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FUNCTIONAL AND COGNITIVE STATUS AND MEDICATION COMPLEXITY IN OLDER ADULTS: THE HEALTH AND RETIREMENT STUDY

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FUNCTIONAL AND COGNITIVE STATUS AND MEDICATION COMPLEXITY IN OLDER ADULTS: THE HEALTH AND RETIREMENT STUDY

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Dedication

To my Husband

Without you this would only be a dream

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As I complete my dissertation and reflect on the journey so far, it has been a period of intense learning on both a personal level and also in the area of science. Working on this dissertation has impacted me positively and I would like to show my gratitude to those people who have supported and helped me through this period.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ADAMS: Aging, Demographics and Memory Study

ADE: Adverse Drug Events

ADL: Activities of Daily Living

CES-D: Center for Epidemiologic Studies Depression Scale

CI: Confidence Interval

CIND: Cognitive Impairment with No Dementia

HRS RAND: An edition of the HRS data files cleaned and aggregated by the RAND Corporation

HRS: Health and Retirement Study

IADL: Instrumental Activities of Daily Living

IQR: Interquartile Range

Log: Logarithm

LTCFs: Long Term Care Facilities

MCI: Mild Cognitive Impairment

mMRCI: Modified Medication Regimen Complexity Index

MRCI: Medication Regimen Complexity Index

NHI: National Health Insurance

OR: Odd Ratio

OTC: Over the Counter

PDS: Prescription Drug Survey

pMRCI: Patient-Level Medication Regimen Complexity Index

RR: Relative Ratio

SD: Standard Deviation

SNAC-K: Swedish National Study of Aging and Care in Kungsholmen

TICS: Telephone Interview for Cognitive Status

US: United States of America

VIF: Variance Inflation Factor

WHO: World Health Organization

Abstract

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By Duaa Bafail, Ph.D.

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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Introduction: Older adults have high prevalence of chronic illnesses that lead to have complex medication regimens. They are also more likely to have cognitive and functional impairments. Both cognitive/functional impairments and medication regimen complexity increase the risk of medication non-adherence. The objective of this study is to evaluate the association between prescription medication regimen complexity and cognitive/functional status at baseline and after two years, and to assess how changes in cognitive/functional status are associated with changes in medication regimen complexity.

Methods: This study used nationally representative sample of community-dwelling older adults from the Health and Retirement Study, followed over a two-year period. The exposures examined were cognitive status, and two types of functional status (Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs). The association between cognitive/functional status and medication regimen complexity was examined at baseline and after two years. Similar models were used to examine the relationship between cognitive/functional impairment and sub-components of complexity, and to assess how changes in cognitive/functional impairment were associated with changes in medication complexity over two years.

Results: Impairment in ADLs were associated with higher medication complexity at baseline ($p=0.0029$) and after two years ($p=0.0243$). Impairments in IADLs were associated with higher regimen complexity at baseline only ($p=0.0130$). Stratifying by depression status, IADL impairment was found to predict higher complexity at both time points, but only in participants without depression. Cognitive impairment was associated with lower medication regimen complexity at baseline ($p<0.0001$) and after two years ($p=0.0392$). Changes in cognitive/functional status were not associated with change in medication complexity over two years.

Conclusion: ADL impairment was strongly associated with higher medication complexity. IADL impairment showed some association with higher medication complexity, but this relationship may vary according to depression status and requires further investigation. Recognition of these impairments may offer health care providers the opportunity to intervene by re-assessing medication regimens for patients with functional impairments. Cognitive impairment was associated with lower medication complexity. Changes in cognitive or

functional were not associated with changes in complexity. Further study is needed to investigate this relationship over a longer period of time.

Chapter 1: Introduction

1.1 Introduction

Complex systems are prone to error, and where complexity exists the large number of interconnected elements increases the opportunity for errors to occur and that applies to medication regimens.[1,2] With increases in the availability of prescription and non-prescription medication, medication regimen burden for patients has grown.[2] Clinicians provide their care to the patient that has multiple comorbidities at a time when the development and the availability of medications has increased, which further complicates the medication regimen making complex medication regimens inevitable.[3]

With increases in life expectancy and a growing range of medications available to treat chronic conditions, the use of prescription medications is likely to continue to increase as well,[4] particularly for community-dwelling older patients. These individuals constitute the largest group of consumers of prescription medication in the US, with approximately 20% taking ten or more prescription medications.[5,6] Current medical practice is largely based on guidelines, which help healthcare providers prescribe the right treatment for each condition. Although the use of guidelines helps reduce the risk of non-evidence-based prescribing, this increases the chances of putting patients with multiple conditions on a large number of medications chronically. Patients with multiple chronic diseases such as diabetes, hypertension, chronic obstructive pulmonary disease and depression are likely to be on several medications[7,8] which is referred to as polypharmacy.[9] The median number of medications prescribed to people aged 65 years or older doubled from 2 to 4 between 1988 and 2010. The proportion of older adults taking five or more medications has nearly tripled from 12.8% in 1988 to 39.0% in 2010.[10]

The increased use of medications is likely attributable to the concurrent increase in age-associated chronic conditions.[11] The estimated prevalence of having 2 or more chronic conditions is 64% among adults aged 65 to 74 years and 71% among those aged 75 years or older.[12] The prevalence of functional impairment and cognitive impairment also increases with age.[13] The aging process generally results in changes and reductions in functional ability, such as declines in physical fitness, flexibility, strength, endurance, and agility, resulting in difficulties preforming normal daily activities.[14,15] As a result, the ability to function independently often declines with age.

Age also plays a role in accelerating the development of neuronal dysfunction, neuronal loss, and cognitive decline, which contributes to multiple problems like decreased intellectual function and neurodegenerative diseases.[16] In addition to age, older adults are often more likely to suffer from conditions such as heart disease, stroke, and arthritis that can lead to functional and/or cognitive decline.[17,18,19] This is particularly concerning in light of the fact that functional and cognitive impairment are risk factors for difficulty adhering to a prescription medication regimen. Reductions in mobility may create difficulties in filling prescriptions; decline in functional ability to manipulate small objects may lead to difficulties opening prescription containers. These functional impairments can act as barriers to compliance with a prescription medication regimen.[20,21] Furthermore, reduction in the ability to remember the details of the medication regimen can also contribute to non-adherence.[22] Adherence to a therapeutic plan is vital for patients in order to get maximum benefits in the form of disease control and health maintenance. This is more important in the older adult population in which a large proportion living with chronic diseases resulting in polypharmacy. Poor adherence to medicines has negative effects on the individual. On a personal level, it results in delayed resolution of

illnesses, the worsening of the symptoms of the disease and can lead to an increase in healthcare costs. In United States, nonadherence is estimated to cost billions of dollars annually.[23,24]

Not taking medications at the correct time, missing doses, or not following other medication-related instructions could potentially result in the patient receiving a suboptimal clinical outcome and therefore lead to therapeutic failure.[25] Poor patient compliance with medication regimens has been estimated to cause about 10% of hospital admissions in the United States.[26] The World Health Organization (WHO) suggests that greater health benefits could be achieved by improving patient compliance with existing treatment regimens than by developing new medical treatments.[27] Medication regimen complexity has been associated in previous studies with poor adherence to treatment, and was also identified by the WHO as one of the factors affecting adherence.[25,28] Several studies have also shown that simplification of medication regimens can reduce non-adherence.[25,29,30] Large numbers of medications, complicated medication schedules, or special instructions/requirements (such as cutting or breaking tablets or food interactions) can all contribute to medication regimen complexity and make it more difficult for patients to comply with the treatment plan.[31,32] Complexity is one of the primary causes of patients' non-adherence, with complex medication regimens reducing the likelihood of adherence to treatment.[31] Therefore simplifications of medication regimens and greater attention to managing complexity are potential remediation strategies for poor adherence, and will be critical in helping patients to use their medications correctly.[33]

1.2 Statement of the Problem

Although medication regimen complexity and cognitive/functional impairments have both been associated with poor medication adherence, there is limited data on the relationship between cognitive/functional impairments and medication regimen complexity. One study by Herson et al. (2015) showed that independence in activities of daily living was inversely

associated with high regimen complexity.[34] Study by Wimmer et al. (2015) showed no significant association between high medication regimen complexity and ADLs. In this study and a study by Lee et al. (2012), the association between medication complexity and cognitive impairment was evaluated, and the results showed medication regimen complexity was lower in participants with cognitive impairment.[35,36]

Further study of this relationship is needed, particularly in the United States population, as most of the existing studies were conducted in a non-United States population, which may have limited the generalizability. Furthermore, all existing studies were cross-sectional; there is a need for longitudinal studies, which may contribute new information to the understanding of this relationship. The proposed study will be the first to use a nationally representative sample of the United States older adult population to assess the relationship between medication regimen complexity and cognitive/functional impairments using a longitudinal design.

1.3 Research Questions and Hypotheses

Research Question: Is there an association between the functional/cognitive status and medication regimen complexity among older adults living in community, both cross-sectionally and over time?

Hypotheses: The hypotheses of this study are as follows:

H1A: There is an association between cognitive status and medication regimen complexity among older adults.

H0A: There is no association between cognitive status and medication regimen complexity among older adults.

H1B: There is an association between functional status and medication regimen complexity among older adults.

H0B: There is no association between functional status and medication regimen complexity among older adults.

1.4 Study Objectives

The objectives of this study are as follows:

I. To characterize medication regimen complexity among community dwelling older adults in the United States

II. To assess the association between medication regimen complexity and cognitive status
    1. Evaluate the association between medication regimen complexity and cognitive status at baseline
    2. Evaluate the association between medication regimen complexity and cognitive status after two years
    3. Compare factors that contribute to medication regimen complexity in participants with and without cognitive impairment.
    4. Assess the change in medication regimen complexity score and its association with change in cognitive status over two years

III. Assess the association between medication regimen complexity and functional status
    1. Evaluate the association between medication regimen complexity and functional status at baseline
    2. Evaluate the association between medication regimen complexity and functional status after two years
    3. Compare factors that contribute to medication regimen complexity in participants with and without functional impairment.
    4. Assess the change in medication regimen complexity score and its association with change in functional status over two years.

1.5 Significance of the Study

This study contributes to understanding the relationship between cognitive/functional impairment and medication regimen complexity in a nationally representative population of older adults. Older adults, who make up a significant percent of the US population, are more susceptible to the negative outcomes of medication use due to the higher chronic disease burden found in this population. This is the first study that will evaluate the association between cognitive/functional impairment and medication regimen complexity in nationally representative population of older adults living in the community in 2004 and 2006 and the change of medication regimen complexity over two years period. More importantly, the associated cognitive and functional decline in this age group also increases the risk of harm from complex medication regimens. This makes it particularly important to examine these populations. This study could assist healthcare providers in identifying older adult's patients who may require cognitive and functional assessments and assessment of medication complexity prior to therapy initiation. These assessments ensure that medication regimes are tailored to individual patients.

In addition, this study will attempt to highlight the importance of cognitive and functional assessments in clinical settings in order to identify individuals who are at risk of poor adherence. This can help to prioritize older adult's patients who need medication reviews and revision of their treatment plan to maintain adherence, which will help them to achieve maximal health benefits. Furthermore, the results will help efforts to maximize medication adherence by increasing healthcare providers' awareness of the need to minimize the complexity of medication regimens.

Chapter 2: Background and Literature Review

The purpose of this study was to examine the association of cognitive and functional status with medication regimen complexity in older adults living in the community. This section will provide background information on the definition of medication regimen complexity, the definition and prevalence of cognitive impairment in older adults, the definition and prevalence of functional impairment in older adults, multiple medication use and medication regimen complexity in older adults, cognitive impairment and adherence in older adults, functional impairment and adherence in older adults, medication regimen complexity, adherence, and other clinical outcomes in older adults and a literature review of the evidence relevant to this research study, namely, literature regarding the association of cognitive or functional impairment and medication regimen complexity in older adults.

2.1 Definition of Medication Regimen Complexity

Medication regimen complexity has been a subject of study for decades,[37] however the exact parameters of what constitutes complexity and how to measure these parameters has led to differing definitions of this construct throughout the literature. With increasing use of multiple medications, the impact of complexity is just beginning to be appreciated by researchers. The idea of polypharmacy, which is based on the number of medications an individual is taking, is not enough on its own to explain the large discrepancies seen with adverse drug events or adverse outcomes. It is also not sufficient for the evaluation of the impact of regimens on outcomes in intervention studies.[38] Additionally; there is a sense amongst clinical providers that the concept of polypharmacy may not fully explain observed results for adverse drug events and

subsequent adverse outcomes. Medication regimen complexity, unlike polypharmacy, provides detailed and nuanced data for researchers and practitioners.[38] Early studies defined medication regimen complexity as dose multiplied by the frequency of administration.[37] Other studies considered medication complexity solely as the number of medications or the number of tablets taken per day. Other researchers went further to account for complexity by combining the number of doses per day, in addition to the number of medications taken, to make up the components of medication complexity.[39–41] Another study evaluated the complexity of medications by multiplying the number of medicines administered by frequency of administration.[42]

Previously, the term 'regimen complexity' has been used interchangeably with 'medication count' in a manner similar to the concept of polypharmacy. This did not take into account other facets of complexity such as different dosage forms and dosing frequencies.[3,43] However, a patient's compliance is influenced not just by the number of medications taken but also by other factors, which make up regimen complexity. These include the number of doses to be taken, the route of administration, the preparation steps prior to administration and variable administration schedules.[37] To examine these factors, the Medication Complexity Index was developed by a graduate student (Kelly, 1988) to evaluate medication regimen complexity.[44] However, limitations in the original design made it quite difficult for users to record information. Due to these difficulties, George et al. (2004) redesigned the Medication Complexity Index and developed a 65-item medication regimen complexity index (MRCI) tool as a way to quantify several components of medication regimen complexity. This redesigned instrument, accounts for the dosage form (e.g. tablet, inhalation), dosing frequency (e.g. once a day, three time a day), and additional directions (such as crush the tablet, or take with food). Other information taken into

account in this tool includes multiple unit dosing (2 tablets, 2 puffs) and specific timing (e.g. at 3pm).[38] Weights were assigned to dosage forms, frequency of doses, and additional directions.

