Am J Ther.* 2007;14(5):488-498.
119. Dimitrow MS, Airaksinen MS, Kivela SL, Lyles A, Leikola SN. Comparison of prescribing criteria to evaluate the appropriateness of drug treatment in individuals aged 65 and older: a systematic review. *J Am Geriatr Soc.* 2011;59(8):1521-1530.
120. Drenth-van Maanen AC, Leendertse AJ, Jansen PAF, et al. The Systematic Tool to Reduce Inappropriate Prescribing (STRIP): Combining implicit and explicit prescribing tools to improve appropriate prescribing. *J Eval Clin Pract.* 2017.
121. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet.* 2007;370(9582):173-184.
122. Shelton PS, Fritsch MA, Scott MA. Assessing medication appropriateness in the elderly: a review of available measures. *Drugs Aging.* 2000;16(6):437-450.
123. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. *European Journal of Clinical Pharmacology.* 2015;71(7):861-875.
124. O'Mahony D, Gallagher P, Ryan C, et al. STOPP & START criteria: A new approach to detecting potentially inappropriate prescribing in old age. *European Geriatric Medicine.*1(1):45-51.
125. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *Cmaj.* 1997;156(3):385-391.
126. Bulloch MN, Olin JL. Instruments for evaluating medication use and prescribing in older adults. *J Am Pharm Assoc (2003).* 2014;54(5):530-537.
127. Wenger NS, Roth CP, Shekelle P. Introduction to the assessing care of vulnerable elders-3 quality indicator measurement set. *J Am Geriatr Soc.* 2007;55 Suppl 2:S247-252.
128. Shrank WH, Polinski JM, Avorn J. Quality indicators for medication use in vulnerable elders. *J Am Geriatr Soc.* 2007;55 Suppl 2:S373-382.
129. RAND Corporation. Quality indicators – ACOVE 3. https://www.rand.org/health/projects/acove/acove3.html. Accessed December 24, 2017.
130. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol.* 1992;45(10):1045-1051.

131. Garfinkel D, Zur-Gil S, Ben-Israel J. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. *Isr Med Assoc J.* 2007;9(6):430-434.
132. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. *Arch Intern Med.* 2010;170(18):1648-1654.
133. Vinks TH, Egberts TC, de Lange TM, de Koning FH. Pharmacist-based medication review reduces potential drug-related problems in the elderly: the SMOG controlled trial. *Drugs Aging.* 2009;26(2):123-133.
134. Haque, R. (2009) Armor: a tool to evaluate polypharmacy in elderly persons. Ann Longterm Care 17: 26–30. https://www.managedhealthcareconnect.com/content/armor-a-tool-evaluate-polypharmacy-elderly-persons. Accessed December 24, 2017.
135. Lee SS, Schwemm AK, Reist J, et al. Pharmacists' and pharmacy students' ability to identify drug-related problems using TIMER (Tool to Improve Medications in the Elderly via Review). *Am J Pharm Educ.* 2009;73(3):52.
136. Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc.* 2006;54(10):1516-1523.
137. Wright RM, Sloane R, Pieper CF, et al. Underuse of indicated medications among physically frail older US veterans at the time of hospital discharge: results of a cross-sectional analysis of data from the Geriatric Evaluation and Management Drug Study. *Am J Geriatr Pharmacother.* 2009;7(5):271-280.
138. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med.* 1991;151(9):1825-1832.
139. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med.* 1997;157(14):1531-1536.
140. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med.* 2003;163(22):2716-2724.
141. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med.* 2002;162(20):2269-2276.
142. Schubert CC, Boustani M, Callahan CM, et al. Comorbidity profile of dementia patients in primary care: are they sicker? *J Am Geriatr Soc.* 2006;54(1):104-109.
143. Boustani M, Peterson B, Harris R, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. *Screening for Dementia*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2003.
144. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging.* 2009;4:225-233.
145. Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis. *Br J Clin Pharmacol.* 2015;80(2):209-220.
146. Joan Heller Brown NL. Muscarinic receptor agonists and antagonists. In: Goodman and Gilman's the Pharmacological Basis of Therapeutics, 12th edn. NY, USA: McGraw Hill. 2011:219-237.
147. Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. *J R Soc Med.* 2000;93(9):457-462.
148. Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry.* 2001;62 Suppl 21:11-14.

