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ASSOCIATION BETWEEN POLYPHARMACY AND FUNCTIONAL STATUS IN COMMUNITY-DWELLING OLDER ADULTS

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

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List of Abbreviations

ADL	Activities of daily living
CESD	Center for Epidemiologic Studies Depression
CI	Confidence Interval
HRS	Health and Retirement Study
IADL	Instrumental activities of daily living
IRB	Institutional Review Board
MAR	Missing at random
MCAR	Missing completely at random
MMSE	Mini mental state examination
MNAR	Missing not at random
NHAT	National Health and Aging Trends Study
OTC	Over-the-counter
PIM	Potentially inappropriate medication
Rx	Prescription medication
SPPB	Short physical performance battery
SRH	Self-reported health
START	Screening tool to alert prescribers to right treatments

STOPP	Screening tool for older people's prescriptions

Abstract

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Background: Polypharmacy has no consensus definition in the literature. Previously used definitions include those based on the number of medications and those based on unnecessary or inappropriate medication use. Polypharmacy has been associated with increased risk of disability and functional limitations that impair a person's ability to live independently. Older adults are a population of interest as they are at increased risk for both polypharmacy and functional impairments. Understanding the relationship between polypharmacy and functional impairment

in older adults could help health care providers and policy makers to target an at-risk population for interventions.

Objectives:

1) To assess the relationship between the number of medications taken and functional status in community-dwelling older adults using a nationally representative dataset.
2) To assess the change in the relationship between the number of medications taken and functional status over time (2 years and 4 years).
3) To study confounders of the relationship between polypharmacy and functional status.

Methods: Data came from the Health and Retirement Study (HRS), collected in the following years: 2004, 2006 and 2008. The primary outcome was functional limitation as measured using the following validated tools: activities of daily living and instrumental activities of daily living (ADL and IADL). The exposure under study was polypharmacy status (no polypharmacy: <5 prescribed medications, and polypharmacy: ≥5 prescribed medications). Both cross-sectional and longitudinal models were used to examine different aspects of the relationship between polypharmacy and functional status.

Results: A total sample size of 1,545 was included in our study. The prevalence of polypharmacy was 35.9% at the beginning of the study. Polypharmacy status was significantly associated with functional decline in both the cross-sectional and longitudinal analyses after controlling for confounders. Self-reported health (SRH) and light exercise were associated with functional decline in all cross-sectional analyses. Age, arthritis, and SRH were also associated

with functional decline in all longitudinal analyses. Other confounders were also associated with functional decline.

Conclusion: Polypharmacy, defined as the use of more than five prescribed medications is a significant risk factor for functional decline in community-dwelling older adults.

Chapter 1 Introduction

Aging is commonly associated with an increase in chronic conditions and medication usage. More than 62% of adults aged 65-74 years old experience multiple chronic diseases (Jokanovic et al. 2015). More than 81.5% of older adults aged 85 years and older have multiple chronic diseases such as diabetes, hypertension, arthritis, heart diseases, and cancer (Jokanovic et al. 2015; Quiñones et al. 2016). As chronic conditions increase with aging, medication usage also increases. One of the main concerns that occurs with medication usage is polypharmacy.

1.1 Polypharmacy definition

Polypharmacy has no consensus definition in the literature. The definition varies, and there are two main ways to define polypharmacy. The first way depends on the number of medications taken, with commonly-used cutoffs defining polypharmacy as the use of five or more medications, excessive polypharmacy as the use of ten or more medications, and oligo-pharmacy as the use of less than five medications (Gnjidic et al. 2012; Jyrkkä et al. 2011a). The numeric definition is considered to be simple and is used often in practice settings. The second definition considers unnecessary or potentially inappropriate use of medications (PIM), including duplication of medications, inappropriate dosing, under-prescribing, adverse drug reactions, drug-drug or drug-disease interactions, unnecessary medications, or (for older adults) the use of medications on the Beer's list, which is a list of medications where the risks generally outweigh the benefits for most older adults (Fulton et al. 2005; Turner et al. 2015). Some definitions

consider only the number of prescribed medications, while others include over-the-counter (OTC) medications. The most common meaning of polypharmacy is the use of multiple medications. Multiple medications do not always have to be problematic (Levy 2017). It is sometimes appropriate with no need for modification. Some older adults are on multiple medications and they are healthy, while others would be better off if their medications were fewer (Levy 2017).

I will be using the number of prescription medications that are taken on a regular basis (every day, every week, etc.) in the last year by participants (excluding OTC, herbal, or nutritional supplement numbers) as a measure to assess drug burden. An advantage of using the number of medications is the simplicity of measuring polypharmacy by this method, which is why this approach is widely used in research and clinical settings. Also, it is a quick screening tool that does not need excessive effort, a complicated equation, or software to calculate in clinical practice. It is a quick screening tool that could be used to identify individuals in need of intervention, and should not increase burden on the healthcare system. The number of medications should ideally include prescribed medications, OTC, herbals, and nutritional supplements that are used regularly (Sharma et al. 2016). Unfortunately, use of as needed and nonprescription products may not be clearly documented in the patient's medical record or in databases used for this research.

There are other alternative measures of assessing drug burden and they mainly look for PIM. For example, the Beer's list contains more than 110 PIM and 60 drug-diseases for older adults to avoid. Other examples are a screening tool for older people's prescriptions (STOPP) which contains 80 indicators for appropriate prescribing, and a screening tool to alert prescribers to right treatments (START) (Barry et al. 2007; Sharma et al. 2016). PIM is a good way to

measure drug burden and individually assess each patient's needs. However, the disadvantage of PIM is that it has many different tools that are time consuming to administer, are not widely used in clinical settings, require training for healthcare providers, and need to be individualized for each patient. Since assessing PIM's use requires individual assessment of each participant's prescription list and health history, it can be difficult to implement in secondary datasets and electronic health records that may be missing some of the necessary information. However, PIM's use is one of the consequences of polypharmacy that should be evaluated in future studies (Lau et al. 2011; Lau et al. 2010).

1.2 Polypharmacy prevalence

The trend of prescribed medication usage by US community-dwelling older adults has been increasing from 1988 to 2010. At least 90% of older adults are taking at least one prescribed medications. In the recent studies, the prevalence of older adults taking more than five medications is 36% to 39%. This percentage has tripled between 1988 to 2010 from 12.8% to 39.0%. This means that 1 in 3 older adults age 65 or older take five or more prescription medications. When adding OTC and supplement usage, the prevalence of older adults age 65 or older taking five or more medications increases to 67% (Charlesworth et al. 2015; Levy 2017). Polypharmacy is also recognized as the most important risk factor for having PIM (Blanco-Reina et al. 2015; Redston et al. 2018). 42.6% community-dwelling older adults had at least one PIM (Davidoff et al. 2015). The prevalence of PIM in older adults living in long-term care range from 21.3% to 63.0% using the 2003 Beers criteria (Redston et al. 2018). The prevalence of PIM in Europe is 22.6% for community-dwelling older adults (Tommelein et al. 2015).