Although number of medications is one contributing factor to the MRCI score, the definition of MRCI is different than the definition of polypharmacy[38] because it also includes other aspects of the medication regimen.[39] The MRCI is a widely used instrument in studies and has been validated in a study by George et al. on chronic obstructive pulmonary disease patients. To measure that prescription medication associated with that disease; the tool was validated by an expert panel who subjectively ranked six regimens to ascertain the criterion validity. This indicated strong agreement (Kendall's W = .8, p = 0.001). The inter-rater and test-retest reliabilities for the total score and scores from the individual sections of the MRCI as ≥0.9 [38]. Further validation was done by Libby et al. included not only prescription medications associated with the disease but also over the counter (OTC) medications and other prescription medications which are often referred to as patient-level MRCI (pMRCI).[32,45] The patient-level MRCI has been used to measure medication complexity in several patient populations including depressed geriatric patients, organ transplant patients, patients with heart failure, HIV patients, hypertensive patients, patients with diabetes, and patients on dialysis.[46–51] Table 2.1 below shows examples of some MRCI components and their weighted scores. The full MRCI is included in Appendix A.

Table 2. 1 Medication regimen complexity index components and scoring

Component category	Elements	Elements score
Dosage form	Once daily	1
	Three times daily	3
	Hour intervals (e.g. Q12 h)	2.5
Dosing frequency	Oral (e.g. tablet)	1
	Topical (e.g. creams, ointments)	2
	Eye drops	3
Additional direction	Break or crush table	1
	Take at specific time (e.g. in the morning)	1
	Relation to food (e.g. take with food)	1

Note: This table contains a subset of MRCI elements for demonstration purposes, the full MRCI can be found in Appendix A

2.2 Definition and Prevalence of Cognitive Impairment

The prevalence of cognitive impairment increases with age.[52] Its effects impact families, carers, and health and social care providers as well as the patient.[53] Cognitive impairment is defined as a state where a person has trouble learning new information, remembering things, and concentrating or making decisions which can affect them to function adequately and independently in everyday life.[54] Cognitive impairment can range from mild to severe.[54]

Mild cognitive impairment (MCI) is a transitional stage which falls between normal ageing and dementia, and is defined as "an overall mild decline across cognitive abilities that is greater than would be expected for an individual's age or education, but is insufficient to interfere with social and occupational functioning, as is required for a dementia syndrome."[55] Patients with mild, cognitive impairment often complain of memory loss but show no evidence of dementia. Individuals may start to notice some minor changes in their cognitive function, including a decline in cognitive abilities such as thinking skills and memory.[52] These progressive changes are usually noticeable by the patients experiencing them or by other people around them

like a family member, however these changes do not significantly affect their functioning and the patients are still able to carry out their activities of everyday living.[54]

In severe cognitive impairment, the patient loses the ability to understand the meaning of or to remember the importance of things and loses the ability to talk or write. The loss of such basic but important functions results in an inability to live independently.[56,57] The underlying causes of mild cognitive impairment are not well understood however, there are some risk factors that are most strongly linked to mild cognitive impairment that are the same as those for dementia, which include a family history of the disease, progressing age, and chronic diseases such as cardiovascular disease in which blood vessels, including those that support brain function, experience reductions in blood flow.[58]

The prevalence of mild cognitive impairment is between 3% and 19% in the older adult population, with an incidence of 8 to 58 cases per 1000 individuals per year.[59] Cognitive impairment is associated with a higher risk for progression to dementia. The progression rates are estimated at 10% to 15% per year amongst older individuals with cognitive impairment compared to 1% to 2.5% among cognitively healthy older adults.[27] A recent study done by Plassman et al. used data from the "Aging, Demographics and Memory Study (ADAMS study)" to estimate the incidence of CIND (Cognitive Impairment with no Dementia) and the progression of CIND to dementia during the follow-up period. The ADAMS study used a longitudinal design, and included individuals from all the regions of the US.[62] The study reported that an estimated 5.4 million older adults (22.2% of the United States older adult population) had cognitive impairment without dementia. At follow-up, 11.7% of those with cognitive impairment had progressed to dementia.[62] A range of diagnostic and screening tests are available to assess cognitive function. Some are more detailed than others, and different tests assess different cognition domains. The Health and Retirement Study used the Telephone Interview for

Cognitive Status (TICS). The TICS is a screening tool not intended for diagnostic purposes, and omits certain areas examined by other tests, such as visuospatial and executive function. Domains assessed by the TICS include orientation, attention, short-term memory, sentence repetition, immediate recall, word opposites, and praxis.[63]

2.3 Definition and Prevalence of Functional Impairment

Functional status is "an individual's ability to perform normal daily activities required to meet basic needs, and maintain health and well-being without support."[64,65] Functional ability is central to overall independence and is a key determinant of quality of life.[66] Difficulties that substantially interfere with or limit role functioning in one or more major life activities is referred to as functional impairment.[66] Individuals with functional impairment often need the assistance of another person to perform one or more daily activities.[66] Functional impairment is assessed by many tools which could be self-reported or caregiver reported and characterized by being unable to carry out activities of daily living, which can be assessed using the activities of daily living tool (ADLs) that assesses tasks such as getting out of bed, dressing oneself and performing personal hygiene. Instrumental activities of daily living (IADLs) tool assesses tasks such as eating, walking, shopping, housekeeping and preparing meals.[66,64]

ADLs are the primary and fundamental elements of self-care. The inability to independently perform even one of these activities may signal the need for supportive services. IADLs are typically higher-level activities people must perform in order to remain independent in the community and are often a basis for assessment of needs for services to assist in maintaining independence.[66,67] The decline of functional status in older adults can lead to an inability to live independently at home and predisposes them to social isolation. This decline can be accelerated by personal risk factors which vary from patient to patient and can lead to a rapid

decline in functional status, or can be slowed by the introduction of external support and the application of appropriate interventions.[68,69]

Health promotion and halting functional decline in older adults is a longstanding public health policy issue in the United States.[70] However, there is no general consensus regarding changes in the trajectory of late-life functional status and disability in the older adult population over time. Some argue that late-life functional status and disability for older Americans has never been better, while others argue that the situation has not been improving [71,72] With the general population getting older, there has been a proportional rise in the decline of functional ability.[17] There has also been a concurrent rise in the prevalence chronic illnesses, which increase the risk of a decline in functional status.

The presence of multiple illnesses often reduces the ability to compensate as one would with a diagnosis of a single illness. As a result of this, comorbidities in older adult patients may lead to greater disability than generally anticipated.[17] Chronic disease includes conditions such as diabetes, cardiac disease, neurological conditions, cancer, obesity, and dementia. Some of these conditions are rare but very highly disabling like stroke, while other conditions such as arthritis are more common but may be less disabling.[73] The disabling effect can vary depending on the task the patient is trying to perform. For example, heart disease is more likely to produce difficulty with tasks involving physical activity such as housework, while neurological conditions such as Parkinson's disease may interfere with tasks requiring fine motor control.[74] Both the impairment and the underlying health condition should be addressed in older adults so that interventions can be developed to reduce the level of disability.

The coexistence of two or more health conditions (comorbidity) can result in more disability. As the number of impairments increases from one to four, the percentage of persons reporting dependence on others for assistance with activities increases exponentially (7%, 14%,

28%, and 60% respectively).[75] A recent study assessing functional status among individuals 65 and older participating in Medicare managed care plans collected data longitudinally from 1993-2007. The results of this study showed declines on all measures of function status (ADLs and IADLs). After an average of 8 years of follow-up, 36.6% of participants showed at least two new ADL limitations, 32.3% developed at least two new IADLs limitations.[76] Among older adults admitted to medical hospital units, the prevalence of pre-admission ADL disability was 20.7% among those 60-69 years, and 41.2% for those aged 70 or older. The prevalence of pre-admission IADL disability was 29.6% among those 60-69 years and 62.9% among those aged 70 years and older.[77]

2.4 Multiple Medications Use and Medication Regimen Complexity in Older Adults

It has been well-documented that older adults in the United States are likely to be taking multiple medications concurrently.[78,79] With medical advancements and public health improvements resulting in increased life expectancy, there are increasing numbers of older adults with multiple chronic conditions who require several medications to manage their conditions.[80,81] Older adults with multiple comorbidities are also more likely to experience cognitive and functional impairments.[82] 13% of older adults who have one or more chronic conditions also experience functional impairment and over 26% of older adults who have five or more chronic disease have functional impairment.[82] Chronic conditions are also associated with cognitive impairment, with approximately 24% of all cases of cognitive impairment without dementia are attributable to chronic medical illness.[62] Because cognitive and functional impairments are associated with chronic disease, it is not surprising that these individuals are more likely to use multiple medications, and more likely to be at risk for medication-related problems.[81,83]

The use of multiple medications can easily result from following clinical practice guidelines for a small number of chronic conditions such as hypertension, osteoarthritis, chronic

obstructive pulmonary disease and diabetes.[84,7] Multiple medications obtained from multiple prescribers and pharmacies, and the use of over-the-counter medications and alternative therapies such as herbal medicines contribute to medication-related problems.[85] Along with the widespread use of multiple drugs, older adults are frequently prescribed medication therapy with varying doses, different frequencies and varying routes of administration,[84] as well as various dosage forms such as tablets, inhalers or injections.[86,87] A sample of older adults aged 65 years and older with a diagnosis of depression was randomly selected in ambulatory clinics at the University of Colorado and University of San Diego. The results of this study showed that the complexity score for individual were on average 17.62 (San Diego) and 19.36 (Colorado). Dosing frequency contributed to 57-58% of the MRCI score, with patients having an average of 7-8 unique dosing frequencies in their regimens. For additional directions attached to a patient medication (e.g. crush pill, take with food, taper dose),at both sites, there was an average of 3 additional directions per regimen to clarify dosing.[46] The increased use of medications is likely attributable to the concurrent increase in age-associated chronic conditions. A study by Libbyet al. (2013) showed that using patient-level MRCI scores which included prescription drugs and over the counter medications across four chronic diseases, found that MRCI was higher in the geriatric depression cohort when compared to other cohorts for other diseases. The next highest complexity was the diabetes cohort followed by the HIV cohort and the hypertension cohort. Across all cohorts, most older adults were using dosage forms other than tablet/capsule. Large numbers of participants also had at least three additional directions and at least three different dosing frequencies.[32] As a result, the complexity of medication regimens increases making it more difficult for patients to comply with their planned treatments.[38] Medication regimen complexity increases the difficulty of self-care in the home for older adults.

Although many factors in medication regimen complexity may contribute to how complicated a medication regimen is, each element of complexity may differ in the extent to which it contributes to total complexity and complicates the medication regimen. A study by Advinha et al. (2014) used the MRCI to assess medication regimen complexity in institutionalized older adults, and found that the factor with the greatest contribution to complexity was number of medications.[88] Another study conducted by Wimmer et al. (2015) also showed that the number of medications was highly correlated with MRCI.[36] In the Advinha study, when they compared regimens with the same number of medications, dosing frequency was most closely associated complexity (r=0.922), followed by dosage form (r=0.768) and then additional directions (r=0.742).[88] A study by Elliott et al. (2011) also found that the most common regimen simplification implemented by hospitals was reduction in dosage frequency, which also led to reduction in the MRCI.[89] Finally, a study by Libby et al. showed that among all contributing factors to patient-level MRCI scores, dosing frequency contributed the most complexity points to the MRCI score (55%–64%), followed by dosage form.[32] Regardless of which component contributes the most to complexity, complexity itself is associated with detrimental outcomes for patients.[89] Complex medication regimens can lead to clinical consequences from both medication over- and under-use, and as the complexity increases, the risk of administration error also increases. Patients with complex medication regimens are less likely to fully comply with therapy compared to patients with simpler treatment regiomens.[33]

2.5 Cognitive Impairment and Adherence in Older Adults

Poor medication adherence is very common and is a major risk factor for health problems. This issue disproportionately affects older adults, as they are the highest users of prescription medications.[90,91] Adherence can be defined as taking the correct amount of a medication at the right time while following the instructions given with the medication, such as

taking it with or without food.[92] Older adults are at a higher risk of suffering the negative effects of non-adherence with therapy, particularly due to the high prevalence of chronic comorbidities in this group.[83] Management of chronic conditions often requires complex medication regimens, which is a known risk factor for poor adherence in older adults.[29,93]

Self-management and the ability to perform self-care helps maintain patient independence and empowers the patient to achieve effective disease management. Age-related reductions in the function and mobility put older patients at a higher risk of non-adherence than younger patients. Declines in cognitive ability further compound the problem and can worsen adherence.[21] Cognitive processes are required in order to manage a medication regimen on a daily basis. As a result, older adults with cognitive impairment are less likely to succeed in following complex medication regimens as intended by the prescriber.[94] Cognitive impairment is among the most important risk factors for medication non-adherence in older adults. Non-adherence is estimated to be almost three times higher in patients with cognitive impairment.[95] Cognitive impairment has also been shown to double the risk of non-adherence among older adults patients using antihypertensive medications.[96] Patients with cognitive impairment often have trouble understanding and following treatment recommendations. Such individuals may forget doses or take a dose multiple times leading to inadvertent overuse. This is often related to impairment of higher-level cognitive functions such as executive function, which is essential for planning and monitoring medication use.[92,94] Even individuals who retain the ability to perform basic tasks related to adherence, such as reading and being able to tell time, may be unable to comply with a complex regimen if elements of executive function such as planning and retaining information are impaired.[97]

Adherence to a medication regimen requires understanding the dosing directions and schedule, which requires planning to be able to take the drug at a specific time or under specific

circumstances such as after a meal. The ability to recall instructions for responding to missed doses and follow through with related plans is also required.[98] Deficits in executive function lead to impairments in the ability to create plans and to organize and carry out tasks. These are key skills involved in managing complex medication regimens, and as a result executive function deficits impair adherence to therapy.[98] This can result in poor disease control, medication errors, increased risk of hospital admission, and loss of independence in the area of medicine management.[99,100] Thus assessment of executive function and cognitive impairment will be critical to identifying older adults patients at risk for therapeutic failure due to poor adherence.[92]

2.6 Functional Impairment and Adherence in Older Adults

Age related and disease related changes are common among older adults and they often experience decreases in functional ability and greater difficulty in performing everyday tasks [101] It is associated with a lower quality of life, a higher risk of health decline and contributes to health care costs.[102] Functional decline can occur as a result of several factors including cognitive impairment, as it has long been part of the diagnostic criteria for cognitive impairment. A study by Farias et al. (2006) examined different types of cognitive impairment and their relationship with functional ability. This study found that compared to controls without cognitive impairment, individuals with mild cognitive impairment experienced more functional limitations, and individuals with dementia experienced an even higher level of functional impairment.[103] Individuals with such impairments often experience difficulty in adhering to medications due to these impairments.[104]