149. Lund BC, Steinman MA, Chrischilles EA, Kaboli PJ. Beers criteria as a proxy for inappropriate prescribing of other medications among older adults. *Ann Pharmacother.* 2011;45(11):1363-1370.
150. Stockl KM, Le L, Zhang S, Harada AS. Clinical and economic outcomes associated with potentially inappropriate prescribing in the elderly. *Am J Manag Care.* 2010;16(1):e1-10.
151. Jano E, Aparasu RR. Healthcare outcomes associated with beers' criteria: a systematic review. *Ann Pharmacother.* 2007;41(3):438-447.
152. Chang CM, Liu PY, Yang YH, Yang YC, Wu CF, Lu FH. Use of the Beers criteria to predict adverse drug reactions among first-visit elderly outpatients. *Pharmacotherapy.* 2005;25(6):831-838.
153. Chrischilles EA, VanGilder R, Wright K, Kelly M, Wallace RB. Inappropriate medication use as a risk factor for self-reported adverse drug effects in older adults. *J Am Geriatr Soc.* 2009;57(6):1000-1006.
154. Dedhiya SD, Hancock E, Craig BA, Doebbeling CC, Thomas J, 3rd. Incident use and outcomes associated with potentially inappropriate medication use in older adults. *Am J Geriatr Pharmacother.* 2010;8(6):562-570.
155. Passarelli MC, Jacob-Filho W, Figueras A. Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. *Drugs Aging.* 2005;22(9):767-777.
156. Page RL, 2nd, Ruscin JM. The risk of adverse drug events and hospital-related morbidity and mortality among older adults with potentially inappropriate medication use. *Am J Geriatr Pharmacother.* 2006;4(4):297-305.
157. Wallace J, Paauw DS. Appropriate prescribing and important drug interactions in older adults. *Med Clin North Am.* 2015;99(2):295-310.
158. Howard VJ, Kleindorfer DO, Judd SE, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. *Ann Neurol.* 2011;69(4):619-627.
159. Howard G, Safford MM, Moy CS, et al. Racial Differences in the Incidence of Cardiovascular Risk Factors in Older Black and White Adults. *J Am Geriatr Soc.* 2017;65(1):83-90.
160. Effect Modification. Boston University School of Public Health. http://sphweb.bumc.bu.edu/otlt/MPH-Modules/BS/BS704_Multivariable/BS704_Multivariable4.html. Accessed March 2, 2018.
161. DECIPHERING INTERACTIONS IN LOGISTIC REGRESSION. https://stats.idre.ucla.edu/stata/seminars/deciphering-interactions-in-logistic-regression/. Accessed March 2, 2018.
162. Logistic Regression: Interaction Terms. http://www.cantab.net/users/filimon/cursoFCDEF/will/logistic_interact.pdf. Accessed March 2, 2018.
163. Chen JJ. COMMUNICATING COMPLEX INFORMATION: THE INTERPRETATION OF STATISTICAL INTERACTION IN MULTIPLE LOGISTIC REGRESSION ANALYSIS. *Am J Public Health.* 2003;93(9):1376-1377.
164. Hansen RA, Khodneva Y, Glasser SP, Qian J, Redmond N, Safford MM. Antidepressant Medication Use and Its Association With Cardiovascular Disease and All-Cause Mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Ann Pharmacother.* 2016;50(4):253-261.
165. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med.* 1991;10(4):585-598.
166. Fedewa SA, McClellan WM, Judd S, Gutierrez OM, Crews DC. The association between race and income on risk of mortality in patients with moderate chronic kidney disease. *BMC Nephrol.* 2014;15:136.

167. INTRODUCTION TO SURVIVAL ANALYSIS IN SAS. https://stats.idre.ucla.edu/sas/seminars/sas-survival/. Accessed March 3, 2018.
168. Xue X, Xie X, Gunter M, et al. Testing the proportional hazards assumption in case-cohort analysis. *BMC Medical Research Methodology.* 2013;13(1):88.
169. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81(3):515-526.
170. SAS_user_guide. Survival analysis. Modeling with categorical predictors. http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_phreg_sect034.htm. Accessed September 03, 2018.
171. Introduction to Survival Analysis in SAS. http://www.ats.ucla.edu/stat/sas/seminars/sas_survival/. Accessed September 28, 2016.
172. Survival analyses. http://www2.sas.com/proceedings/sugi28/254-28.pdf. Accessed September 28, 2016.
173. Wadley VG, Unverzagt FW, McGuire LC, et al. Incident cognitive impairment is elevated in the stroke belt: the REGARDS study. *Ann Neurol.* 2011;70(2):229-236.
174. Wilber ST, Lofgren SD, Mager TG, Blanda M, Gerson LW. An evaluation of two screening tools for cognitive impairment in older emergency department patients. *Acad Emerg Med.* 2005;12(7):612-616.
175. Steffens DC, Snowden M, Fan MY, Hendrie H, Katon WJ, Unutzer J. Cognitive impairment and depression outcomes in the IMPACT study. *Am J Geriatr Psychiatry.* 2006;14(5):401-409.
176. CESD. http://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/depression-scale.aspx. Accessed October 17, 2017.
177. Espeland MA, Gu L, Masaki KH, et al. Association between reported alcohol intake and cognition: results from the Women's Health Initiative Memory Study. *Am J Epidemiol.* 2005;161(3):228-238.
178. Wadley VG, McClure LA, Howard VJ, et al. Cognitive status, stroke symptom reports, and modifiable risk factors among individuals with no diagnosis of stroke or transient ischemic attack in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Stroke.* 2007;38(4):1143-1147.
179. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science.* 2003;301(5631):386-389.
180. Kurella Tamura M, Wadley V, Yaffe K, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Am J Kidney Dis.* 2008;52(2):227-234.
181. Lampela P, Paajanen T, Hartikainen S, Huupponen R. Central Anticholinergic Adverse Effects and Their Measurement. *Drugs Aging.* 2015;32(12):963-974.
182. Weiss N, Miller F, Cazaubon S, Couraud PO. The blood-brain barrier in brain homeostasis and neurological diseases. *Biochim Biophys Acta.* 2009;1788(4):842-857.
183. Pullicino PM, Wadley VG, McClure LA, et al. Factors contributing to global cognitive impairment in heart failure: results from a population-based cohort. *J Card Fail.* 2008;14(4):290-295.
184. Nan Marie Astone SM, Laudan Y. Aron. Death Rates for US Women Ages 15 to 54. Some Unexpected Trends. https://www.urban.org/research/publication/death-rates-us-women-ages-15-54. Accessed August 27, 2018. 2015. 2015.
185. Mundell EJ. U.S. Antidepressant Use Jumps 65 Percent in 15 Years. https://consumer.healthday.com/mental-health-information-25/antidepressants-news-723/u-s-antidepressant-use-jumps-65-percent-in-15-years-725586.html. Accessed August 27, 2018. 2017.