1.3 Polypharmacy risk factors and clinical consequences

Several factors are known to be associated with increased likelihood of polypharmacy, including old age, sex, chronic diseases, multiple prescribers, cognitive impairment and cardiovascular conditions (Jokanovic et al. 2015). Older adults often experience these risk factors. Polypharmacy has been associated with many negative outcomes in older adults, including increased risk of falls, functional decline, frailty, disability, drug-related problems, and higher health costs (Maher et al. 2014). These negative outcomes are observed in older adults in part due to physiological changes associated with aging including decreased hepatic and renal function, changes in body composition, decline in baseline performance and decreased homeostatic reserve. These physiological changes can cause changes in drug pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (receptor and drug action on the body) often resulting in increased drug exposure and exaggerated drug response (Bushardt et al. 2008).

1.4 Functional status

Functional status, the ability to perform typical daily activities, is an important aspect of quality of life and independent living in older adults. Functional status reflects the health status and independency of people. It is measured in different ways, most often assessing ability to performing activities of daily living (ADL). The most commonly used measure of ADL is the basic activities of daily living ADL: toileting, bathing, dressing, walking across a room, getting in or out of bed, and eating as defined by Katz (Katz & Akpom 1976) . Another common measure is instrumental activities of daily living (IADL), which examines the ability to do more

complex activities such as administration of own medications, food preparation, shopping, using the telephone, and managing money. A third way of examining functional status is to assess mobility by asking about the ability of walking several blocks, walking one block, walking across the room, climbing several floors of stairs, and climbing one flight of stairs. Mobility is often one of the first areas to decline (Peron et al. 2011).

1.5 Rate of functional impairment and need for caregiver help

Physical impairment may impact a person's ability to function independently. Some of the risk factors for functional decline are diabetes, hypertension , heart problems, disease burden, depression, sedentary lifestyle, weight problems, and vision impairment (Dunlop et al. 2005; Stuck et al. 1999). One study analyzed the 2011 National Health and Aging Trends Study (NHATS), a study supported by the National Institute of Aging that collects information on older adults in all of the following settings: community, residential care, and nursing home in the USA. It collects comprehensive information about participants' needs and disability, and it reported that 61.5% of adults age 65 and older had no difficulties performing ADL, 19.6 % had difficulty, and 28.7% received help from another person with ADL. The study also looked at IADL and reported that 62.8% of adults age 65 and older had no difficulties doing IADL, 12.4% had difficulty, and 24.8% received help from another person with IADL (Freedman & Spillman 2014) . Overall, 75% of older adults receiving help were community-dwelling, whereas 15% lived in assisted living and 10% lived in a nursing home setting (Schulz et al. 2016).

Another study reported that 35.5% of community-dwelling older adults aged 65 years and older have disabilities including: vision, self-care, independent living, mobility, and cognition

disabilities. However, this study did not address the specific type of functional limitation or condition associated with disabilities (Courtney-Long et al. 2015). Acccording to the Disability Statistics Organization, 7.6 % of commumity-dwelling adults aged 65 to 74 in the USA reported an independent living disability in 2016, while 24.8% of adults above 75 reported an independent living disability (K. Lisa Yang and Hock E. Tan 2018).

1.6 Polypharmacy and functional status

Polypharmacy may increase the risk of functional disability and impair a person's ability to perform ADL thus threatening older adults' independence. A narrative review examined five studies looking at the relationship between functional decline in older adults and suboptimal prescribing, which was defined as "*underuse* or *overuse* of medications or prescribing *potentially inappropriate medications (PIM)"* (Peron et al. 2011). All of the studies included in the review were longitudinal, and the majority were conducted in community-dwelling older adults. In the studies that examined some measure of PIM, two reported an association between PIM and functional decline, and one reported no association (Hanlon et al. 2002; Pugh et al. 2008; Corsonello et al. 2009). Several studies assessing the relationship between polypharmacy and functional status have been conducted since this narrative review. One study used a longitudinal design to evaluate whether polypharmacy (5 or more prescribed drugs) was associated with functional decline among community-dwelling older adults with dementia, and assessed whether this association may be modified by PIM (defined as use of medications on the Beer's list) (Lau et al. 2011). The results showed that participants with dementia and polypharmacy are more likely to have lower functional status in the following visit. PIM did not increase the associated risk, and drugs to avoid in the Beers' list did not show association with functional decline (Lau et

al. 2011). Another study showed that drug interactions impair functional status as measured by gait speed (a measure of mobility) in community-dwelling older adults (Naples et al. 2016). Since it is not ethical nor feasible to do controlled trials on older adults and expose them to multiple medications experimentally, an observational study is the best choice for looking at polypharmacy in older humans. An experimental study using groups of young and old male mice given five commonly used medications (simvastatin, metoprolol, omeprazole, acetaminophen, and citalopram) for 2-4 weeks showed that polypharmacy impaired mobility, balance, and strength in older male mice. The study authors noted that the relationship between physiological changes in aging and body response to medications might influence the relationship between polypharmacy and functional decline (Huizer-Pajkos et al. 2016).

Although existing literature supports the idea of an association between polypharmacy and functional status, many of the current studies suffer from limitations such as the use of small samples. Additionally, although some longitudinal studies exist, none have used a nationally-representative sample. The objective of this study was to use longitudinal data to investigate whether polypharmacy (defined using the number of prescribed medications) increases the risk of functional impairment, using a large nationally-representative sample of older adults in the USA.

1.7 Significance

Prescribing in older adults is challenging, not only because of age-related physiological changes, but also due to the need to weigh the benefit against the potential for harm in patients with multimorbidity and polypharmacy (Holmes et al. 2006). One of the main goals in treating older adults is the preservation of independence. It is important to mention that functional

impairment could be reversed by rehabilitation and controlling for disability risk factors like polypharmacy and depression (Pamoukdjian et al. 2017; Lin et al. 2012). One study showed that de-prescribing showed a significant difference in ADL between the control and intervention groups (Wehling et al. 2016; Thillainadesan et al. 2018). Based on the current published literature, polypharmacy may be an important risk factor for functional decline, but further research is needed to evaluate the impact of polypharmacy and to understand what other risk factors play a role in functional impairment along with polypharmacy. Likewise, most of the previous studies control only for the number of chronic conditions and they do not look at the relationship between functional decline and each chronic condition. To help advance this area of research, I studied functional status as the primary outcome measure and assessed its association with polypharmacy. Functional status is one of the quick screening tools that can predict institutionalization and death (Saliba et al. 2000). This study provides a rigorous extension of existing literature using longitudinal data and a large nationally-representative sample. Further examination of the relationship between polypharmacy and functional status may lead to new information which could help health care providers and policy makers target at risk populations for interventions and help older adults maintain independence.