Functional impairment can also result from other causes such as chronic disease that can result in reduced mobility and poor manual dexterity, leading to reduction in functional ability. When these abilities are necessary for taking medication, this can result in reduced adherence.[105] Medication adherence was examined among Medicare patients with heart failure. Individuals

experiencing functional impairments were found to have lower levels of adherence over a one-year period.[106] Another study compared antihypertensive medication adherence in patients with and without functional impairment using medical claims data of the National Health Insurance (NHI). This study also found that adherence was lower in individuals with functional disabilities.[107] A recent study examined the impact of impaired mobility on medication adherence in older adults. According to this study, patients with severe or moderate mobility impairment had lower adherence rates to medication (62% and 66% respectively) than individuals with no mobility impairment (73%).[108] Reduction in functional ability often makes it difficult for patients to manage their medications and leads to considerable difficulties with tasks such as opening child-proof containers. Several medication types such as nebulizers, inhalers and eye drops require physical manipulation in order to administer them correctly. Conditions which impair joint function or manual dexterity may make the use of these medications difficult.[109] Due to these limitations, individuals with functional impairment are often at greater risk of medication non-adherence.[110,111]

2.7 Medication Complexity, Adherence, and Other Clinical Outcomes in Older Adults

Previous research has shown a correlation between negative clinical outcomes in older adults and complex medication regimens. Medication regimen complexity is reported to be associated with self-administration errors.[40] Family caregiver medication administration problems were also found to increase with medication regimen complexity, leading to the suggestion that complex medication regimens of individual patients could be used to identify caregivers at risk of experiencing difficulties administering medication.[112] Medication regimen complexity is also associated with higher rates of hospitalization, [113,114] and increases in MRCI score increased the probability of adverse drug events (ADE).[113] Higher MRCI scores were associated with an increase in all-cause mortality.[115] Complex medication regimens may be

particularly detrimental to patients who have experienced hospitalization. More complex medication regimens have been shown to be inversely associated with the probability of discharge directly to home from hospital.[116] In addition, complex medication regimens also have an impact on patient knowledge of new medications added to their regimens. Newly prescribed medications are common, with an estimated 40% of patients discharged from the emergency department receiving at least one new medication. In patients with already complex regimens, the addition of another medication to an already complicated list can make it more difficult to be knowledgeable about their medications.[117]

Poor adherence to therapy has been shown to have a negative effect on patients and to result in higher medical costs.[23] The relationship between medication regimen complexity and adherence has been examined in previous studies, demonstrating that high MRCI negatively impacts adherence in older adults.[118,119] The aim of treatment with medication is to optimize the benefit from medication while minimizing side effects. Unfortunately, this balancing act often requires detailed directions, which make treatment plans more complicated. Older adults generally have more difficulty adhering to complex treatment plans.[93] Both overall complexity and specific components of complexity can interfere with adherence.[25] Number of medications is negatively associated with adherence that is, the presence of more medications was associated with worse adherence.[120] Also having simple or complex dosing schedules would affect adherence as adherence to therapy is lower with more complex dosing schedules, and this has a negative impact for patients.[121] A retrospective cohort study investigated adherence in patients with type 2 diabetes taking oral anti-diabetic medications, and reported that complex treatment plans with more frequent dosing schedules were linked with poor adherence to therapy.[122] Patients on twice-a-day treatment plans had lower adherence over time than those on once daily dosing regimens.[123] Having the patient on lower dosing frequency is better and recommended for

improved adherence.[124] Other elements of complexity such as drug instruction and the dosage form can also impact adherence. Less complicated regimens with fewer doses and little or no special instructions (such as food and storage requirements) were associated with better adherence. [125] Multiple dosage forms reduced the adherence rate to treatment regimens with multiple components such as systemic corticosteroids and inhaled and long-acting bronchodilators in patients with severe asthma.[126] These factors all play a part in influencing patient adherence to treatment, and are therefore are important considerations in promoting good adherence to medication therapy.

2.8 Association of Cognitive/Functional Impairment and Medication Complexity in Older Adults

Introduction

The population of the United States is aging rapidly. By 2050, the population aged 65 and over is projected to be 83.7 million, almost double the number of older adults that there were in 2012.[10] Older adults also are the largest consumers of medication in the US, largely due to an age-associated increase in chronic conditions.[1] The management of these chronic conditions often requires the use of multiple medications for a prolonged period of time.[79] Because of this, multiple medication use is a common aspect of providing health care to older adults, leading to increase in prescribed medication use by older adults[2]. In addition, older adults are often prescribed medications with multiple dosing schedules, multiple dosage forms such as tablets and inhalers, and multiple routes of administration, all of which lead to complex treatment plans.[127] Higher medication regimen complexity increases the risk of poor adherence.[118,119] Older adults are also at risk for decline in their cognitive and functional abilities,[13] which can act as barriers to compliance with a prescription medication regimen.[20] It is therefore important to understand the association of cognitive and functional impairment with medication regimen

complexity in older adults. The objectives of this literature review are to identify and synthesize information from studies of cognitive or functional impairment and medication regimen complexity in older adults, to determine the factors associated with medication regimen complexity in older adults, and to identify gaps in the literature that should be examined.

Methods

The literature search was conducted from January 1998 to January 2018 in PUBMED/CINAHL and Google Scholar. In PUBMED and CINAHL, the search used the terms "poly-pharmacy" OR" medication" OR "medicine" OR "pills burden" AND "treatment complexity" OR "regimen complexity" OR "medication regimen complexity" AND "cognitive status" OR "cognitive impairment" OR "cognitive decline" AND "functional status" OR "functional impairment "OR "functional decline". In Google Scholar, targeted searches using individual terms or combinations of terms were used to find additional articles. Title and abstracts were first screened for inclusion and exclusion criteria, and duplicates were removed. Full-text articles were then screened for eligibility. Inclusion criteria included: (1) a study population consisting of older adults aged 60 years or older; (2) Observational studies or intervention-based studies; (3) cross sectional or longitudinal studies; (4) was conducted in or out the United States; and (5) the assessment of cognitive or functional impairment in the study population. Exclusion criteria included: (1) not using a validated tool to assess complexity of medication regimen; and (2) journal articles not written in English. The search over all databases yielded 225 results. In addition, the citations included in review articles were searched for relevant literature that was not captured in the literature search. After applying the inclusion and exclusion criteria at the title, abstract, and full-text screening stages, a total of three original research articles were found. The flow of articles throughout these stages is contained in Figure 2.1 Articles are summarized in Table 2.2

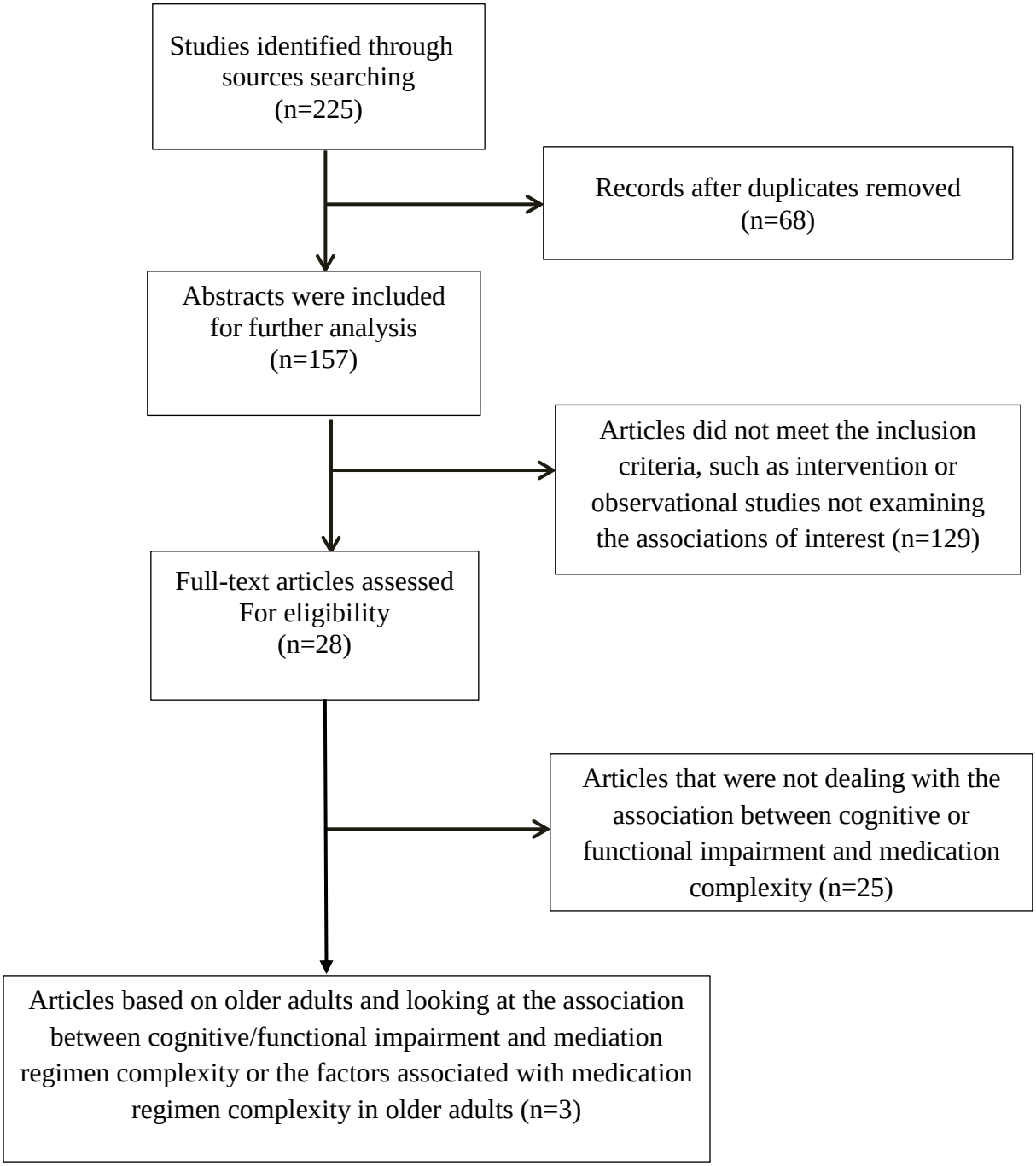

Figure 2.1 The Flow of Articles Throughout the Stages of Literature Review

Table 2. 2 Summary of Literature Assessing the Relationship Between Cognitive/Functional Impairment and Medication Complexity Among Older Adults

Study	Country	Setting and sample size	Assessment	Finding
(Herson et al. 2015)[34]	Australia	People aged 65 years and older living in LTCFs (n= 383)	To investigate factors associated with medication regimen complexity in older resident living in LTCFs	Independence in activities of daily living (ADLs) and dementia were associated with lower regimen complexity.
(Wimmer et al. 2015)[36]	Sweden	People aged 60 years and older in community and in residential aged care, living in Central Stockholm (n=3348)	To investigate factors associated with medication regimen complexity in older people	Medication regimen complexity was lower in participants with cognitive impairment. No significant association was found between (ADLs) and regimen complexity.
(Lee et al. 2012)[35]	USA	US. Older population aged 70- to 79-years, (n=3075)	To evaluate whether cognitive impairment is associated with medication complexity for prescription and over-the-counter (OTC) medications	Medication regimen complexity for prescription and OTC medications was lower in participants with cognitive impairment

Results: Summary of Studies

Two studies assessed the association between cognitive impairment and medication regimen complexity in two different settings. One study assessed dementia and its association to medication regimen complexity. The study by Lee et al. (2012) found that cognitive impairment was associated with lower prescription complexity after adjusting for other health status, demographics, and access to health care (RR 0.89; 95% CI 0.80 to 0.99). The number of prescription medications was not significantly different between cognitively impaired and cognitively intact individuals. Therefore, the lowering in the prescription medication complexity was not due to lowering in the prescription usage but rather due to less complex dosage from, and less dosage. Interactions between cognitive impairment and each chronic condition were assessed and did not produce statistically significant results. Cognitive impairment was also associated with lower over the counter (OTC) medication complexity (RR 0.76; 95% CI 0.64 to 0.93). The number of the (OTC) medications was also lower for those with cognitive impairment (RR 0.76; 95% CI 0.66 to 0.88). Thus, the decreased OTC complexity likely reflects a decreased number of OTC medications, rather than a difference in other components of complexity.[35]

The study by Wimmer et al. (2015) found that among older adults, predictors of being in the highest MRCI quintile were older age (OR=1.04, 95%CI 1.02;1.05), not living at home (OR=0.35, 95 % CI 0.15;0.86), greater chronic disease (OR=2.17, 95 % CI 1.89;2.49), good cognitive performance (OR=1.06, 95%CI 1.01;1.11), self-reported pain during the last 4 weeks (OR=2.85, 95%CI 2.16;3.76), and receiving help in sorting medications (OR=4.43 95 % CI 2.39;8.56) in comparing to those in lowest quintile. This study did not find a significant association between ADL score and medication regimen complexity score (OR=1.15, 95%CI 0.88; 1.52).[36] The study by Herson et al. (2015) assessed the association between several chronic diseases and medication regimen complexity. This study found that diseases associated with

higher complexity included diabetes, heart failure and pulmonary disease. This study also evaluated functional ability using activities of daily living (ADLs) and dementia, found that ADL and dementia were inversely associated with high regimen complexity (OR: 0.72, 95% CI: 0.62–0.84), (OR: 0.34, 95% CI: 0.17–0.67) resprectivey.[34]

Discussion

This review was conducted to understand and summarize the current literature on the association between cognitive/functional impairment and medication regimen complexity among older adults. The search yielded three studies, out of which two were focused on the factors associated with medication regimen complexity in older adults and one study assessed the association between cognitive impairment and medication regimen complexity in older adults.

Lee at al. (2012) evaluated whether cognitive impairment was related to medication regimen complexity for both prescription and over-the-counter (OTC) drugs. They found that cognitive impairment was associated with lower prescription complexity and lower OTC complexity. The authors suggested that prescribers may have simplified medication regimens to make the medication management easier for people with cognitive impairment. They also tested the difference in number of prescriptions and OTC medications between those with and without cognitive impairment and found that only OTC medication was significantly lower in those with cognitive impairment, and number of prescription medications was non-significantly lower. They attributed most of the reduction in prescription medication complexity to lower complexity from form and dosage frequency. Although it provided useful insights, Lee et al. (2012) did have several limitations. This study used a population of older adults in two US cities, Memphis, TN and Pittsburgh, PA. It is possible that prescribing patterns, population demographics, and population health may differ between these cities and other parts of the United States, limiting generalizability of the results. Eligibility for this study was also restricted to individuals who

were free of functional limitations, including having the ability to walk without an assistive device. These restrictions may have limited the representativeness of the study population and may make it difficult to generalize the results to other older adults.