186. Laura A. Pratt DJB, Qiuping Gu. . Antidepressant Use Among Persons Aged 12 and Over: United States, 2011–2014. https://www.cdc.gov/nchs/products/databriefs/db283.htm. Accessed August 27, 2018. 2017.
187. Cantor JC, Miles EL, Baker LC, Barker DC. Physician service to the underserved: implications for affirmative action in medical education. *Inquiry.* 1996;33(2):167-180.
188. Health VCfSa. Why Education Matters to Health: Exploring the Causes. https://societyhealth.vcu.edu/work/the-projects/why-education-matters-to-health-exploring-the-causes.html#healthBenefits. Accessed August 27, 2018. 2015.
189. Khandker RK, Simoni-Wastila LJ. Differences in prescription drug utilization and expenditures between Blacks and Whites in the Georgia Medicaid population. *Inquiry.* 1998;35(1):78-87.
190. Wang J, Zuckerman IH, Miller NA, Shaya FT, Noel JM, Mullins CD. Utilizing New Prescription Drugs: Disparities among Non-Hispanic Whites, Non-Hispanic Blacks, and Hispanic Whites. *Health Serv Res.* 2007;42(4):1499-1519.
191. Singhal A, Tien YY, Hsia RY. Racial-Ethnic Disparities in Opioid Prescriptions at Emergency Department Visits for Conditions Commonly Associated with Prescription Drug Abuse. *PLoS One.* 2016;11(8):e0159224.
192. Cooper LA and Powe RN. 2004. Disparities in Patient Experiences, Health Care Processes, and Outcomes: The Role of Patient-Provider Racial, Ethnic, and Language Concordance. http://www.commonwealthfund.org/~/media/files/publications/fund-report/2004/jul/disparities-in-patient-experiences--health-care-processes--and-outcomes--the-role-of-patient-provide/cooper_disparities_in_patient_experiences_753-pdf.pdf. Accessed February 28, 2018.
193. Zestcott CA, Blair IV, Stone J. Examining the Presence, Consequences, and Reduction of Implicit Bias in Health Care: A Narrative Review. *Group Process Intergroup Relat.* 2016;19(4):528-542.
194. Betancourt JR, Corbett J, Bondaryk MR. Addressing disparities and achieving equity: cultural competence, ethics, and health-care transformation. *Chest.* 2014;145(1):143-148.
195. Dale HE, Polivka BJ, Chaudry RV, Simmonds GC. What young African American women want in a health care provider. *Qual Health Res.* 2010;20(11):1484-1490.
196. Volandes AE, Paasche-Orlow M, Gillick MR, et al. Health literacy not race predicts end-of-life care preferences. *J Palliat Med.* 2008;11(5):754-762.
197. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: A systematic review and meta-analysis. *European Journal of Preventive Cardiology.* 2017;24(14):1555-1566.
198. Healey JS, Oldgren J, Ezekowitz M, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet.* 2016;388(10050):1161-1169.
199. VCU_Center_for_Society_and_Health. Why Education Matters to Health: Exploring the Causes. https://societyhealth.vcu.edu/work/the-projects/why-education-matters-to-health-exploring-the-causes.html#healthBenefits. Accessed August 27, 2018. 2015.
200. Al Odhayani A, Tourkmani A, Alshehri M, Alqahtani H, Mishriky A. Potentially inappropriate medications prescribed for elderly patients through family physicians. *Saudi Journal of Biological Sciences.* 2017;24(1):200-207.
201. Avery G. Endogeneity in Logistic Regression Models. *Emerg Infect Dis.* 2005;11(3):503-505.
202. Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *Bmj.* 2018;361:k1315.
203. McCarrey AC, An Y, Kitner-Triolo MH, Ferrucci L, Resnick SM. Sex differences in cognitive trajectories in clinically normal older adults. *Psychol Aging.* 2016;31(2):166-175.

204. van Exel E, Gussekloo J, de Craen AJM, et al. Cognitive function in the oldest old: women perform better than men. *Journal of Neurology, Neurosurgery & Psychiatry.* 2001;71(1):29.
205. Neurology AAo. MEN MORE LIKELY TO HAVE PROBLEMS WITH MEMORY AND THINKING SKILLS. https://www.aan.com/PressRoom/Home/PressRelease/596. Accessed September 12, 2018. 2008.
206. Sohn D, Shpanskaya K, Lucas JE, et al. Sex Differences in Cognitive Decline in Subjects with High Likelihood of Mild Cognitive Impairment due to Alzheimer's disease. *Scientific Reports.* 2018;8(1):7490.
207. Lin KA, Choudhury KR, Rathakrishnan BG, Marks DM, Petrella JR, Doraiswamy PM. Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimers Dement (N Y).* 2015;1(2):103-110.
208. Zahodne LB, Manly JJ, Azar M, Brickman AM, Glymour MM. Racial Disparities in Cognitive Performance in Mid- and Late Adulthood: Analyses of Two Cohort Studies. *J Am Geriatr Soc.* 2016;64(5):959-964.
209. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA.* 1994;271(13):1004-1010.
210. Manly JJ, Jacobs DM, Touradji P, Small SA, Stern Y. Reading level attenuates differences in neuropsychological test performance between African American and White elders. *J Int Neuropsychol Soc.* 2002;8(3):341-348.
211. Mann E, Haastert B, Bohmdorfer B, et al. Prevalence and associations of potentially inappropriate prescriptions in Austrian nursing home residents: secondary analysis of a cross-sectional study. *Wien Klin Wochenschr.* 2013;125(7-8):180-188.
212. Oliveira MG, Amorim WW, de Jesus SR, Heine JM, Coqueiro HL, Passos LC. A comparison of the Beers and STOPP criteria for identifying the use of potentially inappropriate medications among elderly patients in primary care. *J Eval Clin Pract.* 2015;21(2):320-325.
213. Karuturi MS, Holmes HM, Lei X, et al. Potentially inappropriate medication use in older patients with breast and colorectal cancer. *Cancer.* 2018;124(14):3000-3007.
214. Cross AJ, George J, Woodward MC, et al. Potentially Inappropriate Medication, Anticholinergic Burden, and Mortality in People Attending Memory Clinics. *J Alzheimers Dis.* 2017;60(2):349-358.
215. Dovidio JF, Gaertner SL, Kawakami K, Hodson G. Why can't we just get along? Interpersonal biases and interracial distrust. *Cultur Divers Ethnic Minor Psychol.* 2002;8(2):88-102.
216. Institute of Medicine Committee on U, Eliminating R, Ethnic Disparities in Health C. In: Smedley BD, Stith AY, Nelson AR, eds. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*. Washington (DC): National Academies Press (US)

217. Linda R. Tropp RDG. Overcoming Implicit Bias and Racial Anxiety. https://www.psychologytoday.com/us/blog/sound-science-sound-policy/201501/overcoming-implicit-bias-and-racial-anxiety. Accessed October 03, 2018. 2015.
218. Cooper LA, Roter DL, Johnson RL, Ford DE, Steinwachs DM, Powe NR. Patient-centered communication, ratings of care, and concordance of patient and physician race. *Ann Intern Med.* 2003;139(11):907-915.
219. Frist WH. Overcoming disparities in U.S. health care. *Health Aff (Millwood).* 2005;24(2):445-451.
220. Medicine Io. *Leadership by Example: Coordinating Government Roles in Improving Health Care Quality.* Washington, DC: The National Academies Press; 2002.