1.8 Specific aims

The hypothesis guiding this research is that there is an association between polypharmacy and functional status in community dwelling older adults. The specific aims are to:

1. To determine the prevalence of prescription medication usage and adverse effects among community-dwelling US older adults

    a) To determine the prevalence of prescription medication use and baseline characteristics among community-dwelling US older adults

b) To assess the access to prescription medications among US older adults including: access to pharmacies, source of prescription drug insurance, and costs covered by insurance

c) To determine the prevalence of self-reported side effects and unwanted reactions, and to understand the consequence of these adverse drug reactions (e.g. stopping or cutting down mediations, visiting the doctor's office, or admission to the hospital or the emergency room)

2. To assess the cross-sectional relationship between polypharmacy and functional status using a large nationally-representative dataset
   a) To assess the relationship between polypharmacy status and functional status measured by ADL in community-dwelling older adults in 2004
   b) To assess the relationship between polypharmacy status and functional status measured by ADL in community-dwelling older adults in 2008
   c) To assess the relationship between polypharmacy status and functional status measured by IADL in community-dwelling older adults in 2004
   d) To assess the relationship between polypharmacy status and functional status measured by IADL in community-dwelling older adults in 2008

3. To assess the longitudinal relationship between polypharmacy and functional status using a large nationally-representative dataset

   a) To assess the relationship between polypharmacy status and functional status in community-dwelling older adults over time (4 years)

b) To assess the relationship between polypharmacy at baseline and change in functional status over time (2 years)

4. To identify potential confounders of the relationship between polypharmacy and functional status
    a) To assess the role of chronic conditions in the relationship between polypharmacy and functional status
    b) To identify potential confounders or modifiers of the relationship between polypharmacy and functional status

Chapter 2 Literature Review

2.1 Literature Review

This chapter is an examination of the literature on the relationship between polypharmacy and functional status. Both functional dependency and medication problems are major concerns among the older adult population. A decline in functional status may lead to an increase in health system utilization and mortality, and is a major cause of functional dependency and institutionalization (Fried & Guralnik 1997). Functional decline is usually a gradual process resulting from aging and chronic conditions, which eventually affect the patient's physical abilities, although sometimes an acute event such as a stroke or a fracture could trigger a sudden functional decline. The prognosis of functional decline depends on many factors such as a patient's age, gender, education, physical activity, cognitive status, and social support (Fried & Guralnik 1997). It is important to mention that functional decline can sometimes be slowed or reversed by rehabilitation and managing disability risk factors like polypharmacy (for example: de-prescribing) and depression (Lin et al. 2012; Wehling et al. 2016; Thillainadesan et al. 2018). Thus, if good care and early intervention were available, this may provide functional stability or delayed decline. Older adults utilize a high number of medications, both prescription and nonprescription. However, the consequences of multiple prescription medication use on community-dwelling older adults are not well studied (Magaziner et al. 1989; Lau et al. 2011).

Based on a systematic review of the literature, I examined seven published papers that discuss the relation between polypharmacy or PIM and functional status, The article were selected based on the following inclusion criteria:

1-Observational cross-sectional and longitudinal studies

2-Older adults included in the study

3-Participants were community-dwelling

4-Study published in the English language

and the following exclusion criteria:

1-Restricted to specific drug categories and their relationship to functional decline

I used the following databases: PUBMED, CINAHL, and GOOGLE SCHOLAR. My search strategy combined multiple search terms and MeSH terms to cover articles including the following search terms: “functional status” OR “functional limitation” OR “functional decline” OR “activity of daily living” OR “mobility” AND “polypharmacy” OR “multiple medications” OR “Perception” OR “ADL” OR “IADL”, and filter: from 01/2011 to 01/2018, because there was a review article published in 2011 that reviewed literature published through December 2010. I included the articles identified in this published literature review in my search. My search resulted in 350 articles. I excluded 71 articles as not relevant to the topic based on the title, and I reviewed the abstracts of 279 articles. I excluded 242 articles because they did not meet my inclusion criteria, and fully reviewed 37 articles. Of those 37 articles, I excluded 29 articles that did not address the association between polypharmacy or PIM with functional status. One additional article was excluded because it was conducted in a hospital setting, leaving seven papers for critical review. Four of the seven papers selected were previously gathered in a narrative review (Peron et al. 2011).

I will first review the papers assessing polypharmacy and its relationship to functional status (Table 2.1) followed by the papers discussing PIM and its relationship to functional status (Table 2.2). The first paper by Magaziner et al. (1989) examined the relationship between polypharmacy (number of prescribed medications) and OTC use in community-dwelling older women, and the change in cognition, activities of daily living, and instrumental activities of daily living. This study was a longitudinal study over one year. It looked at white women in the Baltimore area age 65 and older (N= 609). This study examined self-reported ADL and IADL of each participant, and controlled for age, education, and number and severity of chronic conditions. For the analysis, they used a regression model with the function status scores after one year as the outcome variable and number of prescribed medications at baseline as the predictor variable, while controlling for the baseline variables. This study found no association between the number of prescribed medications and change in cognitive function. The number of prescribed medications increased the risk of decline in ADL, IADL, and depression. The OTC medication use was associated with decline in ADL only (J. Magaziner et al. 1989). However, this study had a significant generalizability limitation because only white females from the Baltimore area were included. Also, they did not look at each chronic condition individually. Moreover, they excluded patients who died or who entered institutions during follow up and this may attenuate their observation.

The second study looked at the association between polypharmacy (6-9 medications) and excessive polypharmacy (≥10 medications) with functional, nutritional, and cognitive status. This study was conducted in Finland with a total sample size of (N=294) community-dwelling older adults aged at least 75 years and followed for three years. Polypharmacy in this study included all medication taken regularly including OTC and vitamins. Functional status was

measured by IADL. They controlled for age, sociodemographics, self-reported health, and comorbidity as measured by the functional comorbidity index score. It was found that both polypharmacy and excessive polypharmacy were associated with a decline in IADL. Change in functional status over a three-year period cannot be predicted by polypharmacy. This study had a small sample size and their results cannot be widely generalized. However, despite the small sample size, the association was strong. Moreover, they did not control for each chronic condition individually (Jyrkkä et al. 2011a).

The third study was performed to evaluate the relationship between polypharmacy (≥5 prescribed medications) and functional decline among community-dwelling older adults with dementia. They also wanted to evaluate whether PIMs (high risk drugs as defined by the 2003 Beers criteria) could modify this relationship. This study analyzed data from the National Alzheimer's Coordinating Center (NACC), where community-dwelling adults with dementia aged 65 years and older (N=1,994) were included. Polypharmacy was defined as the use of ≥5 prescribed medications and they excluded patients with no prescription medication. The functional status was measured by both ADL and IADL. They controlled for age, race, and number of comorbid conditions from this list: hypertension, diabetes, hypercholesterolemia, thyroid disease, urinary/bowel incontinence, heart disease, and cerebrovascular disease. They found that participants with dementia and polypharmacy are more likely to have lower functional status. PIMs did not modify this relationship (Lau et al. 2011). The limitation of this study was that they did not account for OTC medications. The dataset used in this study did not have random sampling and thus its results cannot be nationally representative. Moreover, they only

controlled for the number of chronic conditions and they did not look at the effect of each condition on the relationship individually.