The other two studies, Wimmer et al. (2015) and Herson et al. (2015), were conducted to investigate factors associated with regimen complexity in older adults. Both of these studies occurred outside of the United States. Wimmer et al. used data from the Swedish National Study of Aging and Care in Kungsholmen (SNAC-K), and Herson et al. used data from six long-term care facilities in Southern Australia. These countries differ from the United States which may limit the generalizability of their results to the United States. The results in Wimmer et al. showed that participants with the most complex regimens had higher cognitive scores than participants with less complex regimens. The authors noted that this was consistent with the findings of Lee et al. and supported the idea that prescribers might have simplified medication regimens to facilitate easier medication management in people with cognitive impairment. However, Wimmer et al. mentioned that their results should be interpreted cautiously because there was only a small variation in Mini Mental State Examination score across complexity groups. Finally, Herson et al. (2015) focused on a population receiving assistance from nurses and independent living facilities, which means that their results are unlikely to be applicable to community-dwelling older adults who must manage their own medications.

Both Wimmer et al. and Herson et al. assessed the association between medication regimen complexity and functional impairment (as measured using the index developed by Katz et al.[128]). Wimmer et al. showed no association between functional impairment and medication regimen and did not interpret this result further in their discussion. Herson et al. reported that independence in ADLs was associated with lower medication regimen complexity, but also did not interpret this result in their discussion, which suggests that they may interpret ADL

impairment as being a manifestation of dementia. Herson et al. also stated that clinicians discontinued or 'deprescribed' medications to residents with reduced life expectancy. The inconsistent results for the relationship between functional impairment and medication regimen complexity make it difficult to draw a clear conclusion from the existing literature. Additionally, it would be desirable to investigate functional impairment using both ADLs and IADLs to obtain more clear and precise data about functional ability. All of the studies included in this review are cross sectional in design, which does not allow for the examination of changes over time. A longitudinal study would be desirable to examine how cognitive and functional status is associated with changes in medication regimen complexity over time. Additionally, no study has investigated association between prescription medication regimen complexity and cognitive or functional impairment in a nationally-representative dataset. This study will be the first study to examine the relationship between cognitive/functional impairment and prescription regimen complexity in older adults using a longitudinal design and nationally-representative data.

Conclusion

The review of the literature suggests that older adults with good cognition may have higher medication regimen complexity than those with cognitive impairment. Two studies provide two different results for the association between functional impairment in ADL and medication regimen complexity, with one study reporting no significant association, and the other reporting that independence in ADLs was inversely associated with high regimen complexity. However, most of these studies used data from outside of the United States and had other restrictions that may limit their generalizability. There is a need for further studies investigating the association between cognitive/functional impairment and medication regimen complexity, particularly studies using a longitudinal design and a nationally-representative sample.

Chapter 3: Methods

3.1 Data Source

This study used a nationally representative sample of individuals aged 65 and over, using data from the Health and Retirement Study (HRS). HRS is nationally representative longitudinal survey of more than 37,000 individuals over age 50 living in more than 23,000 households in the United States. The HRS is supported by the National Institute on Aging and the Social Security Administration. The survey began in 1992 and is conducted every two years, following the same cohort of adults age 50 years or older, with new individuals added to the cohort at each wave. The HRS collects data on physical and mental health, family support systems, financial status, insurance coverage, and retirement planning. The HRS data is collected by interviewing the participants either in person or via a telephone interview. For individuals who are unable to complete the interview personally, a proxy completes the interview on their behalf. The main HRS survey is a free and publicly available data set, while some specialized sub-components of the survey are considered sensitive information and require a special approval to access restricted-use data. This study used data from the HRS surveys administered in 2004 and 2006, and also used data from the Prescription Drug Survey (PDS) sub-component of the HRS administered only in 2005 and 2007. An additional follow-up was administered in 2009 (the HRS 2009 Health and Well-Being Study), however the data release for the 2009 study did not include the detailed descriptions of participants' prescriptions, and therefore was not used for this study.

3.2 Study Design

This study used a retrospective cohort design, longitudinally following individuals over a two-year period. Baseline data came from the 2004 HRS questionnaire and the 2005 PDS questionnaire. Follow-up data came from the 2006 HRS questionnaire and the 2007 PDS questionnaire. The data from these years was used to assess the association between medication regimen complexity and cognitive/functional status at baseline and to assess the change in medication regimen complexity over a two-year period.

3.3 Eligibility of Study Participants

This study included respondents who, at baseline in 2004, were age 65 years or older and living in the community. In order to be eligible, participants must have been present in waves 7 (2004) and 8 (2006) of the HRS and must have completed the 2005 and 2007 PDS questionnaires. Participants with missing data for the outcome variable (medication regimen complexity) or the main predictors (functional or cognitive status) were excluded. In addition, participants who lived in a nursing home at baseline or who were interviewed by proxy at baseline were excluded. Thus, the study sample is representative of community-dwelling older adults aged 65 years or older.

3.4 Outcome Variable

The outcome under study was medication regimen complexity, which was assessed using a modified version of the medication regimen complexity index (mMRCI). the modified version of the tool was done and was administered by Lee et al.[35] The original MRCI is a validated tool developed by George et al. (2004). The MRCI has strong inter-rater and test-retest reliability.[38] The MRCI is a 65-item tool designed to quantify three components of medication regimen complexity. MRCI component "A" scores dosage form (e.g. tablets, injections, nasal spray) as a contributor to complexity, component "B" scores dosage frequencies (e.g. once a day,

every 12 hours) as a contributor to complexity and component "C" scores additional instructions (e.g. “break the tablet in half” or “take with food”) as a measure of complexity. Each dosage form is counted only once within a regimen. For example, if a patient's regimen consists of four tablets that are taken orally, their MRCI component “A” sub-score would be one. The MRCI component "B" measures dosing frequency (e.g. once a day, every 12 hours, alternate days) for each medication. A weight is given to each medication frequency, with higher weights assigned to greater frequencies. For example, if a patient is taking six medications with a frequency of once a day for each medication, the MRCI component B sub score would be six. MRCI component “C” measures additional directions (e.g. crush pill, take with food, taper dose). A weight is given for each instruction per medication. For example, if a patient is on a single medication that needs to be crushed and taken with meals, the component C score for that medication is two. The Medication Regimen Complexity Index is a summary score of all three components.

There is no limitation to the number of medications or special directions that may be counted for a patient, and as a result the MRCI is an open index without an upper limit to the possible range of scores.[38] For the purpose of this study, a modified version of the medication regimen complexity was created to account for the lack of information about additional instructions in the HRS 2007 Prescription Drug Study. For consistency, the same modified scale was applied to the 2005 data. The modified MRCI (mMRCI) score was calculated using the dosage forms and dosage frequencies with the same weightings applied as in the MRCI except in the scoring for frequencies in 2005, were coded as time per day not time per hrs. (for example: in 2005 some phrases like “take one tablet every 12 hrs.” the frequency was giving a score of 2 instead of 2.5 to ensure consistency across years. Details regarding dosage forms/dosage frequencies and their assigned weights are shown in the original MRCI tool that is attached in the

appendix A. The modifications to the MRCI resulted in a lower complexity score than the full MRCI score since points for additional instructions were not included. As with the MRCI, higher mMRCI scores indicate greater medication regimen complexity. In the analysis, the mMRCI was used as a continuous variable.

3.5 HRS Prescription Drug Study

HRS 2005 Prescription Drug Study

The HRS 2005 Prescription Drug Study is a supplemental study that was conducted in 2005. It is the first wave of a two-wave mail survey designed to track changes in prescription drug utilization. The PDS was intended to capture changes in prescription drug use associated with the implementation of Medicare Part D in 2006, with the 2005 wave recording data prior to the implementation of this program. The sample for the Prescription Drug Study (PDS) was drawn from respondents to the main HRS survey in 2004. This questionnaire also included a section containing detailed medication data, including drug names and information on dosage.

HRS 2007 Prescription Drug Survey

The HRS 2007 Prescription Drug Study (PDS) is the second wave of the PDS, conducted in 2007 after the rollout of Medicare part D. The second wave was designed to capture similar information to the first wave, but post-implementation. The sample for the 2007 wave of the PDS consisted of everyone from the original 2005 sample who responded to either the PDS 2005 or to the HRS interview in 2006.

3.6 Drug information in HRS 2005 and 2007 Prescription Drug Study

The survey used in the 2005 Prescription Drug Study asked the participants to provide information about each of the different medications they were taking and asked them to list all of

their prescribed medications. Space was provided in Section E to list up to ten prescription medications. Participants taking more than ten medications were asked to provide detailed information about the ten medications they considered to be the most important, and then to list all remaining medications in Section F. In section E, participants were asked to provide information from the label on the prescription bottle such as the name and dose of the medication (e.g. "Phenytoin (Dilantin) 100 mg") and dosage instructions such as "Take one capsule by mouth as directed in the morning and at bedtime." Section F asked for drug names only and did not include any other details.

The same instructions were used to collect prescription medication data in the 2007 Prescription Drug Study. However, in the 2007 survey, medication details in section E were provided in a different format. The 2007 version of section E contained separate fields for medication name (generic and brand name), medication strength (mgs or other units), format/unit (e.g. capsule, tablet, inhalant, liquid, drop, other), and dosage frequency instructions (number of units and number of times per day/week/month). Because the data fields provided about medication regimen complexity components differed between the two years, data recoding was necessary. The steps involved in the recoding process are shown in Table 3.1 below.

Table 3. 1 Summery of the Steps Involved in the Recoding Process of the mMRCI

Steps
1. (In 2005) All medication instructions, such as "Take one capsule by mouth in the morning and at bedtime" and were extracted and exported to an Excel spreadsheet to be manually interpreted and coded in a manner consistent with the 2007 drug variables. Details: • Scoring was based on the original MRCI as described in Appendix A, except where specified below • Dosage frequencies given in hours, such as "every 12 hours" or "every 6 hours" were converted to number of times per day and scored accordingly. (This differs from the original MRCI, in which "every 12 hours" was scored as 2.5, but "twice per day" was scored as 2.) • If prescription instructions were provided in a foreign language, they were translated using Google Translate and then coded • In instructions where multiple dosage frequencies were provided (such as "3-4 times per day") the more conservative (lower) score was assigned • Drugs for which a dosage frequency could not be reliably determined but where a dosage form was included were retained in the MRCI calculation.
2. (In 2007) All medication instructions such as (inhalant, drop, other) were extracted and exported to an Excel spreadsheet to be manually interpreted and coded. Lexicomp® and drugs.com were used to check the applicable sub format based on format, brand name, generic name and the strength of the drug e.g. "1 drop daily" the brand name, generic name and the strength of the drug would be used to check the Lexicomp® and drugs.com databases to determine whether the medication was eardrops or eyedrops.
3. (Both years 2005 and 2007) • For drugs with ambiguous dosage forms where the Lexicomp® or drugs.com databases found multiple plausible matches, and the forms of the plausible matches would have different MRCI scores, the form with the lowest MRCI score was used. e.g. for a drug such as insulin, which can be available as a vial (score=4) or a prefilled syringe (score=3) with identical strength and brand name, the lower score (3) was used to calculate the MRCI • Drugs for which a dosage form could not be reliably determined but where a frequency was included were retained in the MRCI calculation. • Drugs for which no information on dosage form and no information on frequency were available, were excluded from the MRCI calculation.

3.7 Creating the Complexity Variable and the Total Number of Medications Scoring Procedure for the mMRCI

The mMRCI was computed by adding the summary scores for dosage form and frequency from all of an individual's prescriptions. Prescriptions with partial information (e.g. missing form but known frequency, or missing frequency but known form) had all available information counted towards the score. Prescriptions for which both form and frequency were missing were considered invalid and did not contribute to an individual's mMRCI score. Individuals for whom all listed prescriptions were invalid were excluded. Some individuals in 2007 were found to have reported implausible values for drug frequency, such as reporting that a prescription was taken 90 times per day. These individuals after applying the inclusion and exclusion were 26 participants and were excluded from the study.

Creating the Total Number of Medications

The variable for number of medications was created based on the number of prescriptions participants reported in section E. Because section E allowed for a maximum of 10 prescriptions, this created a maximum value of 10 for this variable. Although participants were able to report additional drugs in section F, section F did not provide details about drug frequency and format, so these drugs could not be counted towards a participants mMRCI score. The PDS questionnaire also included a question about how many drugs a participant took regularly, where participants were able to provide a numeric answer with no upper limit, however, because dosage form and frequency information for any drugs not reported in section E would not be available, this variable was not suited for use in the present study. Total number of drugs was created by taking the number of prescription medications reported by each individual in section E and subtracting the number of medications for which both the frequency and the format were missing, so that drugs that provided no information towards the mMRCI score would be excluded.

Individuals who had no prescriptions reported in section E, but who had answered "yes" to earlier questions about medication use in section A were given a missing sample weight by the PDS. All individuals with a missing PDS weight were excluded. Individuals who did not complete section E but who had earlier reported that they were not using medications had positive sample weights and were not excluded and were assigned a complexity of 0. After scoring, the 2005 and 2007 data prescription drug surveys were merged. The two merged years of the PDS were then merged with the HRS RAND data.

3.8 Predictor Variables

The main predictors under study were cognitive status and functional status.

Cognitive Status

Cognitive status as measured using the total cognition score from the HRS data. This score was calculated as a sum of several tests comprising the Telephone Interview for Cognitive Status (TICS) battery.[129] The highest possible score was 35 points, with lower scores indicating poorer cognitive function. Tests in the battery included total recall, a test of working memory, and the mental status test. Total recall consisted of immediate free-recall (ability to remember a list of 10 nouns the respondent has just heard) and delayed word recall (ability to remember the same words after 5 minutes). The test of working memory was the serial 7s test, which asked the participant to subtract 7 from 100, and to continue subtracting 7 from each subsequent number for a total of five trials. The test of mental status included backward counting from 20 to 10, date naming where respondents were asked to report "today's date", object naming where respondent asked "What do you usually use to cut paper?" and "What do you call the kind of prickly plant that grows in the desert?" and president/vice president naming where respondents were asked to name the current president and vice president of the United States.