221. Roberts ET, Zaslavsky AM, McWilliams J. The value-based payment modifier: Program outcomes and implications for disparities. *Ann Intern Med.* 2018;168(4):255-265.
222. Gupta A, Allen LA, Bhatt DL, et al. Association of the hospital readmissions reduction program implementation with readmission and mortality outcomes in heart failure. *JAMA Cardiology.* 2018;3(1):44-53.
223. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. *J Neurol Neurosurg Psychiatry.* 2007;78(8):790-799.
224. Venturini CD, Engroff P, Ely LS, et al. Gender differences, polypharmacy, and potential pharmacological interactions in the elderly. *Clinics (Sao Paulo).* 2011;66(11):1867-1872.

APPENDIX A

Table. Clinically significant drug-drug interactions[10]

INTERACTIONS	POTENTIAL EFFECT	TIME TO EFFECT	RECOMMENDATIONS AND COMMENTS
Warfarin plus ciprofloxacin, clarithromycin, erythromycin, metronidazole or trimethoprim-sulfamethoxazole	Increased effect of warfarin	Generally within 1 week	Select alternative antibiotic.
Warfarin plus acetaminophen	Increased bleeding, increased INR	Any time	Use lowest possible acetaminophen dosage and monitor INR.
Warfarin plus acetylsalicylic acid (aspirin)	Increased bleeding, increased INR	Any time	Limit aspirin dosage to 100 mg per day and monitor INR.
Warfarin plus NSAID	Increased bleeding, increased INR	Any time	Avoid concomitant use if possible; if co-administration is necessary, use a cyclooxygenase-2 inhibitor and monitor INR.
Fluoroquinolone plus divalent/trivalent cations or sucralfate	Decreased absorption of fluoroquinolone	Any time	Space administration by 2 to 4 hours.
Carbamazepine plus cimetidine, erythromycin, clarithromycin or fluconazole	Increased carbamazepine levels	Generally within 1 week	Monitor carbamazepine levels.
Phenytoin plus cimetidine, erythromycin, clarithromycin or fluconazole	Increased phenytoin levels	Generally within 1 week	Monitor phenytoin levels.
Phenobarbital plus cimetidine, erythromycin, clarithromycin or fluconazole	Increased phenobarbital levels	Generally within 1 week	Clinical significance has not been established. Monitor phenobarbital levels.
Phenytoin plus rifampin	Decreased phenytoin levels	Generally within 1 week	Clinical significance has not been established. Monitor phenytoin levels.

INTERACTIONS	POTENTIAL EFFECT	TIME TO EFFECT	RECOMMENDATIONS AND COMMENTS
Phenobarbital plus rifampin	Decreased phenobarbital levels	Generally within 1 week	Monitor phenobarbital levels.
Carbamazepine plus rifampin	Decreased carbamazepine levels	Generally within 1 week	Clinical significance has not been established. Monitor carbamazepine levels.
Lithium plus NSAID or diuretic	Increased lithium levels	Any time	Decrease lithium dosage by 50% and monitor lithium levels.
Oral contraceptive pills plus rifampin	Decreased effectiveness of oral contraception	Any time	Avoid if possible. If combination therapy is necessary, have the patient take an oral contraceptive pill with a higher estrogen content (>35 µg of ethinyl estradiol) or recommend alternative method of contraception.
Oral contraceptive pills plus antibiotics	Decreased effectiveness of oral contraception	Any time	Avoid if possible. If combination therapy is necessary, recommend use of alternative contraceptive method during cycle.
Oral contraceptive pills plus troglitazone	Decreased effectiveness of oral contraception	Any time	Have the patient take an oral contraceptive pill with a higher estrogen content or recommend alternative method of contraception.
Cisapride plus erythromycin, clarithromycin, fluconazole, itraconazole, ketoconazole, nefazodone, indinavir or ritonavir	Prolongation of QT interval along with arrhythmias secondary to inhibited cisapride metabolism	Generally within 1 week	Avoid. Consider whether metoclopromide therapy is appropriate for the patient.
Cisapride plus class IA or class III antiarrhythmic agents, tricyclic antidepressants or phenothiazine	Prolongation of QT interval along with arrhythmias	Any time	Avoid. Consider whether metoclopromide therapy is appropriate for the patient.

INTERACTIONS	POTENTIAL EFFECT	TIME TO EFFECT	RECOMMENDATIONS AND COMMENTS
Sildenafil plus nitrates	Dramatic hypotension	Soon after taking sildenafil	Absolute contraindication.
Sildenafil plus cimetidine, erythromycin, itraconazole or ketoconazole	Increased sildenafil levels	Any time	Initiate sildenafil at a 25-mg dose.
HMG-CoA reductase inhibitor plus niacin, gemfibrozil, erythromycin or itraconazole	Possible rhabdomyolysis	Any time	Avoid if possible. If combination therapy is necessary, monitor the patient for toxicity.
Lovastatin plus warfarin	Increased effect of warfarin	Any time	Monitor INR.
SSRI plus tricyclic antidepressant	Increased tricyclic antidepressant level	Any time	Monitor for anticholinergic excess and consider lower dosage of tricyclic antidepressant.
SSRI plus selegiline or nonselective monoamine oxidase inhibitor	Hypertensive crisis	Soon after initiation	Avoid.
SSRI plus tramadol	Increased potential for seizures; serotonin syndrome	Any time	Monitor the patient for signs and symptoms of serotonin syndrome.
SSRI plus St. John's wort	Serotonin syndrome	Any time	Avoid.
SSRI plus naratriptan, rizatriptan, sumatriptan or zolmitriptan	Serotonin syndrome	Possibly after initial dose	Avoid if possible. If combination therapy is necessary, monitor the patient for signs and symptoms of serotonin syndrome.