The aim of the fourth study was to evaluate the association between three types of potentially suboptimal prescribing of medications: 1) drugs-to-avoid in the 1997 Beer's list, 2) drug-drug interactions, and 3) polypharmacy defined as ≥ 5 medications (prescription and OTC), with a latent variable representing a timed performance measure of functional status, the short physical performance battery (SPPB). The SPPB can be used to measure functional status by evaluating a person's ability to perform three tasks: a balance score, a timed 3-meter walk, and a repeated sitting to standing up from a chair. This study used the Hispanic Established Populations for Epidemiologic Studies of the Elderly (HEPESE) of Mexican-American community-dwelling older adults. They followed participants for seven years and the sample size was (N=1,682). They controlled for sociodemographic characteristics along with smoking, weight, self-reported health conditions, cognition status, and specific chronic conditions (diabetes, hypertension, cancer, arthritis, stroke, and cardiovascular conditions) recognized by the National Center for Health Statistics as the leading cause of mortality and disability in the US. This study concluded that only polypharmacy defined as ≥5 medications was associated with a change in SPPB. One of the strengths of this study was that it looked at the relationship between specific chronic conditions and functional status and it reported a relationship between diabetes, arthritis, and stroke with functional decline. However, this study is only generalizable among community-dwelling Mexican-American older adults. Also, their high dropout rate and death rate in this study population may attenuate the results (Pugh et al. 2008).

The fifth study was a cross-sectional study, performed to identify factors associated with disability specially polypharmacy (≥5 medications) among community-dwelling older adults in

the Irish longitudinal study. They also wanted to identify other factors that could be associated with functional decline. The study participants were (N=3,499). Polypharmacy was defined as the use of ≥5 medications. The functional status was measured by ADL, IADL and combined ADL/IADL. They controlled for twenty-five possible confounders. They found that polypharmacy was the third strongest factor associated with decline in ADL and IADL/IADL, after age and pain. Polypharmacy was the sixth strongest factor associated with IADL decline. (Connolly et al. 2017). The limitations of this study were the use of self-reported questionnaire which could introduce source of bias. Also, the definition of polypharmacy was not clear and not well-defined. They also had lots of missing data.

Table 2.1: Studies examining the relationship between polypharmacy and functional status

Author & year	Study population	Design	Polypharmacy definition	Functional status Measurement	Results & conclusion
Magaziner et al. 1989	Community-dwelling white women in the Baltimore area age 65 and older (N= 609)	Longitudinal study over one year	1-Number of prescribed medications taken in last month 2-Number of OTC taken last month	Self-reported ADL, IADL	1-Decline in both ADL and IADL with prescription medication usage 2-Decline in ADL only with OTC usage
Jyrkkä et al. 2011	Community-dwelling older adults aged at least 75 years (N=294)	Longitudinal study for three years	1-Non-polypharmacy ≤ 5medications* 2-Polypharmacy 6-9 medications* 3-Excessive polypharmacy ≥10 medications*	Self-reported IADL	1-Polypharmacy and excessive polypharmacy were associated with a decline in IADL 2- Change in functional status over a three-year period cannot be predicted by polypharmacy
Lau et al. 2011	Community-dwelling adults with dementia	Longitudinal for 4 years	1-Ppolypharmacy ≥5 Rx 2-PIMs (high risk drugs as defined	Self-reported ADL and IADL (decline was defined as	1-Polypharmacy was associated with functional decline

	aged 65 years and older (N=1,994)		by the 2003 Beers criteria) as a modifier for the relation	any decline in ADL and/or IADL)	2-Participants with dementia and polypharmacy had a lower functional status 3-PIMs did not modify the relation
Pugh et al. 2008¥	Community-dwelling Mexican-American older adults aged 65 years and older (N=1,682)	Longitudinal study for seven years	Polypharmacy defined as ≥5 medications (prescription and OTC)	The short physical performance battery (SPPB)	1-Polypharmacy showed an association with functional decline
Connolly et al. 2017	Community-dwelling Irish longitudinal survey of ageing (N=3,499)	Cross-sectional	Polypharmacy defined as ≥5 medications	ADL, IADL and ADL/IADL	1-Polypharmacy was the third strongest factor associated with ADL and IADL/ADL decline, after age and pain 2-Polypharmacy was the sixth strongest factor associated with IADL decline.

Rx: prescription medication only, * All medications taken regularly (including prescribed, OTC, and vitamins)
¥ This study assessed both polypharmacy and PIM

Hanlon et al. (2002) discussed the relationship between PIMs and functional decline. The definition of PIM in this study was the use of drug-to-avoid in the1997 Beer's list or dosage, duplication, duration, drug-drug, or drug-disease interaction with eight medications classes (digoxin, nonsteroidal anti-inflammatory medications, calcium channel blockers, antihistamines, angiotensin converting enzyme inhibitors, benzodiazepines, antipsychotics, and antidepressants). This study used the fourth wave of the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE) and included community-dwelling older adults in North Carolina. The sample size was (N=3,234) and the study was longitudinal for 3 years. This paper evaluated the decline in the ADL, IADL, and the abbreviated Rosow-Breslau scale, which measures the

person's ability to do heavy physical work around the house. They found no association between the use of PIMs and mortality. There was an association between PIMs (drug-drug or drug-disease interaction) and decline in ADL. This study had several limitations including self-reported functional status measures and limited generalizability. Furthermore, the drugs-to-avoid were only measured by looking at the classes of medications, and not the individual medications, that the patient used. It is important for health care providers to note that even though a medication may be on the Beers, it might be appropriate for the patient's needs (Hanlon et al. 2002).

The last paper discussed the impact of PIMs (drug-drug and drug-disease interactions) on functional status. This four-year longitudinal study used data from the Health, Aging and Body Composition Study (Health ABC) and participants were community-dwelling older adults Medicare recipients living in Pittsburgh, Pennsylvania, and Memphis, Tennessee (N=2,402). Gait speed decline ≥0.1 m/s was used to measure functional status. They controlled for self-reported health, hospitalization in the last year, number of prescribed medications, number of OTC medications, depression, self-reported coronary heart disease, peripheral artery disease, diabetes, osteoarthritis, osteoporosis, pulmonary disease, and stroke. Results showed that drug interactions may increase the likelihood of gait speed decline among older adults. Generalizability and selection bias are the primary limitations in this study (Naples et al. 2016).