Cognitive score was used as a continuous variable when modeling relationships with overall complexity (at baseline, at follow-up, and longitudinally). For models examining sub-components of complexity, cognitive impairment was dichotomized using cutoffs identified in previous research using the HRS, with scores of 11 to 35 classified as "normal cognitive function" and scores of 10 or lower classified as "cognitive impairment". [130,131]

Functional Status

Functional status was measured using Activities of Daily Living (ADLs)[128], which are the basic activities performed at home, and Instrumental Activities of Daily Living (IADLs)[132], which are the activities required for living independently in the community. The ADLs scale included questions assessing the difficulty respondents experienced in walking across a room, dressing, bathing, eating, and transferring (getting in and out of bed). The IADL scale included questions assessing the difficulty respondents experienced when using the telephone, shopping, preparing food, taking medication, and handling finances. Each score (ADL and IADL) ranged from 0-5, with a higher score indicating that a respondent was able to perform a larger number of activities without impairment. The scores were summary variables constructed as counts of the number of ADL or IADL activities with which individuals reported at least "some difficulty", so an individual with a score of 0 reported impairments in 0 activities, while an individual with a score of 5 reported impairments in all 5 activities.

Both scores were used as continuous variables when modeling relationships with overall complexity (at baseline, at follow-up, and longitudinally). For models examining sub-components of complexity, each score was dichotomized into categories of "no impairment" and "one or more impairments".

3.9 Covariates

Socio-demographic covariates included age, gender, marital status, income (annual household income in dollars), years of education (0 to 17+), race, perceived health status, history of hospital stay in the previous two years, health insurance coverage, Medicare part D status, depression, number of people in the household, and number of chronic conditions.

Demographic Data Variables

Older adults were categorized into three age groups (in years): 65-74, 75-84, and 85 and above. Gender was categorized as male or female. Race was categorized as white, black, or other. Marital status was categorized as married or non-married (non-married includes never married, divorced, separated, and widowed). Annual income was grouped into five categories based on rounded cutoffs for the 25^{th}, 50^{th}, 75^{th}, and 95^{th} percentiles. This resulted in categories of $0-$15,999, $16,000-$28,999, $29,000-$50,999, $51,000-$134,999 and over $135,000. Years of education was classified as “no degree”, “high school”, “some college”, and “college degree”. Number of individuals in the household included the respondent, and was grouped into categories of 1, 2-3, 4 or more.

Access to Health Care Variables

Insurance coverage status was treated as a dichotomous variable based on whether the participant had any form of coverage (covered by federal government health insurance program, covered by health insurance from a current or previous employer, covered by other health insurance) or no coverage. Medicare Part D prescription coverage was introduced between the 2005 and 2007 waves, and thus was included only in follow-up and longitudinal models, but not in the baseline models. In models that included Medicare Part D, it was treated as a type of insurance coverage and incorporated into the dichotomous insurance coverage variable. History

of hospital stays in the previous 2 years was treated as a dichotomous variable coded as yes or no.

Health Status Variables

The health status variable was obtained from the survey question asking participants to self-rate their current general health condition. Excellent, very good and good were grouped together and the variable was categorized as (excellent/very good/good, fair, or poor). Number of chronic conditions was based on the number of questions to which participants had answered yes when asked "Has a doctor ever told you that you have [condition]?" Conditions included in the questionnaire were 1) high blood pressure or hypertension 2) diabetes or high blood sugar 3) cancer or a malignant tumor of any kind except skin cancer 4) chronic lung disease such as chronic bronchitis or emphysema 5) heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems 6) stroke or transient ischemic attack 7) emotional, nervous, or psychiatric problems and 8) arthritis or rheumatism. The number of chronic conditions variable was then categorized into none, 1-2, 3-4, and 5 or more. Depression was measured using a continuous score derived from the Center for Epidemiologic Studies Depression (CES-D) scale and was dichotomized into depression or no depression.

3.10 Missing Data

Following the initial application of inclusion and exclusion criteria, individuals were checked for missing or invalid data. 11% of individuals who had met the initial criteria were excluded for missing or invalid data on one or more variables. 2% of individuals had only invalid prescriptions (prescription for which no frequency or format data was available). A further 8% of individuals had not completed the prescription inventory despite answering "yes" to one or more questions about taking medication. 1% of participants were excluded for reporting implausibly high dosage frequency in 2007. For all other variables, including the main exposures (cognitive

and functional impairment) less than 5% of participants had missing data. Complete case deletion was used to address the problem of missing data. To ensure that this deletion did not create selection bias, individuals who were excluded for reasons related to the prescription inventory (missing prescription inventory, invalid entries, or implausible dosage frequencies) were compared to the rest of the sample on all major covariates using chi-square tests or Fisher exact tests (depending on cell size). Individuals who were missing data on complexity were significantly more likely to be unmarried, have a low income, more likely to have less than a high school education, and more likely to be African American.

3.11 Statistical Analyses

Descriptive statistics were used to describe the baseline characteristics of our sample. Continuous variables were expressed as the weighted mean ± standard deviation (SD). Categorical variables were expressed as the unweighted frequency and weighted percent. For both continuous and categorical variables, results were weighted to account for complex sample design. To ensure comparability to the general HRS population, including in more recent years, descriptive statistics were repeated using all participants in the 2012 wave of the HRS. The results of this 2012 descriptive analysis can be found in Appendix B.

The predictors were then examined for compatibility with the assumptions of the linear regression model. For continuous predictors, linearity of association with the outcome, normality of residuals, and homoscedasticity of residuals were checked. The residuals were not normally distributed, so the outcome variable complexity was log transformed, after which the regression assumptions were met. Residuals were also examined to detect extreme outliers. For categorical predictors, equal variance of residuals across categories was checked. All analyses were conducted using survey procedures to account for complex sample design. Because it is possible

that the structure or composition of the PDS sample may have differed from that of the broader HRS sample, weights specific to the PDS sample were used instead of the original HRS weights.

For aim I, characterization of medication regimen complexity among community dwelling older adults, distributions of each complexity sub-component were checked for normality. Because non-normal distributions were detected, the median and inter-quartiles ranges were used to summarize the total mMRCI score and each portion of the mMRCI calculation (number of medications, dosage form and dosage frequency). Dosage form and frequency were treated as categorical variables and were summarized by reporting the most prevalent dosage form and the most frequently observed dosage frequency among the population.

For the analysis for aims II and III, sub-aims 1, 2 (assessing the association between medication regimen complexity and cognitive and functional status), survey-weighted multivariable linear regression was used to examine the cross-sectional association between mMRCI and each exposure (cognitive status and ADL status, and IADL status). For the association between mMRCI score and cognitive status, multivariable linear regression models were performed cross-sectionally at baseline and at follow-up. Similar analyses were applied to assess the association between mMRCI score and functional status, with initial models assessing cross-sectional associations. ADLs and IADLs were assessed separately. The assumptions of the linear regression model were assessed. The residuals of the bivariate analysis between each sub-score for dosage form or dosage frequency and the main predictors were not normally distributed therefore log transformation was applied for the outcome. Finally, the "difficulty taking medication" IADL was examined separately in association with complexity in both years. The association between mMRCI score and both cognitive and functional impairment at baseline and after two years was also examined. Due to low sample sizes in both groups, the analyses could not be performed.

For the analysis for aim II.3 and III.3 ("Compare factors that contribute to medication regimen complexity in participants with and without cognitive impairment at baseline") survey-weighted linear regression was used to compare each individual element of the mMRCI between individuals with and without cognitive/functional impairments at baseline and after two years. The assumptions of the linear regression model were assessed. The residuals of the bivariate analysis between each sub-score for dosage form or dosage frequency and the main predictors were not normally distributed therefore log transformation was applied for the outcome.

For II.4 and III.4, survey-weighted multivariable linear regression was used to examine the change in mMRCI (2007 score - 2005 score) and its association with the change in cognitive status at baseline as well as its association with the change in functional status (ADL score, and IADL score separately). The assumptions of the linear regression model were assessed. Although the residuals in the bivariate analysis were normally distributed, there residual vs. predictor plot indicated heteroscedasticity, so the main predictors were categorized.

Change in yes/no covariates such as insurance coverage and history hospital stay were assessed by taking the 2007 value and subtracting the 2005 value. The result from the subtraction is (0, -1, and 1) which can then be used as a categorical variable. For the predictors ADLs, IADLs and cognitive status, changes were created by subtracting across the years, then coding the subtracted values into categories (0 = no change, < 0 = score decreased, > 0 = score increased). Changes in ordinal variables such as self-rated health were also categorized into no change, increase, and decrease. Other continuous variables (income, number of individuals in the household, and number of health conditions) were categorized by change status. Change in marital status was detected using subtraction, with a value of 0 indicating no change and values above or below 0 indicating a change.

Other covariates that were unlikely to change over the follow-up period such as gender and years of education were represented by using the baseline variable. Additionally, because all participants are expected to experience the same increase in age over the two-year follow-up period, the baseline variable for age was used.

1. Sensitivity analyses were performed to determine how the interview types (face to face vs telephone) would affect the results. Sensitivity analysis was done by performing the main analysis between cognition status and medication complexity at baseline and after two years with and without adjusting for the interview type variable and the same was done for functional status (ADL and IADL) with medication complexity at baseline and after two years. The results showed that after factoring in the interview type, the beta estimates of cognition, ADL, and IADL changed by less than 1%. This indicates that the interview type has no confounding effect.
2. Sensitivity analysis was performed, on the same people at baseline and after two years, by repeating the multivariable linear analysis of comparing complexity factors in participants with and without cognitive/functional impairment (ADL, IADL). The analysis was done on two groups and then on three groups (impaired at both timepoints, no impairment at both timepoints, and change in impairment between timepoints) and since the result produced similar results, it was decided to use only two groups for simplicity.
3. A sensitivity analysis was performed using cognitive decline (defined as score below 20) to contrast the result with the results when using cognitive impairment (defined as a score below 11).
4. The 2-way interaction was to test if any disease condition changed the association of mMRCI with cognitive/functional impairment. If no 2-way interactions were observed,

this would suggest that the other disease conditions did not change the association between mMRCI and cognitive or functional impairment. Interactions between cognition, ADL and IADL impairments and each disease conditions (cancer, heart disease, lung disease, arthritis, psyche, stroke, diabetes, hypertension and depression) were tested at baseline and after two years in the multivariable analysis. No significant interactions were detected for cognition and ADLs. However, significant interactions were found for IADLs and depression, therefore, stratified analysis was performed for IADL analysis by depression status.

5. Multicollinearity was examined among the continuous variables by checking the Pearson's correlation coefficient. Since a high level of correlation was found between ADL score and IADL score ($r = 0.5$, $p<0.001$) the two variables were kept in separate models, and neither variable was used as a covariate when examining the other. All statistical analyses were conducted using the SAS statistical software version 9.4 and using an alpha cutoff of 0.05.

3.12 Human Subject Protection and Data Privacy

The data from the main HRS survey is free and publicly available, however the Prescription Drug Study (PDS) is considered sensitive data and requires completing the Sensitive Data Access Use Agreement. The study also was reviewed and approved as exempt by the VCU IRB.

3.13 Sample Size of the study

The starting sample size was 3412 participants. After applying eligibility criteria, 2433 members of the sample remained, and 979 participants were excluded. After excluding individuals who were missing data, 294 individuals were removed, and 2139 participant were remained. The exclusion of individuals in 2007 who were found to have reported implausible

values for drug frequency, resulting in a final sample size of 2113 participant. The diagram in figure 3.1 shows the details of this process.

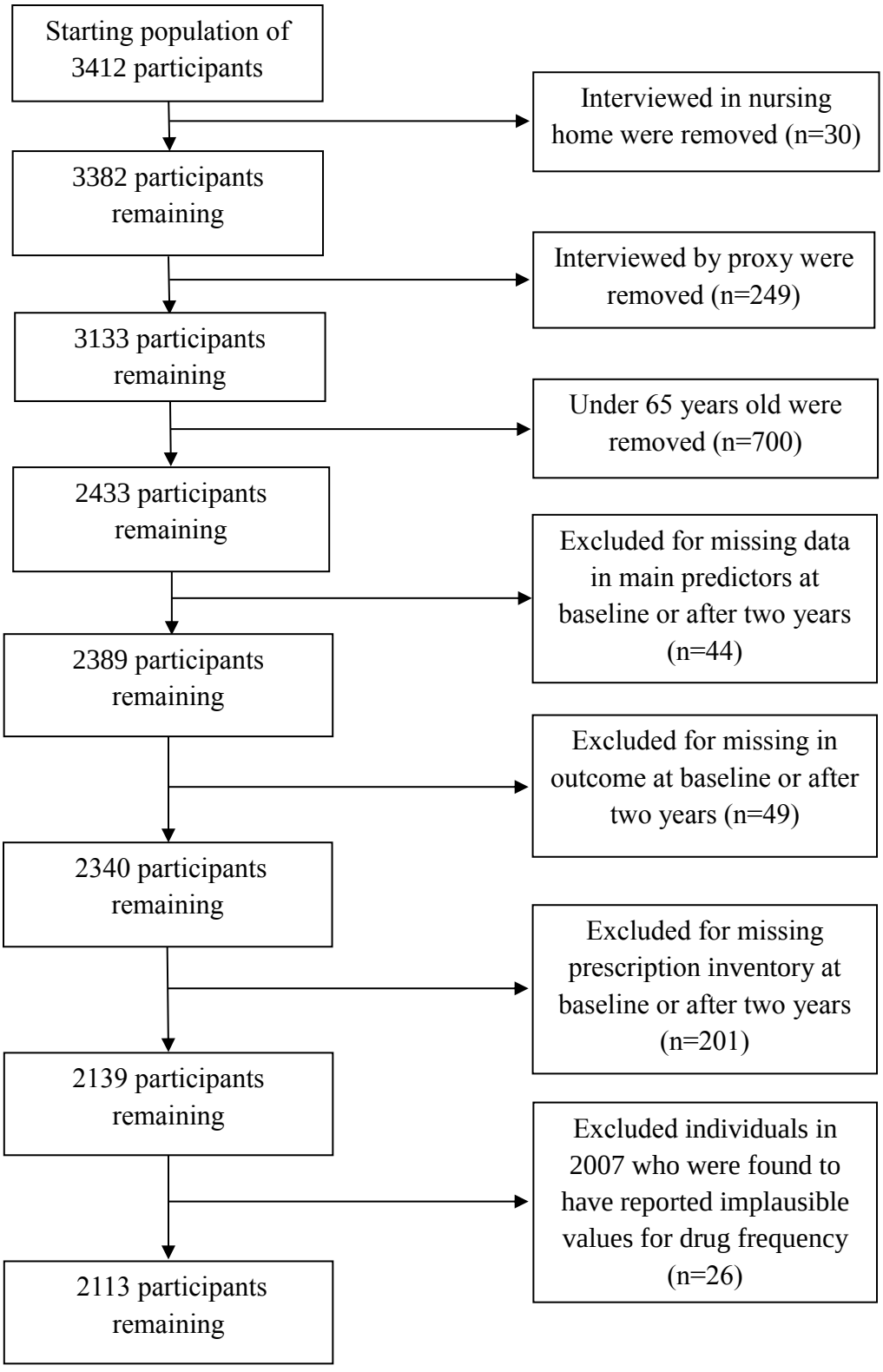

Figure 1.1 Flow Chart Representing Inclusion and Exclusion for the Final Sample

Chapter 4: Results

4.1 Characteristics of the Study Sample

Of the 2113 eligible participants, 58.75% were between the ages of 65 and 74 years, 58.37% were female, 90.97% were white, 78.61% had a high school or more advanced level of education, 60.70 % were married, and 57.32% earned more than $28,000 per year. A large majority (99.37%) were covered by insurance, and 77.19% reported their health was “excellent”, “very good” or “good”. Approximately 12.30 % of participants reported having difficulty in performing at least one of the ADLs, and approximately 9.80% reported having difficulty in performing at least one of the IADLs. Only 1.01% of the sample had cognitive impairment. In the 2007 data, the sample was slightly older, and had slightly higher prevalence for cognitive and functional impairments and chronic conditions. Demographic characteristics of the study sample at baseline and follow-up are summarized in Table 4.1. The results are weighted to account for the complex sample design.