* INR = International Normalized Ratio; NSAID = nonsteroidal anti-inflammatory drug; HMG-CoA = 3-hydroxy-3- methylglutaryl–coenzyme A reductase inhibitor; SSRI = selective serotonin reuptake inhibitor.

APPENDIX B

Table. Drugs with strong anticholinergic properties[9]

Class	Drugs
Antihistamines	Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Dimenhydrinate Diphenhydramine (oral) Doxylamine Hydroxyzine Meclizine Triprolidine
Antidepressants	Amitriptyline Amoxapine Clomipramine Desipramine Doxepin (>6 mg) Imipramine Nortriptyline Paroxetine Protriptyline Trimipramine
Antimuscarinics (urinary incontinence)	Darifenacin Fesoterodine Flavoxate Oxybutynin Solifenacin Tolterodine Trospium
Antiparkinsonian agents	Benztropine Trihexyphenidyl
Skeletal muscle relaxants	Cyclobenzaprine Orphenadrine
Antipsychotics	Chlorpromazine Clozapine Loxapine Olanzapine Perphenazine Thioridazine Trifluoperazine
Antiarrhythmic	Disopyramide

Class	Drugs
Antispasmodics	Atropine (excludes ophthalmic) Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Homatropine (excludes ophthalmic) Hyoscyamine Propantheline Scopolamine (excludes ophthalmic)
Antiemetic	Prochlorperazine Promethazine

APPENDIX C

A B

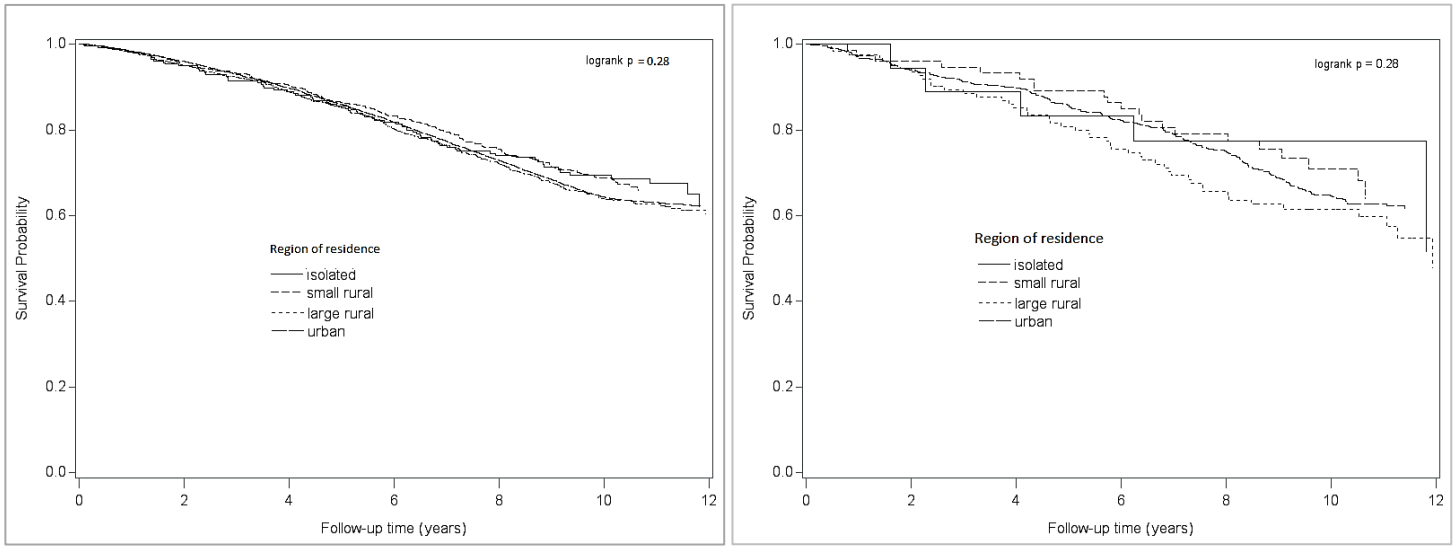

Figure. Survival probability of participants with PIM use (panel A) and DDIs (panel B) across different location of residence.

For both PIMs and DDIs, the location of residence did not satisfy the proportionality of hazard assumption and thus was excluded from further analyses.

APPENDIX D

Table. Association between PIM use and all-cause mortality and the effect of health disparities on this relationship (methods 2, 3, and 4)