Table 2.2: Studies examining the relationship between PIMs and functional status

Author & year	Study population	Design	PIMs definition	Functional status Measurement	Results & conclusion
Hanlon et al. 2002	Community-dwelling older adults aged 65 years and older	Longitudinal study over three years	1-drugs-to-avoid in 1997 Beer's list 2-dosage 3-duplication	Self-reported ADL, IADL,	1- Decline in ADL only with drug-drug, or drug-disease interaction

	in North Carolina (N=3,234)		4-duration 5-drug-drug or drug-disease interaction with 8 medications classes	Rosow-Breslau scale	2- No association between the use of PIMs and mortality
Naples et al. 2016	Community-dwelling older adults aged 65 and older (N=2,402).	Longitudinal study over four years	PIMs: drug-drug and drug-disease interactions	Gait speed decline ≥0.1 m/s	Drug interactions may increase the likelihood of gait speed decline among older adults
Pugh et al. 2008¥	Community-dwelling Mexican-American older adults aged 65 years and older (N=1,682)	Longitudinal study for seven years	1-Drugs-to-avoid in 1997 Beer's list 2-Drug-drug interactions	The short physical performance battery (SPPB)	Drug to avoid and drug-drug interaction showed no association with decline in SPPB

¥ This study assessed both polypharmacy and PIM

2.2 Gaps in the literature

The literature is sparse, but it suggests that there is an association between polypharmacy and functional status, and that polypharmacy is one of the important risk factors not only for functional decline but also for PIM use (Lau et al. 2010). Polypharmacy's relationship with functional status needs further study. There is not as much research done in this area (Jyrkkä et al. 2011; Peron et al. 2011). Limitations in the studies reviewed in this chapter lead to some gaps in the literature that need to be addressed. The generalizability of all the studies is limited, since none of them used nationally representative datasets. Some of the studies used all medications including prescription and nonprescription for the number of medications, while others studies used only prescribed medications. An inconsistent definition of polypharmacy may lead to conflicting results. Using self-reported measures of polypharmacy, functional status or confounding variables can introduce bias such as information bias, which occurs when there is an inaccurate measurement or misclassification of diseases or exposures. Information bias can be

introduced by: 1) the instruments used to measure the exposure or 2) the study participants, if a participant cannot remember the information needed accurately (recall bias), having missing data, or giving a socially desirable response or 3) investigators asking leading questions or lacking proper training.

Moreover, the studies that used PIMs did not individualize the process for each patient's need to check whether medications on the drugs-to-avoid list might be appropriate for that patient, and thus results may be inaccurate. Another limitation is that each study had different potential confounders that were adjusted for. Most of the studies controlled for the number of chronic conditions and only one study looked at each chronic condition individually. Since polypharmacy is associated with chronic conditions, then it is important to look not only at the number of chronic conditions but also at each chronic condition. Understanding the relationship between each chronic condition, polypharmacy and functional decline will enrich the literature and help us to better understand these relationships. In conclusion, polypharmacy, defined as the use of a certain number of medications, is an important risk factor for functional decline and increases the risk of PIMs, adverse drug reactions. Polypharmacy needs more attention and we need to look at the potential confounders of the relationship. In my study, I will use a nationally representative dataset to understand the relationship between polypharmacy and functional status among community-dwelling older adults in the US. I will also look at each chronic condition as a potential confounder to better understand the relationship between polypharmacy and functional decline.

Chapter 3 Methodology

In Chapter 3, the methodology employed to address the specific aims posed in Chapter 1 will be discussed. Data source, study design, study population and study variables will be elaborated. This study was reviewed and approved as exempt by Virginia Commonwealth University Institutional Review Board (IRB) (ID:HM20011568).

3.1 Data source

The Health and Retirement Study (HRS) is a nationally representative health survey of older adults in the United States. HRS follows an open cohort of adults age 50 years or older in the United States, with repeat surveys and new additions to the cohort every two years. This is a uniquely rich, longitudinal data set for the community of scientific and policy researchers who study the health, economics, and demography of aging. The National Institute on Aging sponsors the HRS and the Institute for Social Research at the University of Michigan collects the data. The main HRS longitudinal survey is publicly available, and supplementary surveys with potentially sensitive data are available with an application for restricted use data. HRS data collection is conducted by an in-person interview (face-to-face) for a random half of the sample followed by a telephone interview for the next survey which takes place after two years. The next cycle goes back to the in-person interview and so on. A by-proxy interview is conducted if the person is unable to answer for himself or herself. Self-reported questionnaires are used for supplementary surveys.

3.2 Study design

This study is a retrospective longitudinal study that follows the same cohort of people in HRS biannually from 2004-2009. The first aim was to determine the prevalence of prescription medication usage and common response to adverse effects among community-dwelling US older adults. Data used in this study were collected by HRS biannually in 2004, 2006, and 2008 which corresponds to waves seven, eight and nine, and the supplementary drug survey data collected in 2005, 2007, 2009 which correspond to Prescription Drug Survey (PDS)05, PDS07, and the Health and Well-Being Study (HWB)09. The HRS data is publicly available. The supplementary drug survey was collected by mail, and a special request through the HRS website was made to obtain these datasets.

3.3 Data merge

All waves were merged and cleaned, and all long data (PDS05, PDS07, HWB09) were converted to wide data to merge them with wide HRS waves (7, 8, 9). HRS waves used in this study were cleaned and compiled by RAND Corporation. Common participant identifiers (PN, HHID) were used to merges the files together. All variables in PDS05, PDS07, and HWB09 were given a prefix, except for PN and HHID, to be able to merge them without overlapping since some variables have common names. After that, cleaning the dataset and recoding the variables needed for this study was performed. Details regarding merged files and recoding are available in the Appendix (Tables A, B, and C).

3.4 Study population

This study used data from HRS waves 7, 8 and 9, which were collected in 2004, 2006 and 2008, and from the supplementary surveys: 2005 and 2007 PDS, and 2009 HWB. The supplementary surveys provide data about medications. The PDS includes a subsample of the participants in the HRS; it is composed of two surveys, one of which was done in 2005 and the other in 2007. It is considered a supplementary survey designed to capture the change in prescription medication utilization before the implementation of Medicare part D and afterward. This survey is intended to capture prescription medication use, coverage, and satisfaction. The HWB (2009) is a continuation of the PDS survey to track and capture changes in prescription drug utilization and registration in Medicare Part D. The HWB followed the same people in PDS plus an additional 22% random sample from HRS.

This study included respondents who were:

1- Adults aged 65 years and older
2- Community-dwelling at baseline

Respondents were excluded if they were:

1- Missing data about their functional status, number of medications, or necessary model covariates.
2- Not followed in waves 7, 8, and 9
3- Living in a nursing home at baseline
4- Interviewed by proxy at baseline

After merging all files, all participants who had medication information and functional status information totaled 2259 participants. Inclusion and exclusion criteria were applied: removing participants younger than 65 years at baseline (593 were deleted) => 1666, removing participants interviewed by proxy at baseline (105 were deleted) =>1561, removing participants living in nursing homes at baseline (3 were deleted) => 1558, and removing participants who were alive but did not respond (13 were deleted) => 1545, resulting in 1545 participants included in the analysis.