Table 4.1 Summarizes the Demographic Characteristics of the Study Sample

Variables Total population n=2113	N, weighted frequency (%) (2005)	N, weighted frequency (%) (2007)
Age		
65–74 years	1302 (58.75)	1097 (45.75)
75–84 years	671 (34.84)	794 (41.84)
85 years or older	140 (6.40)	222 (12.40)
Gender		
Male	850 (41.62)	850 (41.62)
Female	1263 (58.37)	1263 (58.37)
Marital status		
married	1334 (60.70)	1261 (54.70)
non-married	778 (39.29)	852 (45.29)
Race		
White	1822 (90.97)	1822 (90.97)
Black	229 (6.02)	229 (6.02)
Other	62 (3.00)	62 (3.00)
Years of education		
No degree	535 (21.37)	535 (21.37)
High school	930 (43.90)	930 (43.90)
Some college	249 (12.95)	249 (12.95)
College degree	399 (21.76)	399 (21.76)
Income		
$ 0 to 15999	500 (20.24)	483 (23.24)
$16000 to 28999	512 (22.43)	511 (22.43)
$ 29000 to 50999	547 (27.40)	567 (27.40)
$ 51000 to 134999	445 (23.90)	457 (22.90)
$ over 135000	109 (6.01)	95 (4.01)
Covered by insurance		
No	18 (0.62)	17 (0.75)
Yes	2092 (99.37)	2094 (99.24)

Variables Total population n=2113	N, weighted frequency (%) (2005)	N, weighted frequency (%) (2007)
Number of people living at house		
1	563 (28.63)	628 (33.63)
2-3	1441 (67.20)	1372 (62.20)
4 or more	109 (4.16)	113 (4.16)
Previous hospital stay		
No	1492 (71.37)	1441 (67.63)
Yes	618 (28.62)	669 (32.36)
Health		
Excellent/very good/good	1581 (77.19)	1525 (70.19)
Fair	402 (17.59)	439 (21.59)
Poor	129 (5.20)	144 (8.20)
ADL		
None	1836 (87.69)	1749 (81.03)
Impaired	277 (12.30)	364 (18.96)
IADL		
None	1894 (90.19)	1834 (85.16)
Impaired	219 (9.80)	279 (14.83)
Cognitive status		
Cognitive intact	2080 (98.98)	2040 (97.58)
Impaired	33 (1.01)	46 (2.41)
Number of conditions		
none	241 (11.40)	178 (8.40)
1-2	1118 (53.35)	1061 (49.35)
3-4	659 (30.88)	747 (35.88)
5 or more	95 (4.35)	127 (6.35)
Depression		
No	1854 (88.80)	1828 (86.31)
Yes	259 (11.19)	285 (13.68)

4.2 Characterize Medication Complexity among the Population

Table 4.2 shows the survey-weighted and unweighted median values and interquartile ranges for total medication complexity and each of its subscores. The survey-weighted median will be presented in the results. The prescription complexity score ranged from 0 to 35, with a median of 5.24 and interquartile range (IQR) of 2.65 to 8.98 The number of medications ranged from 0 to 10 medications. The upper limit of 10 was created because the space provided for participants to fill out section "E" in the survey was limited to only 10 medications. Additional medications could be listed in a separate file but did not include details such as form and frequency, these medications were not counted towards complexity. The median number of medications was 2.86 (IQR 1.29 to 5.02). The complexity subscore from dosage form ranged from 0 to 14 with a median of 0.80 (IQR 0.33 to 1.75). Lastly, the complexity subscore from dosage frequency ranged from 0 to 27 with a median of 3.56 (IQR 1.49 to 6.78). All measurements showed small increases in 2007, as shown in Table 4.3.

In Table 4.4, the most common dosage form among the participants was oral medication (tables/capsule) with 91.68% of the population taking at least one tablet or capsule. The next most common form was inhaled medication, used by 9.02% of the population, followed by other dosage forms (ointment, cream, injection, etc.) used by 7.54%, and lastly drops (eyedrops or ear drops) used by 5.63%. The most common dosage frequency among the population was once per day with 87.79% taking at least one medication on this schedule, followed by two times per day with 47.39% of the population, followed by three times with 10.36% and lastly four times a day with 9.47% of the population. The prevalence of most dosage frequencies and forms showed small increases in 2007, as shown in Table 4.5.

Table 4.2 Medication Complexity Sub-Component Scores (2005)

Variables	Score range	Weighted median (IQR)	Un-weighted median (IQR)
Medication complexity	0-35	5.24 (2.65 to 8.98)	6.00 (3.00 to 9.00)
Number of medications	0-10	2.86 (1.29 to 5.02)	3.00 (2.00 to 5.00)
Dosage form score	0-14	0.80 (0.33 to 1.75)	1.00 (1.00 to 2.00)
Dosage frequency score	0-27	3.56 (1.49 to 6.78)	4.00 (2.00 to 7.00)

Table 4.3 Medication Complexity Sub-Component Scores (2007)

Variables	Score range	Weighted median (IQR)	Un-weighted median (IQR)
Medication complexity	0-35	6.45 (3.39 to 10.61)	7.00 (4.00 to 11.00)
Number of medications	0-10	3.73 (1.97 to 6.13)	4.00 (2.00 to 6.00)
Dosage form score	0-18	1.10 (0.46 to 1.95)	2.00 (1.00 to 2.00)
Dosage frequency score	0-23	4.47 (1.97 to 7.88)	5.00 (2.00 to 8.00)

Table 4.4 Percent of People Having Each Dosage Form and Dosage Frequency in 2005

Dosage form	**Weighted percentage**
Tablet/ Capsule	91.68%
Inhalation	9.02%
Others	7.54%
Drops	5.63%
Dosage frequency	**Weighted percentage**
Once/day	87.79%
Twice/day	47.39%
Three/day	10.36%
Four or more/day	9.47%

Table 4.5 Percent of People Having Each Dosage Form and Dosage Frequency in 2007

Dosage form	**Weighted percentage**
Tablet/ Capsule	92.81%
Inhalation	10.69%
Others	9.14%
Drops	5.93%
Dosage frequency	**Weighted percentage**
Once/day	88.59%
Twice/day	46.61%
Three/day	13.42%
Four or more/day	9.43%

4.3 The Association between Medication Complexity and Cognitive Status at Baseline and after Two Years

The fully-adjusted model at baseline showed that after adjusting for all covariates, for every one-unit increase in cognition score, the medication complexity score was 1.02 times higher ($p<0.0001$). This was confirmed by repeating the model after two years: in the 2007 data, it was found that after adjusting for all covariates, for every one-unit increase in cognition score, complexity increased by a factor of 1.01 ($p= 0.0392$). (Table 4.6)

Table 4.6 Adjusted Association between Cognitive Status and Medication Complexity

Variables	ß Coefficient*	P-value
At baseline		
Cognitive status	1.02	<0.0001
After two years		
Cognitive status	1.01	0.0392

* Due to a violation of the linearity assumption for regression, tests were performed on a log-transformed version of the variable, but results have been exponentiated to return to original values

4.4 Compare Factors that Contribute to Medication Complexity in Participants with and without Cognitive Impairment at Baseline and after Two Years

Comparing the complexity factors in those with and without cognitive impairment (defined as score below 11) at baseline indicated that there were no statistically significant differences in the number of medications score, dosage form score, or dosage frequency score between the two groups ($p = 0.5087$), ($p=0.9348$), and ($p=0.9691$), respectively. The analysis was repeated after two years, and again did not detect any significant differences in the number of medications ($p=0.4156$), dosage form score ($p=0.0512$), or dosage frequency score ($p=0.1687$) between the two groups. (Table 4.7)

A sensitivity analysis was performed using cognitive decline (defined as score below 20) to contrast this with the results when using cognitive impairment (defined as a score below 11). While 1.01% of the sample met the criteria for cognitive impairment, 20.12% of the sample met the criteria for cognitive decline. Table 4.6 shows the results of the sensitivity analysis using the exposure of cognitive decline. These results indicated that there were significant differences between those with cognitive decline and good cognition in number of medications ($\beta = 0.90$, $p=0.0037$) and dosage frequency scores ($\beta = 0.86$, $p=0.0019$) at baseline. After adjusting for all covariates, individuals with cognitive decline had lower dosage frequency ($\beta = 0.92$, $p=0.0368$) and dosage form ($\beta = 0.91$, $p=0.0305$), than those who had good cognition, and no significant difference in the number of medications between the two groups after two years. (Table 4.8)

Table 4.7 Comparison of Complexity Factors in Participants with and without Cognitive Impairment

Variables at baseline	ß Coefficient*	p-value
Number of medications		
Cognitive impairment	0.94	0.5087
Dosage form		
Cognitive impairment	0.93	0.9348
Dosage frequency		
Cognitive impairment	0.99	0.9691
Variables after two years	**ß Coefficient***	**p-value**
Number of medications		
Cognitive impairment	0.95	0.4156
Dosage form		
Cognitive impairment	0.87	0.0512
Dosage frequency		
Cognitive impairment	0.86	0.1687

* Tests were performed on a log-transformed version of the variable, but results have been exponentiated to return to original values.

Table 4.8 Comparison of Complexity Factors in Participants with and without Cognitive Decline

Variables at baseline	ß Coefficient*	p-value
Number of medications		
Cognitive impairment	0.90	0.0037
Dosage form		
Cognitive impairment	0.95	0.1585
Dosage frequency		
Cognitive impairment	0.86	0.0019
Variables after two years	**ß Coefficient***	**p-value**
Number of medications		
Cognitive impairment	0.92	0.1902
Dosage form		
Cognitive impairment	0.91	0.0305
Dosage frequency		
Cognitive impairment	0.92	0.0368

* Tests were performed on a log-transformed version of the variable, but results have been exponentiated to return to original values.

4.5 The Association between Medication Complexity and Functional (ADL and IADL) Status at Baseline and after Two Years

ADL Impairments

At baseline, adjusted comparison of complexity score and ADL score showed that after adjusting for all covariates, for one-unit increase in ADL score, medication complexity was 1.06 times higher (p=0.0029). This association remained significant after two years (p=0.0243). (Table 4.9)

Table 4.9 Adjusted Association between ADL Functional Status and Medication Complexity

Variables	ß Coefficient*	p-value
ADL at baseline		
Functional status	1.06	0.0029
ADL after two years		
Functional status	1.04	0.0243

* Tests were performed on a log-transformed version of the variable, but results have been exponentiated to return to original values.

IADL Impairments

At baseline, there was significant association between IADL score and medication complexity. For one-unit increase in IADL score, complexity was 1.07 times higher (p=0.0130). This association did not remain significant after two years (p=0.2412). (Table 4.10)

Interactions between number of IADL impairments and each disease participant have been tested at baseline and after two years. Significant interactions were detected between depression and IADL score at both baseline and follow-up. Due to this interaction, the analyses were repeated using stratification by depression status. (Table 4.11)

For participants without depression, at baseline after adjusting for all covariates, for one-unit increase in IADL score, medication complexity was 1.14 times higher (p=0.0001) and for participants with depression, no significant association between IADL score and complexity score was detected at baseline (p=0.4679). After two years, for participants without depression, after adjusting for all covariates, for one-unit increase in IADL score, medication complexity was 1.05 times higher (p=0.0334) and for participants with depression, no significant association between IADL score and complexity score was detected (p=0.4003). (Table 4.11).

The number of individual who reported having difficulty taking medication in the IADL measure was 26. In addition to that, the number of individuals with both cognitive impairment and ADL impairment (n = 8) and both cognitive impairment and IADL impairment (n = 12) were too low to provide adequate power for statistical testing, so individuals with difficulty taking medication and multiple categories of impairment could not be analyzed as a separate group.

Table 4.10 Association between IADL Functional Status and Medication Complexity

Variables	ß Coefficient*	p-value
IADL (unstratified) analysis at baseline		
Functional status	1.07	0.0130
IADL (unstratified) analysis at after two years		
Functional status	1.02	0.2412

* Tests were performed on a log-transformed version of the variable, but results have been exponentiated to return to original values

Table 4.11 Association between IADL Functional Status and Medication Complexity, Stratified by Depression

Variables	Not depressed ß Coefficient*	p-value	Depressed ß Coefficient *	p-value
IADLs at baseline	1.14	0.0001	0.97	0.4679
IADLs after two years	1.05	0.0334	0.96	0.4003

* Tests were performed on a log-transformed version of the variable, but results have been exponentiated to return to original values.

4.6 Compare Factors that Contribute to Medication Complexity in Participants with and without Functional Impairment (ADL and IADL) at Baseline and after Two Years

ADL Impairments

There was a significant difference in the number of medications and dosage frequency between the ADL-impaired and the ADL-unimpaired groups. After adjusting for all covariates, ADL functional impairment was associated with a higher number of medications (β =1.13, p=<.0001) and a higher dosage frequency (β =1.14, p=0.0005) compared to those without ADL impairment. There was no significant difference in the dosage form score between the two groups at baseline (p=0.9174). These results were repeated after two years, and results showed the same. After adjusting for all covariates, individual who have ADL impairment are associated with higher number of medications and higher dosage frequency than those without ADL impairment (β =1.09, p=0.0170), (β =1.07, p=0.0431) respectively. (Table 4.12)

Table 4.12 Comparison of Complexity Factors in Participants with and without Functional Impairment in ADLs

Variables at baseline	ß Coefficient*	p-value
Number of medications		
Functional impairment	1.13	<0.0001
Dosage form		
Functional impairment	1.00	0.9174
Dosage frequency		
Functional impairment	1.14	0.0005
Variables after two years	**ß Coefficient***	**p-value**
Number of medications		
Functional impairment	1.09	0.0170
Dosage form		
Functional impairment	1.02	0.3294
Dosage frequency		
Functional impairment	1.07	0.0431

* Tests were performed on a log-transformed version of the variable, but results have been exponentiated to return to original values.