Characteristics	**Censored at 2 years (method 2), HR (95% CI)**			**Censored at 4 years (method 3), HR (95% CI)**			**Censored at 6 years (method 4), HR (95% CI)**		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3 ¶	Model 1	Model 2	Model 3 ¥
PIM use									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	**2.12 (1.50 - 3.01)**	a	b,c,d,e,f	**1.47 (1.22 - 1.77)**	a	a,c,d,f	**1.45 (1.26 - 1.68)**	g	g,d,f
Gender									
Male	-	Ref	Ref	-	Ref	Ref	-	Ref	Ref
Female	-	**0.41 (0.34 - 0.50)**	**0.43 (0.35 - 0.52)**	-	**0.47 (0.42 - 0.53)**	**0.51 (0.45 - 0.57)**	-	**0.51 (0.47 - 0.56)**	**0.54 (0.49 - 0.59)**
Race									
White	-	Ref	Ref	-	Ref	Ref	-	Ref	Ref
Black	-	1.14 (0.95 - 1.37)	1.19 (0.98 - 1.44)	-	1.04 (0.92 - 1.16)	1.09 (0.96 - 1.24)	-	g	g
Income									
≥ $75,000	-	Ref	Ref	-	Ref	Ref	-	Ref	Ref
Less than $20,000	-	a	**3.67 (2.18 - 6.17)**	-	a	a	-	**2.77 (2.23 - 3.43)**	**2.67 (2.16 - 3.29)**
$20,000- $34,999	-		**2.88 (1.75 - 4.74)**	-			-	**2.07 (1.69 - 2.53)**	**2.10 (1.71 - 2.57)**
$35,000- $74,999	-		**1.77 (1.07 - 2.94)**	-			-	**1.41 (1.15 - 1.73)**	**1.45 (1.18 - 1.79)**
Education									
College graduate and above	-	Ref	Ref	-	Ref	Ref	-	Ref	Ref
Less than high school	-	**1.41 (1.08 - 1.85)**	1.13 (0.85 - 1.50)	-	**1.30 (1.09 - 1.55)**	1.12 (0.93 - 1.34)	-	**1.32 (1.15 - 1.51)**	**1.17 (1.01 - 1.34)**
High school or some college	-	1.07 (0.86 - 1.34)	1.00 (0.80 - 1.26)	-	1.08 (0.94 - 1.24)	1.03 (0.89 - 1.18)	-	**1.13 (1.02 - 1.26)**	1.09 (0.98 - 1.22)
Total number of medications use									
First quartile	-	-	Ref	-	-	Ref	-	-	Ref
Second quartile	-	-	1.39 (0.95-2.04)	-	-	1.15 (0.93-1.42)	-	-	1.12 (0.95-1.32)
Third quartile	-	-	1.41 (0.94-2.11)	-	-	1.19 (0.94-1.50)	-	-	1.19 (1.00-1.42)
Fourth quartile	-	-	**1.82 (1.20-2.77)**	-	-	**1.44 (1.13-1.84)**	-	-	**1.46 (1.21-1.75)**
Total PIM use									
First quartile	-	-	Ref	-	-	Ref	-	-	Ref
Second quartile	-	-	1.24 (0.83-1.86)	-	-	1.00 (0.80-1.25)	-	-	1.02 (0.86-1.20)

Third quartile	-	-	**1.60 (1.07-2.39)**	-	-	1.24 (0.99-1.55)	-	-	**1.21 (1.02-1.44)**
Fourth quartile	-	-	**2.36 (1.54-3.62)**	-	-	**1.68 (1.31-2.15)**	-	-	**1.64 (1.36-1.98)**
Significant interactions									
Income-PIM [a]									
Less than $20,000 vs. ≥ $75,000; PIM = Yes	-	**4.05 (2.44 - 6.71)**	-	-	**3.51 (2.65 - 4.65)**	**2.98 (2.22 - 4.01)**	-	-	-
$20,000- $34,999 vs. ≥ $75,000; PIM = Yes	-	**2.77 (1.70 - 4.52)**	-	-	**2.34 (1.77 - 3.09)**	**2.19 (1.63 - 2.92)**	-	-	-
$35,000- $74,999 vs. ≥ $75,000; PIM = Yes	-	**1.74 (1.06 - 2.85)**	-	-	**1.49 (1.12 - 1.98)**	**1.50 (1.11 - 2.02)**	-	-	-
Less than $20,000 vs. ≥ $75,000; PIM = No	-	2.93 (0.33 - 26.32)	-	-	3.80 (1.29 - 11.18)	3.19 (0.99 - 9.67)	-	-	-
$20,000- $34,999 vs. ≥ $75,000; PIM = No	-	8.07 (1.00 - 60.40)	-	-	5.20 (0.98 - 14.46)	4.07 (0.98 - 12.68)	-	-	-
$35,000- $74,999 vs. ≥ $75,000; PIM = No	-	1.93 (0.23 - 16.52)	-	-	2.68 (0.94 - 7.67)	2.49 (0.87 - 7.12)	-	-	-
Race-PIM [g]									
PIM Yes vs. No; Race = Black	-	-	-	-	-	-	-	1.19 (0.97 - 1.46)	0.94 (0.76 - 1.16)
PIM Yes vs. No; Race = White	-	-	-	-	-	-	-	**1.66 (1.36 - 2.03)**	1.26 (1.02 - 1.55)
Black vs. White; PIM = Yes	-	-	-	-	-	-	-	0.98 (0.89 - 1.07)	1.04 (0.95 - 1.15)
Black vs. White; PIM = No	-	-	-	-	-	-	-	**1.37 (1.04 - 1.8)**	1.40 (1.06 - 1.85)
CVD-PIM [b]									
CVD: Yes vs. No; PIM = No	-	-	1.77 (0.77-4.02	-	-	-	-	-	-
CVD: Yes vs. No; PIM = Yes	-	-	**1.79 (1.47-2.17)**	-	-	-	-	-	-
Stroke-PIM [c]									
Stroke: Yes vs. No; PIM = No	-	-	2.39 (0.68-2.43)	-	-	1.51 (0.68-3.34)	-	-	-
Stroke: Yes vs. No; PIM = Yes	-	-	**1.59 (1.25-2.02)**	-	-	**1.62 (1.39-1.90)**	-	-	-
Diabetes-PIM [d]									
Diabetes: Yes vs. No; PIM = No	-	-	1.54 (0.64-3.68)	-	-	1.29 (0.80-2.60)	-	-	1.32 (0.92-1.88)
Diabetes: Yes vs. No; PIM = Yes	-	-	**1.56 (1.29-1.90)**	-	-	**1.43 (1.26-1.62)**	-	-	**1.35 (1.23-1.48)**
CKD-PIM [e]									
CKD: Yes vs. No; PIM = No	-	-	2.26 (0.99-5.15)	-	-	-	-	-	-
CKD: Yes vs. No; PIM = Yes	-	-	**2.19 (1.81-2.65)**	-	-	-	-	-	-
Afib-PIM [f]									
Afib: Yes vs. No; PIM = No	-	-	1.19 (0.27-5.14)	-	-	1.08 (0.49-2.36)	-	-	0.94 (0.49-1.79)
Afib: Yes vs. No; PIM = Yes	-	-	**1.72 (1.37-2.16)**	-	-	**1.61 (1.38-1.88)**	-	-	**1.53 (1.36-1.72)**

PIM: potentially inappropriate medication, HR: hazard ratio; CVD: history of cardiovascular diseases; CKD: chronic kidney disease; Afib: atrial fibrillation; [a] Significant income-PIM interaction; [b] Significant CVD-PIM interaction; [c] Significant stroke-PIM interaction; [d] Significant diabetes-PIM interaction; [e] Significant CKD-PIM interaction; [f] Significant Afib-PIM interaction; [g] Significant race-PIM interaction; Bold refers to P <0.05.