3.5 Study variables

3.5.1 Main exposure variable

The primary exposure in this study was polypharmacy, defined as the number of prescribed medications used regularly. This is the most commonly used definition in the literature (Masnoon et al. 2017), facilitating comparison of our results with other published studies. HRS participants were asked if they were taking prescribed medications last year and if yes, then how many prescribed medications do they take regularly? Evidence of polypharmacy was also identified in the PDS and HWB datasets. Polypharmacy was categorized as present or absent using a definition that is commonly used in other studies (Pugh et al. 2008; Jyrkkä et al. 2011; Lau et al. 2011):

1-non-polypharmacy: using <5 prescribed medications

2-polypharmacy: using ≥5 prescribed medications

In the ***sensitivity analysis,*** different cut-offs were assessed as well:

1-non-polypharmacy: using <5 prescribed medications

2-polypharmacy: using 5-9 prescribed medications

3-excessive polypharmacy: using 10 or more prescribed medications

3.5.2 PDS and HWB variables:

From the medication drug survey data, the following information about prescribed medications were merged, cleaned, and coded: drug names, duration of medication use, side effects, response to side effects and unwanted drug reactions, and source of prescribed medications. Prescription medication coverage at baseline was categorized as: some by self and rest by insurance, small discounts, full price, pay nothing, and other. However, at the end of the study the categories were collapsed into having a prescription medication coverage (yes, no).

3.5.3 Main outcome

The outcome examined in this study was functional status, which was assessed with two widely used and well-validated measures: activities of daily living (ADL) and instrumental activities of daily living (IADL). ADL in this data set include five basic activities: bathing, dressing, walking across a room, getting in or out of bed, and eating. IADL include food preparation, shopping, medication administration, using the telephone and managing money. Counts were used to measure the number of activities in which participants experience impairments, with a possible range of 0-5 for ADL and 0-5 for IADL, with lower scores indicating better function and higher scores indicating greater disability (Germain et al. 2016). Each score was dichotomized into a yes/no variable to represent whether participants experience difficulty performing tasks in that category (score ≥1) and those able to function without difficulties (score=0).

3.5.4 HRS variables

All the variables were cleaned, and the missing observations were recoded to (.) for analysis purposes. Demographics were age, gender, race, ethnicity, years of education, marital status, and number of residents living in the same house including participant and spouse. Household income/wealth, which is the sum of all income in a household, was re-categorized according to the four quartiles (low, mid-low, mid-high, and high). Other variables used were self-reported health, smoking, and alcohol drinking. Obesity was measured by the body mass index (BMI), which measures the body fat by calculating the ratio of weight to height. If BMI ≥ 30 kg/m^2, the participant was considered obese. The amount of monthly light physical exercise was also used in our study. For health insurance, participants were asked whether they are covered by any government health insurance program. Other variables were proxy interviewed participants, and institutionalized participants in a nursing home or a health care facility. (See Table 3.1).

Table 3.1 HRS variables considered in the study

The confounder	The category
Age	65-74 years ≥75years
Gender	Male Female
Race and ethnicity	Non-Hispanic white Non-Hispanic African American Others Hispanic
Years of education	0-6 years 7-12 years >13 years

Marital status	Married Divorced Widowed Never married
Number of residents living in the same house including participant and spouse	Alone Two persons More than two
Household income (wealth)	Low quartile <$16.000 Mid-low quartile $16,000-$29,999.9 Mid-high quartile $30,000-$54,999.9 High quartile ≥ $55,000
Self-reported health	Excellent Very good Good Fair Poor
Smoking	Current smoker Former smoker Never smoker
Alcohol drinking	Yes No
Obesity	Obese Not obese
Light exercise	Every day More than once per week Once per week One to three times per month Never
Governmental health insurance	Yes No
Proxy interview	Yes No
Institutionalization	Yes No

3.5.5 Health conditions

The number of chronic conditions is a count variable for how many chronic conditions each participant has ever been told that he/she had out of the eight following chronic conditions: 1) high blood pressure or hypertension, 2) high blood sugar or diabetes, 3) heart diseases including heart attack, angina, coronary heart conditions, angina, or congestive heart failure, 4) cancer or malignancy of any kind except skin cancer, 5) stroke or transient ischemic attack, 6) chronic lung disease, chronic bronchitis or emphysema except asthma, 7) psychiatric problems, and 8) arthritis or rheumatism. Each of the chronic conditions were coded as yes/no. Depression was measured using the Center for Epidemiologic Studies Depression (CESD) scale score. This score is the sum of 1) the "negative" indicators which include a yes answer to the following: depression, felt sad, lonely, everything was an effort, restless sleep, and could not get going and 2) the "positive" indictors which includes a no answer to the following: feeling happy, and enjoying life. A score of four or more was considered depression. For cognitive impairment, I used the total cognition score, which is the sum of the total word recall and mental status summary scores, resulting in a score range of 0-35. As in prior HRS studies, 10 or lower in cognitive scores was considered impairment.

Three common terms will be used in the upcoming chapters:

1) Baseline (2004): data collected in the beginning of the study and files used were HRS 2004 and PDS 2005
2) Midline (2006): data collected in the middle of the study and files used were HRS 2006 and PDS 2007
3) Endline (2008): data collected in the end of the study and files used were HRS 2008 and HWB 2009

3.6 Statistical analyses

Aim 1: To determine the prevalence of prescription medication usage and adverse effects among community-dwelling US older adults

Descriptive statistics were reported for the study variables. For continuous variables (age, years of education, number of people in the same house, and total household income) normality was assessed to choose between parametric and non-parametric tests. Normality was assessed by looking at the histogram and the Q_Q plot. Moreover, Goodness-of-fit tests (Kolmogorov-Smirnov, Cramer-von Mises, and Anderson-Darling) were also used to assess normality and p-value <0.05 suggests non-normality. For categorical variables, PROC SURVEY was used to report unweighted N and PROC SURVEYFREQ procedure was used to report the weighted percent in each category.

Aim 2: To assess the cross-sectional relationship between polypharmacy and functional status using a large nationally-representative dataset

After re-coding baseline, midline, and endline characteristics, Chi-square was performed to report un-weighted N followed by PROC SURVEYFREQ to report weighted % and Rao-Scott Chi-Square test to report the p-value. These tests were done between each variable of interest and participants with or without ADL impairment at baseline. A bivariate analysis between each one of our study variables and the main outcomes (ADL and IADL) at both baseline and end line was done using PROC SURVEYLOGISTIC procedure, the unadjusted odds ratio (OR) along with the 95% CI and p-value were recorded. Logistic regression was chosen because the main outcome variables (ADL and IADL) were dichotomous. The variables that showed an association with the outcomes (ADL and IADL) were then tested by building a model and using the manual backward elimination method (p=0.1). In this method, the least significant variable

was dropped, except the main predictor, until all remaining variables had p-value of 0.1 or less. This method allows us to keep the important variables in the model even if it was not significant. A collinearity check was not performed because all variables were categorical. These regressions analyses were weighted by the HRS sampling weights and accounted for the complex sampling by using PROC SURVEYLOGISTIC and PROC SURVEYFREQ. The subsample groups in the PDS and HWB files were accounted for by using appropriate HRS sampling weights (An & Lu,2016)**.** Interactions were added to the model for self-reported health and polypharmacy, and self-reported health and each of the eight chronic conditions, but none were significant.