IADL Impairments

There was a significant difference in the number of medications and dosage frequency between the IADL-impaired and IADL-unimpaired groups. After adjusting for all covariates, IADL functional impairment was associated with higher number of medications (β =1.17, p=0.0017) and a higher dosage frequency score (β =1.23, p=0.0002) compared to those without IADL impairment. There was no significant difference in the dosage form score between the two groups at baseline (p=0.1505). These results were repeated after two years, results showed that no significant difference was found for number of medications, dosage form and dosage frequency between the two groups (Table 4.13).

IADL Impairments Stratified by Depression

After adjusting for all covariates, individuals with IADL impairment and who were not depressed had significantly higher numbers of medications than individuals without impairments (β=1.24, p=0.0002). Individuals with IADL impairments also had significantly higher scores for dosage frequency (β=1.32, p <.0001) and dosage form (β=1.12, p= 0.0366) at baseline. These differences remained significant only for number of medications but not for dosage form and dosage frequency after two years. Those with IADL impairment and not depressed had higher number of medication (β =1.13, p=0.0426) than those without IADL impairment. Among individuals with depression, those with and without IADL impairments did not differ in number of medications, dosage form score, or dosage frequency score. This result was the same at baseline and after two years. (Table 4.14).

Table 4.13 Comparison of Complexity Factors in Participants with and without Functional Impairment in IADLs

Variables at baseline	ß Coefficient*	p-value
Number of medications		
Functional impairment	1.17	0.0017
Dosage form		
Functional impairment	1.07	0.1505
Dosage frequency		
Functional impairment	1.23	0.0002
Variables after two years	**ß Coefficient***	**p-value**
Number of medications		
Functional impairment	1.03	0.4267
Dosage form		
Functional impairment	1.05	0.2146
Dosage frequency		
Functional impairment	1.04	0.3568

* Tests were performed on a log-transformed version of the variable, but results have been exponentiated to return to original values.

Table 4.14 Comparison of Complexity Factors in Participants with and without Functional Impairment in IADLs

Variables at baseline	Not depressed ß Coefficient*	p-value	Depressed ß Coefficient*	p-value
Number of medications				
Functional impairment	1.24	0.0002	1.00	0.9573
Dosage form				
Functional impairment	1.12	0.0366	0.96	0.6458
Dosage frequency				
Functional impairment	1.32	<.0001	1.01	0.9310
Variables after two years	**Not depressed ß Coefficient***	**p-value**	**Depressed ß Coefficient***	**p-value**
Number of medications				
Functional impairment	1.13	0.0426	0.92	0.3277
Dosage form				
Functional impairment	1.06	0.2145	1.03	0.6464
Dosage frequency				
Functional impairment	1.10	0.0899	0.89	0.1806

* Tests were performed on a log-transformed version of the variable, but results have been exponentiated to return to original values.

4.7 Assess the Change in Medication Regimen Complexity Score and its Association with Change in Cognitive and Functional Status over Two Years

The analysis of the association between the change in mMRCI score and the change in each of the main predictors (ADL status, IADL status, and cognitive status) showed that there were no significant differences in the changes in mMRCI score after two years. (Table 4.15)

Table 4.15 Association Between Change in Predictors and Changes in Medication Complexity

Variables	ß Coefficient	p-value
Cognitive status		
No change	Ref	Ref
Cognitive declined	-0.19	0.5068
Cognitive improved	0.01	0.9956
Functional status (ADL)		
No change	Ref	Ref
Functional declined	0.19	0.7579
Functional improved	0.24	0.6003
Functional status (IADL)		
No change	Ref	Ref
Functional declined	0.67	0.3166
Functional improved	0.57	0.2614

4.8 Summery

These results support the existence of a relationship between good cognition and complexity, with cognitive impairment associated with lower medication regimen complexity. The decreased complexity was primarily due to the less complicated dosage forms and dosage frequencies prescribed to these individuals. ADL impairment shows more robust association with the increasing of medication regimen complexity than IADL impairment. ADL impairment was associated with higher medication regimen complexity at both baseline and after two years, with the number of medications and dosage frequency showing similar increases. The association between IADL and medication regimen complexity needs further investigation. Stratifying by depression status, IADL impairment was found to predict higher complexity in participants without depression but not participants with depression. There was no significant relationship between changes in cognitive/functional status and changes in medication regimen complexity over two years, however there is a need to continue to assess these changes over a longer period of time.

Chapter 5: Discussion

5.1 The Relationship between Cognitive Status and Medication Regimen Complexity

Higher cognitive scores were associated with higher medication regimen complexity, and lower cognitive scores were associated with lower complexity. This association could be the result of prescribers stopping or decreasing medications for cognitively impaired patients in consideration of the disease trajectory, treatment care goals, and life expectancy of the patients.[133] The observed decrease in medication complexity was present regardless of the type of chronic disease affecting the patient. This might reflect a switch from potentially curative therapy intended to prolong the patient's life to palliative treatment intended to provide symptomatic relief while reducing the adverse effects from medication.[134] Furthermore, the deterioration of the cognitive function might lead the physicians to reassess the patient's medication regimen which leads to reductions in medication regimen complexity.[133] Patients or care providers may also request that physicians prescribe a simpler regimen in response to subclinical or overt cognitive impairment. This is consistent with a previous study by Lee et al. which reported that cognitive impairment was inversely associated with medication regimen complexity and suggested that clinicians may have made the regimens less complicated in order to make it more convenient for the patients to manage their medications.[35] This is also consistent with the results of Wimmer et al. who found that patients with more complex regimens had higher cognitive scores than patients with less complex regimens.[36]

The attributable reason of why cognitive impairment was associated with lower complexity was further investigated. Using a cutoff score of 11 to define cognitive impairment[135,131], the

cognitively impaired group did have fewer medications and less complex dosage forms and dosage frequencies, but these differences were not statistically significant. The results may not have reached significance because only a very small proportion of the sample (1.01%) had a cognitive score below the cutoff. Sensitivity analysis using a higher cutoff of 20 to represent cognitive decline,[136] resulted in 20.12% of the sample being classified as having lower cognitive performance. With this definition, the results showed that at baseline those with cognitive decline had significantly lower number of medication and less dosage frequencies.

After two years still, those with cognitive decline had less dosage frequencies in addition to less complex dosage forms. However, number of medication no longer become significant with the higher cognitive score cutoff; there were no differences in the number of medications between the cognitive decline and normal cognitive function groups after two years. This is consistent with the results of Lee et al. who found no difference in number of medications between groups, and who suggested that the differences in complexity could result from other factors such as form and frequency.[35]

5.2 The Relationship between Functional Status and Medication Regimen Complexity

Higher ADL scores (which indicate greater functional impairment) were associated with higher medication regimen complexity at baseline and after two years. This was consistent with the results of Herson et al.[34] who found that independence in activities of daily living (ADLs) was associated with low regimen complexity. Our results indicated that the higher medication regimen complexity in the functionally impaired group was attributable to significantly higher numbers of prescriptions, as well as higher dosage frequencies. Many chronic conditions require treatment, thus multiple comorbidities are associated with higher medication regimen complexity.[36] Depending on the severity of the conditions, patients may have increased number of medications, dosage forms, and frequencies of intake. Chronic conditions may also lead to difficulties in

walking, standing, and fine motor skills, contributing to functional impairment.[137] However, no interactions were found between functional impairment and specific chronic conditions, indicating that functional impairment was associated with increased complexity regardless of which specific chronic conditions were present.

The findings from this study show that ADL functional impairment scores can serve as a predictor of medication regimen complexity, which suggests that there are opportunities for health care providers to intervene by re-assessing medication regimens for functionally impaired patients. Complex medication regimes have been linked with poor adherence.[25,27] Functional impairment is also known to reduce compliance with medication regimens.[105,106] These results indicate that more effort is required to reduce medication regimen complexity in geriatric patients with impaired ADLs.

Although there was an association between ADL impairment and complexity, there was no clear association between IADL impairment and medication complexity. The association was significant at baseline but not after two years. Therefore, this association requires further investigation. One way to interpret the results would be to look at the relationship between IADL and cognitive impairment. The high correlation between cognitive decline and a decline in the ability to perform IADLs has been shown in previous studies.[138,139] IADLs require more complex neuropsychological processing capacity than ADLs and therefore are more prone to deterioration triggered by cognitive decline.[140,141] In particular, a decline in executive function can be a key contributor to impairment in IADLs.[138] Functional deficits have been observed early in the course of cognitive decline.[142,143] Nygård et al. reported that IADLs can be impaired before the onset of dementia, and should therefore be included in the diagnosis of mild cognitive impairment.[144]

Therefore, we could assume that doctors tend to reduce the medication complexity for their patients based on their cognitive function. Meanwhile, the functional status of the patients is often

not investigated as much. Establishing a baseline of cognitive function and functional status is not the current standard of practice. The functional and cognitive status of patients has been shown to correlate well with multiple outcomes such as their length of hospitalization, recovery and their ability to carry out their activities post recovery. In order to have better data to assess the relationship between functional status IADLs and medication regimen complexity, we must promote their assessment as the standard of care in various medical settings.[145]

When stratifying by depression status, the result showed that IADL impairment was significantly associated with higher medication regimen complexity only in the strata of individuals without depression, and that there was no significant association between IADL impairment and medication regimen complexity for individuals with depression. The lack of a significant result in the depression strata could have been due to the relatively small sample size of this strata (259 people) which may have reduced statistical power, however the interaction term between IADL impairment and depression status was significant in the unstratified model which suggests that there may be a true underlying difference.

Although depression treatment may lead to increases in medication regimen complexity[35], individuals with depression often do not seek help or receive treatment. Individuals with depression are also more likely to neglect their health, less likely to seek medical advice, and more likely to forget to take their medications or even pick them up.[146] Depression may be a barrier to adherence with a complicated medication regimen, with patients who are depressed being less likely to take their medications as prescribed.[147] It has been reported that there is a threefold increase in the odds of non-compliance among individuals with depression.[148] As such, this lack of significance could be explained by the fact that even if these individuals should have had a high number of medications, they may not have sought help or been compliant with their medication regimens, leading to lower medication use and therefore lower reported complexity.

5.3 The Relationship between Changes in Cognitive/Functional Status and Changes in the Medication Regimen Complexity

There were no significant associations between changes in cognitive impairment, ADL impairment, or IADL impairment and changes in complexity over two years. In an aging population, there are some characteristics like cognition, functional ability, and medication complexity that are expected to change over time. Cognition and function will likely decline, due in part to the natural process of aging.[149] Similarly, as older adults age they face more health issues, that often require them to take multiple medications to treat chronic health problems and, based on that, the nature of medication complexity will also change becoming more complex.[10,11,12] These changes may take years to manifest, and the ages at which they occur may differ between individuals based on genetics, lifestyle, and prior medical history.[150] Rates of decline may become more rapid in the later stages of disease, which may not be captured with only two years of follow-up.[151] Another important factor to consider is hospitalization, which is associated with greater changes in cognitive and functional impairment and with increases in complexity.[152] Only 28.6% of our sample reported hospitalization during the two years of follow up, which may have limited our ability to detect hospitalization-related changes.

Descriptive analysis found that the majority of the sample (58.75%) was in the youngest age group of 65-74 years old. Most of the sample (98.98%) had good cognition, and the prevalence of ADL impairments and IADL impairments was low (12.30% and 9.80% respectively). 77.19% of participants reported that their health was excellent, very good, or good. The prevalence of most chronic conditions was low, with the exceptions of hypertension (66.52%) and arthritis (62.83%). These results indicate that participants in the Prescription Drug Study were a fairly healthy sample. The prevalence of most chronic conditions, and the prevalence of ADL and IADL impairments, did not differ between the PDS sample and the overall HRS sample.

For comparison, the sample used in this study was compared to a more recent HRS sample from 2012. Similar to the PDS, the majority of the HRS 2012 participants (57.12%) were in the youngest age group (65 to 74 years old). The majority of the sample had good cognition (96.55%), 15.02% reported IADL impairments, and 16.84% reported ADL impairment. As in the PDS sample, the prevalence of most of the chronic conditions was low, with the exceptions of hypertension (68.34%) and arthritis (68.94%). 73.13% of participants reported that their health was excellent, very good, or good. Details of the 2012 comparison sample can be found in appendix B.

Over the two years of follow-up, the PDS sample did not experience large changes in the prevalence of cognitive impairment (1.01% vs. 2.41%), IADL impairment (9.80% vs. 14.83%), or ADL impairment (12.30% vs. 18.90%). This may also help to explain why no significant relationship was detected between changes in these predictors and changes in complexity between the two periods.

5.4 Strengths and Limitations

Results should be interpreted in light of the strengths and limitations of this study. Although the data was longitudinal, only two years of follow-up were available in the PDS, so any changes occurring beyond these two years were not captured. Although a longer follow-up period would be desirable this data is not currently available. PDS data was not captured at the same time as the primary HRS survey data, thus it is possible that undetected changes between times of measurement may influence results (for example, an individual with low impairment in the 2004 HRS survey may have suffered a stroke and experienced increased impairment before the 2005 PDS survey). Because the HRS used both telephone and face-to-face interview modes, and only a subset of cognitive tests could be performed during the telephone interviews, it was not possible to measure all aspects of cognitive function such as executive function.

As with all survey data, bias affecting self-reported answers cannot be eliminated. The medication inventory is completed by the participants as part of a mail-in survey or telephone interview. Cognitive impairment may have impacted the reporting of medication because people with cognitive impairment may be less able to provide accurate medication information, creating recall bias. It was possible to check for certain types of missing information. The impaired and unimpaired groups did not show large differences in the percent of individuals leaving the prescription inventory section blank (5.7% and 6.4%, respectively). The percent of individuals who omitted frequency or format details for at least one prescriptions also did not show large differences (29.8% in those without cognitive impairment, and 28.7% in those with cognitive impairment). Other missing information could not be checked, such as individuals leaving prescriptions out of the inventory or providing inaccurate details, so it is still possible that this could have contributed to bias. The measures used in HRS to assess functional status are also based on self-report of participants' functional status at the time of interview and may not capture fluctuations in functional status over time unless they are substantial.