[¶] Significant covariates include: CVD (HR = 1.52, 95% CI 1.35 – 1.72) and CKD (HR = 2.02, 95% CI 1.80 – 2.28).

[¥] Significant covariates include: CVD (HR = 1.45, 95% CI 1.32 – 1.60), stroke (HR = 1.61, 95% CI 1.42 – 1.81), and CKD (HR = 1.99, 95% CI 1.81 – 2.18).

Consistent with our survival plots, the unadjusted HR (model 1) in all the censored follow-up time intervals indicated an increased risk of all-cause mortality with PIM use. However, the magnitude of the HRs decreased gradually as the censoring time interval increased. Our iterative model building approach demonstrated differences in HR interpretation. For method 2 (follow-up time censored at 2 years), where we adjusted for demographic and socioeconomic status (model 2), the income-PIM use interaction was found to be significant. This illustrates that PIM use among lower income individuals was significantly associated with higher risks of mortality than their higher income counterparts. For example, among the PIM users, income less than $20,000 vs. ≥ $75,000: HR = 4.05, 95% CI 2.44 – 6.71. We also observed that as income increases, the magnitude of the HR decreases. Education (less than high school vs. college graduate and above: HR = 1.41, 95% CI 1.08 – 1.85) also was independently associated with higher mortality risk. In the fully adjusted model (model 3), males compared with females and individuals with lower income had significantly higher risks of all-cause mortality. Significant CVD-PIM, stroke-PIM, diabetes-PIM, CKD-PIM, and Afib-PIM interactions illustrated that CVD (HR = 1.79, 95% CI 1.47 – 2.17), stroke (HR= 1.59, 95% CI 1.25 – 2.02), diabetes (HR = 1.56, 95% CI 1.29 – 1.90), CKD (HR = 2.19, 95% CI 1.81 – 2.65), and Afib (HR = 1.72, 95% CI 1.37 – 2.16) were significantly associated with an increased risk of mortality only among the PIM users. Males had a higher risk of mortality independent of PIM use across all the models in all the censored follow-up time intervals.

For method 3 (follow-up time censored at 4 years), individuals with lower education had higher risks of mortality. In both the models 2 and 3, similar to the follow-up time

censored at 2 years, significant income-PIM interaction also illustrated that individuals with lower income had significantly higher risks of all-cause mortality. Similarly, significant stroke-PIM, diabetes-PIM, and Afib-PIM interaction indicated that stroke, diabetes, and Afib were significantly associated with an increased risk of mortality only among the PIM users.

Similarly, for method 4 (follow-up time censored at 6 years), individuals with lower income and education had an increased risk or mortality compared to their higher income or educated counterparts (in both the models 2 and 3). Significant Race-PIM interaction in both the censored time intervals illustrated that PIM use was a significant predictor of mortality among whites. However, blacks had a higher mortality rate even without PIM use. Additionally, diabetes and Afib were significantly associated with higher risk of mortality with PIM use.

APPENDIX E

Table. Association between DDIs and all-cause mortality and the effect of health disparities on this relationship (methods 2, 3, and 4)