Aim 3: To assess the longitudinal relationship between polypharmacy and functional status using a large nationally-representative dataset and Aim 4: To identify potential confounders of the relationship between polypharmacy and functional status

For longitudinal models, the adjustment was performed for the baseline variables, and the backward elimination method was also used. Polypharmacy status was kept in the model even if it was not significant. Moreover, multiple interactions were added to the model, but none was significant. Model assumptions and diagnostics were checked by PROC LOGISTIC procedure and the LACKFIT option to perform a Hosmer and Lemeshow Goodness-of-Fit Test. A non-significant p-value rules out a gross lack of fit. Influential points were also checked to detect any unusual observations.

3.7 Missing data

Dealing with missing data in SAS starts with cleaning the data:

1) checking for missing data for each variable we want to use,

2) re-coding the missing for answer like (refusal, no response, unknown, etc.), and

3) rechecking if variables are coded correctly, and

4) making a new data set with the variables of interest to ensure that no unneeded variables were included, especially in a large data set like HRS, which may increase the amount of missing information. Listwise deletion or complete case analysis was used in our study. Listwise deletion is a convenient simple method and it is the most commonly used method in research. Because of the large sample size available in this study, listwise deletion can be used without substantial loss of statistical power (Dong & Peng 2013). Moreover, the missing data is acceptable when it is less than 10% of the sample, which is the case in our study (Dong & Peng 2013). HRS is a large survey with no intervention, so drop out because of an intervention resulting in not at random (MNAR) missing data is unlikely. The missing data in this study is most likely missing completely at random (MCAR) which means the missed information is not related to the study, or missing at random (MAR) which means that the missed information can be explained, and there is a pattern but the reason is not related to the primary dependent variable.

Chapter 4 Results

Aim 1: Descriptive results

A total of 1558 HRS participants met our inclusion and exclusion criteria in 2004 and were followed up until 2008. However, 13 of these participants were lost to follow up but were still alive at the end of the study period so they were excluded, leaving 1545 participants in our study. Table 4.1 shows the baseline and endline characteristics of the study participants. Regarding our main study predictor polypharmacy, 64.1 % were taking less than five prescribed medications, and 35.9% were considered having polypharmacy and taking five or more prescribed medications at baseline. For self-reported health, we have quite good perceived health, as most reported very good to good health status. Regarding our primary outcome, ADL and IADL, 11.5% and 9.5% reported difficulties in those two outcomes at baseline. Also, the most common chronic health conditions were hypertension (55.7%) and arthritis (60.4%). Looking at the same participants after four years, 19.4% have shifted their age category from 64-74 years to 75+ years. For polypharmacy, the percentage of individuals taking less than five prescribed medications decreased and the percentage meeting the criteria for polypharmacy increased over 4 years, indicating that drug burden increased over time in these participants. Participants reported difficulties in ADL (16.2%) and IADL (13.8%) at the endline, indicating a decline in functional status over time in this population. The percentage of individuals suffering from hypertension and arthritis also increased over time.

Table 4.1: Baseline and endline characteristics of the study population 2004 -2008

Variables	2004 Unweighted n (weighted %)	2008 Unweighted n (weighted %)
Age (years)		
65-74	1159 (70.8%)	844 (51.4%)
≥75	386 (29.2%)	701(48.6%)
Gender		
Male	628 (41.0%)	628 (40.8%)
Female	917 (59.0%)	917 (59.2%)
Race and Ethnicity		
Non-Hispanic white	1219 (86.2%)	1205 (86.1%)
Non-Hispanic African American	189 (6.8%)	186 (6.5%)
Others	26 (1.9%)	26 (1.9%)
Hispanic	111 (5.1%)	109 (5.4%)
Marital status		
Married	984 (63.8%)	884 (56.2%)
Divorced	137 (7.9%)	137 (7.9%)
Widowed	389 (25.9%)	490 (33.5%)
Never married	35 (2.4%)	34 (2.4%)
Polypharmacy		
0-4 medications	986 (64.1%)	897 (59.3%)
≥5 medications	559 (35.9%)	647 (40.7%)
ADL		
No difficulty	1366 (88.5%)	1284 (83.8%)
Difficulty	179 (11.5%)	261 (16.2%)
IADL		
No difficulty	1403 (90.9%)	1326 (86.2%)
Difficulty	142 (9.1%)	219 (13.8%)
Self-reported health		
Excellent	168 (10.7%)	115 (7.4%)
Very good	476 (32.1%)	460 (31.7%)
Good	524 (34.7%)	540 (35.8%)
Fair	290 (17.6%)	316 (18.4%)
Poor	86 (4.8%)	114 (6.7%)
# of chronic condition		
0	182 (12.4%)	105 (7.3%)
1	409 (27.0%)	300 (20.1%)
2	456 (29.7%)	463 (30.1%)
3	313 (19.5%)	367 (24.3%)
4	129 (7.9%)	184 (11.2%)
5	39 (2.4%)	81 (4.1%)
6	15 (1.0%)	29 (1.8%)
7	2 (0.1%)	7 (0.4%)

Hypertension		
No	662 (44.3%)	[b]521 (35.9%)
yes	881 (55.7%)	1021 (64.1%)
Diabetes		
No	1281 (84.3%)	[a]1217 (80.1%)
Yes	261 (15.7%)	326 (19.9%)
Heart conditions		
No	1168 (75.8%)	1063 (69.5%)
Yes	377 (24.2%)	482 (30.5%)
Lung conditions		
No	1433 (93.2%)	[a]1367 (89.4%)
Yes	111 (6.8%)	167 (10.6%)
Cancer		
No	1291 (83.2%)	[c]1224 (79.3%)
Yes	246 (16.8%)	311 (20.7%)
Stroke		
No	1143 (93.5%)	[b]1377 (89.1%)
Yes	102 (6.5%)	165 (10.9%)
Psychiatric conditions		
No	1396 (90.8%)	[a]1350 (88.1%)
Yes	148 (9.2%)	191 (11.9%)
Arthritis		
No	595 (39.6%)	[a]488 (32.6%)
Yes	949 (60.4%)	1055 (67.4%)

Total sample size N= 1545, a= 2 missing, b= 3 missing, c= 10 missing, PROC SURVEY was used for this analysis.

Aim 1-A) To determine the prevalence of prescribed medication usage among community-dwelling US older adults

In our study, 9.8% did not take any prescribed medications, 54.3 % were taking 1-4 prescribed medications, and 35.9% were taking five or more prescribed medications at baseline. The most commonly prescribed medications at baseline are presented in Table 4.2. Atorvastatin was the most commonly used prescribed medication in our study population in 2004. Atorvastatin is an HMG CoA reductase inhibitor, which helps lower blood cholesterol levels, and it helps reduce the risk of cardiovascular events. The second most common medication was levothyroxine, used to treat hypothyroidism. Metoprolol was the third most commonly used

medication. It is a beta-blocker used to control hypertension, manage patients after myocardial infarction, and to treat heart failure, tachycardia, and angina.