Although the PDS survey asked participants to report their over the counter medications in a separate section, this section did not include any details about dosage form and dosage frequency, so only prescription medications were considered when calculating the complexity score. Individuals with partially missing prescription details were included in the study, which likely led to lower complexity scores for these participants as the missing data could not count towards their complexity scores. Although the low scores for these individuals are not ideal, including these individuals in the sample was still preferable, because omitting them would have excluded a large proportion of the sample and would also have led to biased and non-representative sample. The detailed drug report section allowed a maximum of 10 prescriptions, so individuals with more than 10 prescriptions could not report all their medications and would also

have received lower complexity scores. Of the 2113 participants, only 54 people (2.6%) at baseline and 83 people (3.9%) at follow-up responded to the question "How many medications do you take regularly?" with a number greater than 10. This means that most of the sample would have been able to report all of their medications in the prescription inventory, which reduces the potential impact of this limitation. Finally, because the PDS data lacked information about additional directions included with the prescription, the complexity measurement instrument used in this study was a modified scale that did not account for this dimension of complexity, leading to a lower total complexity score. Although this reduces comparability with other studies that used the full instrument, the modified instrument has also been used in other studies, so it is possible to compare the results of this study with some existing literature. (cite) Additionally, existing literature using the full complexity instrument has reported that form and frequency are the two components with the greatest effect on complexity, and these two factors are included in the modified instrument.

It was not possible to perform analysis of individuals with both functional and cognitive impairment due to small sample sizes (8 people had both cognitive and ADL impairments, and 12 people had both cognitive and IADL impairments). The criteria excluding those interviewed by proxy at baseline (7.3% of the population) is likely to have led to underrepresentation of those with the most severe cognitive or functional impairments and may also have led to underrepresentation of individuals with both cognitive and functional impairment. However, the purpose of this study was to examine complexity among people who were able to care for themselves and were likely to be managing their own medications, and such individuals would be unlikely to be interviewed by proxy, so the exclusion criteria were consistent with the study intentions. However, future studies examining complexity in more severely impaired individuals are recommended.

Due to the data usage agreement with the HRS, it was not possible to share the prescription details with others. With only one person coding the prescriptions, it was not possible to test inter-rater reliability. However, the differences between prescription complexity in 2005 (where prescription details were coded by hand) and 2007 (where the majority of prescription details were coded by HRS staff) were not large and were in the expected direction (as study participants got older, their complexity was expected to increase) which suggests that the hand-coded details were fairly consistent with the HRS-coded details.

The PDS data was collected in 2005 and 2007, and it is possible that there may have been some changes in clinical and prescribing practices since then. However, recent literature suggests that the need to assess for cognitive and functional impairments in clinical settings is still an important issue, which would suggest that practitioners are still often not accounting for these factors. Thus, although this study uses older data, it still contributes important information to support the need for prescribers to assess impairment and review medication complexity to improve adherence in older adults.

This study also had several strengths, including the use of a complexity score that reflected multiple dimension of complexity (number of medications, dosage form, and dosage frequency), the use of longitudinal data, and the availability of detailed covariates that allowed for thorough assessment of confounding. This study also assessed ADL, IADL, and cognitive impairment in tandem in the same sample, and was the first study to do so using longitudinal data from a nationally-representative sample. Another strength of this study was that interactions were examined between chronic conditions and each of the main predictors, which confirmed that the associations between impairment and complexity were robust across a variety of conditions.

5.5 Implications and Future Directions

The results of this study have three main implications for clinical practice. First, regular assessment of cognitive and functional impairments should be a standard of care for older adults. Second, it is important to review medications to identify complex regimens that increase risk of poor adherence. Finally, it is important to combine this information to identify individuals with impairments and complex medication regimens who may be particularly in need of interventions to reduce their regimen complexity while still meeting their medical needs.

To facilitate these recommendations, it will be important to have an interconnected system to manage information from all of a patient's healthcare providers, so doctors can be aware of all of their patients' prescriptions from different sources and be able to account for this in their own prescribing and to communicate any concerns to the patient's other providers. Doctors should also routinely assess for cognitive and functional impairment that may indicate a particularly strong need to reduce a patient's prescription complexity. Some programs, such as Medicare, have implemented a requirement for assessment of cognitive impairment as part of an annual wellness appointment, however more frequent assessments including both cognitive and functional impairment should become a routine standard of care.

The findings of this study can play a significant role in encouraging further research in this area. Although this is an observational study that cannot demonstrate causation, it does provide evidence of an association between complexity and impairment. Existing studies have shown that individuals with impairment are at higher risk poor adherence, and that higher complexity is also a risk factor for poor adherence. Based on this information, it seems reasonable to suggest an intervention study to assess whether reducing complexity for those with cognitive/functional impairment would improve their adherence. The intervention study could also include individuals without impairments, to see if the intervention has a greater impact for individuals with

impairments, especially individuals with functional impairments who are likely to have higher complexity. Also, more studies are needed to assess the association between cognitive/functional impairment and medication complexity over longer periods of time, particularly to clarify the relationship between IADL impairment and complexity. Further research is also needed to investigate how changes in cognitive/functional status would predict changes in medication complexity over longer periods of time. This would help determine how the changes in functional status would predict the changes in MRCI. Also, it would be interesting to include all prescriptions and over the counter medications in the study to determine which has the greatest effect on complexity. We were not able to determine this in our study because of the nature of HRS data that only captures full details for prescription medication.

5.6 Conclusion

This population-based retrospective longitudinal study was conducted to understand the cross-sectional associations between cognitive status, functional status and medication regimen complexity among older adults, and to examine how changes in these factors would predict the changes in medication regimen complexity over a period of two years. The analysis found that ADL impairment was a key predictor of higher medication regimen complexity but IADL impairment association with medication complexity needed further investigation. Cognitive impairment was associated with lower medication regimen complexity. None of the changes in these factors were predictors of change in medication regimen complexity over two years. Suggestions for future research in this area include 1) investigating the relationship between IADL impairment and medication regimen complexity among older adults, 2) studying the association between the change in cognitive/functional status and the change in medication regimen complexity over longer period of time, 3) studying the effect of medication regimen complexity on adherence of those with and without cognitive/functional impairment and 4) whether functional

status assessment in clinical practice would result in reduced medication complexity and therefore improved medication adherence.

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Appendix A

The Medication Regimen Complexity Index, Section A (George et al., 2004, p. 1374)

Appendix II. Medication Regimen Complexity Index (MRCI)

MEDICATION REGIMEN COMPLEXITY INDEX

Patient ID: ----------

Total no. of medications (including prn/sos medications): ----------

Instructions

1. MRCI applies only to prescribed medications. All entries are to be made only based on information on the label or drug chart (at the time of dispensing or discharge). No assumptions are to be made based on clinical judgement.
2. There are three sections in the scale. Complete each section before proceeding to the next. At the end, add the scores for the three sections to give the MRCI.
3. If the same medication (same brand and same dosage form) is present more than once in different strengths in a regimen (e.g. Marevan 5mg, 3mg and 1 mg mdu), it is still considered as one medication.
4. In cases where the dosage is optional, choose the dosing instruction with the smallest dose/frequency. (e.g. Ventolin MDI 1-2 puffs, 2-3 times daily will get weightings for 'metered dose inhalers', 'variable dose' and 'twice daily'; but not for 'multiple units at one time')
5. In certain cases the dosing frequency needs to be calculated (e.g. Ranitidine 1mane and 1nocte is 1twice daily)
6. It is possible that with certain 'use as directed' instructions, the regimen will not get a score under dosing frequency (e.g. Prednisolone 5mg mdu)
7. If there is more than one dosing frequency direction, they should be scored for all the dosing frequency directions (e.g. Ventolin MDI 2 puffs bd and prn, will get scores for 'metered dose inhalers', 'multiple units at one time', 'twice daily' as well as 'prn')
8. Instances where two or more medications are mutually exclusive, they need to be scored twice or more as prn with the recommended dosing frequency (e.g. Ventolin MDI or Ventolin nebuliser twice daily will get scores for both 'metered dose inhalers' and 'nebuliser' under dosage forms, but needs to be scored two times for 'twice daily prn')
9. In cases where there is no matching option, choose the closest option (e.g. six times daily could be considered as 'q4h')

A) Circle the weighting corresponding to each dosage form (ONCE ONLY) present in the regimen.

	Dosage Forms	Weighting
ORAL	Capsules/Tablets	1
	Gargles/Mouthwashes	2
	Gums/Lozenges	2
	Liquids	2
	Powders/Granules	2
	Sublingual sprays/tabs	2
TOPICAL	Creams/Gels/Ointments	2
	Dressings	3
	Paints/Solutions	2
	Pastes	3
	Patches	2
	Sprays	1
EAR, EYE & NOSE	Ear drops/creams/ointments	3
	Eye drops	3
	Eye gels/ointments	3
	Nasal drops/cream/ointment	3
	Nasal spray	2
INHALATION	Accuhalers	3
	Aerolizers	3
	Metered dose inhalers	4
	Nebuliser	5
	Oxygen/Concentrator	3
	Turbuhalers	3
	Other DPIs	3
OTHERS	Dialysate	5
	Enemas	2
	Injections: Prefilled	3
	Ampoules/Vials	4
	Pessaries	3
	Patient controlled analgesia	2
	Suppositories	2
	Vaginal creams	2
	Total for Section A	

DPI = dry-powder inhaler; MDI = metered-dose inhaler.

The Medication Regimen Complexity Index, Sections B and C (George et al., 2004, p. 1375)

Appendix II. Medication Regimen Complexity Index (MRCI) (continued)

B) For each medication in the regimen tick a box [√] corresponding to the dosing frequency. Then, add the no. of [√] in each category and multiply by the assigned weighting. In cases where there is no exact option, choose the best option.

Dosing Frequency	Medications	Total	Weighting	Weighting × No. of medications
Once daily			1	
Once daily prn			0.5	
Twice daily			2	
Twice daily prn			1	
Three times daily			3	
Three times daily prn			1.5	
Four times daily			4	
Four times daily prn			2	
q 12h			2.5	
q 12h prn			1.5	
q 8h			3.5	
q 8h prn			2	
q 6h			4.5	
q 6h prn			2.5	
q 4h			6.5	
q 4h prn			3.5	
q 2h			12.5	
q 2h prn			6.5	
prn/sos			0.5	
On alternate days or less frequently			2	
Oxygen prn			1	
Oxygen <15hrs			2	
Oxygen >15hrs			3	
			Total for Section B	

C) Tick a box [√] corresponding to the additional directions, if present in the regimen. Then, add the no. of [√] in each category and multiply by the assigned weighting.

Additional Directions	Medications	Total	Weighting	Weighting × No. of medications
Break or crush tablet			1	
Dissolve tablet/powder			1	
Multiple units at one time (e.g. 2 tabs, 2 puffs)			1	
Variable dose (e.g. 1-2 caps, 2-3 puffs)			1	
Take/use at specified time/s (e.g. mane, nocte, 8 AM)			1	
Relation to food (e.g. pc, ac, with food)			1	
Take with specific fluid			1	
Take/use as directed			2	
Tapering/increasing dose			2	
Alternating dose (e.g. one mane & two nocte, one/ two on alternate days)			2	
			Total for Section C	

Medication Regimen Complexity = Total (A) + Total (B) + Total (C)=

DPI = dry-powder inhaler; MDI = metered-dose inhaler.

Appendix B

Table 4.1 Summarizes the Demographic Characteristics of the Study Sample at 2012

Variables **Total population n= 9694**	**N, weighted frequency (%)**
Age	
65–74 years	4834 (57.06)
75–84 years	3724 (31.47)
85 years or older	1136 (11.46)
Gender	
Male	4026 (43.02)
Female	5668 (56.97)
Marital status	
married	5799 (58.81)
non-married	3893 (41.18)
Race	
White	7977 (87.47)
Black	1324 (8.58)
Other	389 (3.94)
Years of education	
No degree	2189 (19.63)
High school	4060 (41.52)
Some college	1353 (14.40)
College degree	2085 (24.43)
Income	
$ 0 to 15999	1810 (17.26)
$16000 to 28999	2051 (19.46)
$ 29000 to 50999	2628 (26.31)
$ 51000 to 134999	2584 (28.98)
$ over 135000	621 (7.96)
Number of people living at house	
1	2747 (31.18)
2-3	6219 (62.11)
4 or more	728 (6.69)
Covered by insurance	
No	0 (0)
Yes	9512 (100)

Previous hospital stay	
No	6697 (70.02)
Yes	2943 (29.97)
Health	
excellent/very good/good	6917 (73.13)
fair	2031 (19.78)
Poor	733 (7.07)
ADL	
None	7958 (83.15)
Impaired	1728 (16.84)
IADL	
None	8129 (84.97)
Impaired	1557 (15.02)
Difficulty taking medication	
No	9271 (97.19)
Yes	291 (2.67)
Cognitive status	
Cognitive intact	9301 (96.55)
Impaired	393 (3.44)
Cognitive and ADL	
No	9538 (98.67)
Yes	156 (1.32)
Cognitive and IADL	
No	9500 (98.25)
Yes	194 (1.74)
Number of conditions	
none	557 (6.56)
1-2	4294 (45.59)
3-4	3893 (38.60)
5 or more	945 (9.23)
Hypertension	
No	2798 (31.65)
Yes	6744 (68.34)
Heart disease	
No	6509 (68.39)
Yes	3168 (31.60)

Lung disease	
No	8465 (87.70)
Yes	1215 (12.29)
Arthritis	
No	2863 (31.05)
Yes	6817 (68.94)
Stroke	
No	8598 (89.53)
Yes	1084 (10.46)
Depression	
No	8418 (87.52)
Yes	1276 (12.47)
Cancer	
No	7637 (79.36)
Yes	2023 (20.63)
Psyche	
No	8061 (82.46)
Yes	1618 (17.53)
Diabetes	
No	7345 (83.38)
Yes	1641 (16.61)

Vita

Duaa Bafail was born on December 22, 1985 in Arizona, USA. She graduated with Pharm.D. degree in pharmacy from King Abdullaziz University, Jeddah, Saudi Arabia in 2009. She worked as instructor in the department of pharmacology in school of medicine at King Abdullaziz University. She came to Virginia Commonwealth University in 2012 to do her Master of Science degree in Pharmacology and Toxicology. In 2014 she enrolled in the PhD program in Pharmaceutical Science with a concentration in pharmacotherapy and outcomes science. She also completed the Preparing Future Faculty program at Virginia Commonwealth University and received a Certificate for Teaching Excellence at the conclusion of the program.