Characteristics	Censored at 2 years (method 2), HR (95% CI)			Censored at 4 years (method 3), HR (95% CI)			Censored at 6 years (method 4), HR (95% CI)		
	Model 1	Model 2	Model 3 ¶	Model 1	Model 2	Model 3 ¥	Model 1	Model 2	Model 3 ǂ
DDI use									
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	**2.22 (1.68 - 2.92)**	a	a	**1.62 (1.33 - 1.98)**	**1.40 (1.14 - 1.71)**	0.91 (0.74 - 1.14)	**1.69 (1.45 - 1.96)**	**1.44 (1.23 - 1.68)**	0.97 (0.82 - 1.14)
Age group, years									
< 60	-	Ref	Ref	-	Ref	Ref	-	Ref	Ref
60-64	-	1.30 (0.96 - 1.76)	1.12 (0.82 - 1.52)	-	**1.33 (1.10 - 1.60)**	1.18 (0.97 - 1.44)	-	**1.47 (1.26 - 1.70)**	**1.34 (1.15 - 1.56)**
65-75	-	**2.13 (1.66 - 2.73)**	**1.69 (1.31 - 2.17)**	-	**2.11 (1.80 - 2.46)**	**1.80 (1.53 - 2.11)**	-	**2.41 (2.13 - 2.72)**	**2.09 (1.84 - 2.37)**
≥ 75	-	**4.33 (3.36 - 5.58)**	**2.93 (2.25 - 3.80)**	-	**4.59 (3.91 - 5.8)**	**3.42 (2.89 - 4.04)**	-	**5.58 (4.92 - 6.33)**	**4.33 (3.80 - 4.94)**
Gender									
Male	-	Ref	Ref	-	Ref	Ref	-	Ref	Ref
Female	-	a	a	-	**0.48 (0.44 - 0.53)**	**0.52 (0.47 - 0.58)**	-	**0.51 (0.48 - 0.55)**	**0.55 (0.51 - 0.59)**
Race									
White	-	Ref	Ref	-	Ref	Ref	-	Ref	Ref
Black	-	**1.20 (1.03 - 1.41)**	**1.23 (1.04 - 1.50)**	-	**1.13 (1.02 - 1.25)**	**1.13 (1.02 - 1.26)**	-	**1.13 (1.04 - 1.22)**	**1.13 (1.04 - 1.22)**
Income									
≥ $75,000	-	Ref	Ref	-	Ref	Ref	-	Ref	Ref
Less than $20,000	-	**3.38 (2.33 - 4.89)**	**3.27 (2.27 - 4.71)**	-	**3.01 (2.40 - 3.77)**	**2.63 (2.08 - 3.32)**	-	**2.67 (2.25 - 3.17)**	**2.34 (1.96 - 2.79)**
$20,000- $34,999	-	**2.30 (1.61 - 3.29)**	**2.29 (1.60 - 3.27)**	-	**2.06 (1.70 - 2.56)**	**1.92 (1.54 - 2.40)**	-	**1.91 (1.62 - 2.24)**	**1.79 (1.51 - 2.11)**
$35,000- $74,999	-	1.38 (0.96 - 1.97)	1.41 (0.97 - 2.04)	-	**1.36 (1.10 - 1.69)**	**1.33 (1.07 - 1.66)**	-	**1.31 (1.11 - 1.54)**	**1.27 (1.08 - 1.51)**
Education									
College graduate and above	-	Ref	Ref	-	Ref	Ref	-	Ref	Ref
Less than high school	-	**1.47 (1.15 - 1.87)**	1.20 (0.94 - 1.55)	-	**1.37 (1.17 - 1.61)**	1.16 (0.99 - 1.37)	-	**1.36 (1.21 - 1.54)**	**1.19 (1.05 - 1.35)**
High school or some college	-	1.19 (0.98 - 1.44)	1.11 (0.91 - 1.36)	-	**1.19 (1.05 - 1.34)**	1.11 (0.98 - 1.26)	-	**1.22 (1.12 - 1.34)**	**1.16 (1.06 - 1.28)**
Total number of medications use									
First quartile	-	-	Ref	-	-	Ref	-	-	Ref
Second quartile	-	-	**1.54 (1.17-2.03)**	-	-	**1.34 (1.14-1.58)**	-	-	**1.33 (1.17-1.51)**
Third quartile	-	-	**1.96 (1.49-2.60)**	-	-	**1.74 (1.48-2.06)**	-	-	**1.79 (1.58-2.03)**
Fourth quartile	-	-	**3.31 (2.53-4.32)**	-	-	**2.74 (2.34-3.21)**	-	-	**2.74 (2.43-3.09)**

Significant interactions									
Gender-DDI									
DDI Yes vs. No; Gender = Female	-	**2.72 (1.76 - 4.21)**	**1.77 (1.11 - 2.80)**	-	-	-	-	-	-
DDI Yes vs. No; Gender = Male	-	**1.62 (1.13 - 2.31)**	0.95 (0.65 - 1.39)	-	-	-	-	-	-
Female vs. Male; DDI = No	-	**0.43 (0.36 - 0.50)**	**0.45 (0.38 - 0.53)**	-	-	-	-	-	-
Female vs. Male; DDI = Yes	-	0.71 (0.42 - 1.23)	0.83 (0.47 - 1.46)	-	-	-	-	-	-

[a] Significant gender-DDI interaction; DDI: drug-drug interaction. Bold refers to P <0.05.

[¶] Significant covariates include: CVD (HR = 1.77, 95% CI 1.50 – 2.09), stroke (HR = 1.58, 95% CI 1.28 – 1.96), diabetes (HR = 1.61, 95% CI 1.37 – 1.89), CKD (HR = 2.24, 95% CI 1.90 – 2.65), and Afib (HR = 1.77, 95% CI 1.46 – 2.16).

[¥] Significant covariates include: CVD (HR = 1.61, 95% CI 1.50 – 1.80), stroke (HR = 1.65, 95% CI 1.44 – 1.89), diabetes (HR = 1.55, 95% CI 1.40 – 1.72), CKD (HR = 1.99, 95% CI 1.79 – 2.21), and Afib (HR = 1.57, 95% CI 1.38 – 1.79).

[ǂ] Significant covariates include: CVD (HR = 1.52, 95% CI 1.40 – 1.65), stroke (HR = 1.63, 95% CI 1.47 – 1.82), diabetes (HR = 1.47, 95% CI 1.36 – 1.60), CKD (HR = 1.92, 95% CI 1.77 – 2.08), and Afib (HR = 1.49, 95% CI 1.34 – 1.65).

Similar to the PIM analyses, the unadjusted model (model 1) suggested that individuals with DDIs had an increased risk of all-cause mortality across all the censored follow-up time intervals (Table 3). A gender-DDI interaction was found to be significant in method 2. Males compared with females had a higher risk of mortality regardless of having DDIs in both the adjusted models. However, females had an increased risk of mortality with the use of DDIs (model 2: HR = 2.72, 95% CI 1.76 – 4.21; model 3: HR = 1.77, 95% CI 1.11 – 2.80). No other interaction terms were found to be significant in any other censored follow-up time intervals. DDIs were significantly associated with higher risk of mortality in adjusted model 2 across methods 3 and 4; however, DDIs were not found to be a significant predictor of mortality in any of the fully adjusted model. Older age, males compared with females, blacks compared with whites, and individuals with lower income and education had significantly higher risk of mortality compared with individuals with higher income and education across all the censored follow-up time intervals. Individuals with higher medication use also had higher risk of mortality. Additionally, CVD, stroke, diabetes, CKD, and Afib were significantly associated with higher mortality rates irrespective of having DDIs.

Although all the unadjusted models showed higher risks of mortality with DDIs, none of the adjusted model (except for the method 2) showed such association. For method 2, the fully adjusted model suggests that females with DDIs had an increased risk of mortality. Prior research also found that older women are more likely than men to receive more drugs and have more DDIs.[224] However, this finding is inconclusive given no other models in our study found such relationship. Higher risks of mortality among

blacks, individuals with lower income, and education irrespective of DDIs also support our above discussion.