Table 4.2: The most commonly prescribed medications at baseline

Drug name	N (%)	Pharmacological category
Atorvastatin	234 (15.1%)	HMG CoA reductase inhibitor (lowers cholesterol)
Levothyroxine	213 (13.8%)	Synthetic thyroxine to treat hypothyroidism
Metoprolol	201 (13.0%)	Beta-blocker for angina and hypertension
Lisinopril	183 (11.8%)	ACE inhibitor for hypertension and heart failure
Atenolol	142 (9.2%)	Beta-blocker for angina and hypertension
Hydrochlorothiazide	141 (9.1%)	Diuretic for hypertension
Furosemide	130 (8.4%)	Potent loop diuretic
Simvastatin	126 (8.2%)	HMG CoA reductase inhibitor (lowers cholesterol)
Amlodipine	124 (8.0%)	Calcium channel blocker for angina and hypertension and kidney problems
Metformin	124 (8.0%)	Oral antidiabetic agent that helps control blood sugar levels
Warfarin	59 (3.8%)	Oral anticoagulant

Aim 1-B) To assess the access to prescribed medications among US older adults including pharmacies, prescription insurance and source of payment

The most common source for filling prescriptions in this community-dwelling older adult population was drug store chains (29.2%), followed by mail order (21.7%) and independent pharmacies (21.5%). Only 6.3% used clinic and hospital pharmacies. Filling prescribed

medications over the internet was the least used method (1%) at the time that this data was collected. Table 4.3 displays the sources were prescribed medications were obtained by participants in the HRS. The participants were allowed to choose more than one source for filling their prescribed medications. In Table 4.4 we can see the source of the prescription insurance. 36.7% had employment-based drug insurance. 19.4% and 14.7% had Medicare HMO and Medicaid prescription insurance. The payment sources for prescribed medications among HRS participants is presented in Figure 4.1.

Table 4.3: The source for obtaining prescribed medications from most common to least common source

Source of prescribed medications	Yes n (%)	No n (%)
Drug store chain	410 (29.2%)	994 (70.8%)
Mail order	305 (21.7%)	1099 (78.3%)
Independent pharmacy	302 (21.5%)	1101 (78.5%)
Supermarket	208 (14.8%)	1196 (85.2%)
Department store chain	170 (12.1%)	1234 (87.9%)
Others	136 (9.7%)	1268 (90.3%)
Free samples	130 (9.3%)	1274 (90.7%)
Veterans' Administration pharmacy	103 (7.3%)	1301 (92.7%)
Clinics or hospital	89 (6.3%)	1315 (93.7%)
Internet	12 (0.9%)	1392 (99.1%)

Total n = 1404; missing =141

Table 4.4: The source of prescribed medications insurance

Source of prescription insurance	Yes n (%)	No n (%)
Employment insurance	411(36.7%)	708(63.3%)
Medicare HMO	217(19.4%)	902(80.6%)
Medicaid	165(14.7%)	954(85.3%)
Purchase from insurance	94(8.4%)	1025(91.6%)
Veterans' Administration pharmacy	92(8.2%)	1027(91.8%)
State pharmacy assistance	49(4.4%)	1070(95.6%)
Others	207 (18.5%)	912(81.5%)
Total n =1119; missing = 426		

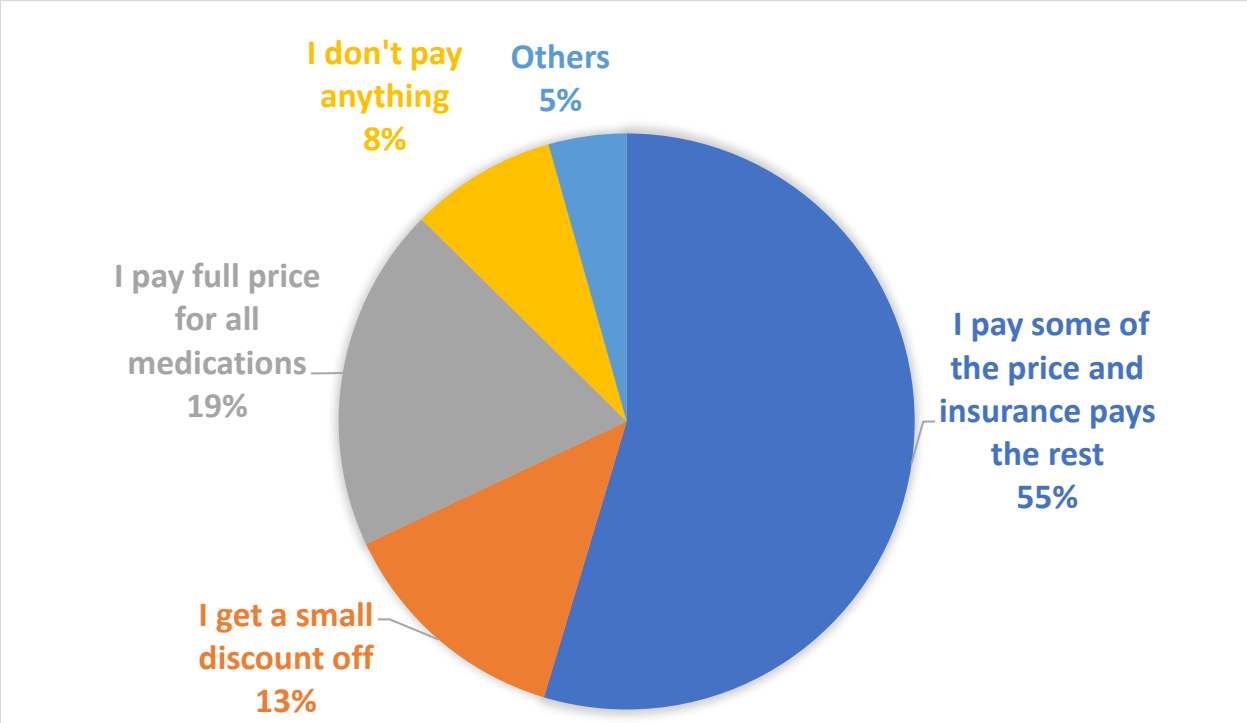


Figure 4.1: Prescription coverage and payment

Aim 1 -C) To determine the prevalence of self-reported side effects and unwanted reactions, and to understand the consequences of adverse drug reactions (e.g. stopping or cutting down mediations, visiting the doctor's office, admission to the hospital or the emergency room)

This analysis investigates self-reported side effects, adverse reactions, and other medication-related problems in community-dwelling US older adults. HRS participants were asked if they had any side effects, unwanted reactions, or other health problems from medications in past year. 1060 participants responded "no," 246 responded "yes" and 239 did not respond. Participants were then asked additional questions about the most severe unwanted reactions and their responses are summarized in Table 4.5.

Table 4.5: Self-reported side effects, unwanted reactions, and the action taken in response to this reaction

Questions asked	Yes	No
1-Cut down or stop taking the drug on your own [a]	106	98
2-Talk to a doctor about this reaction [b]	206	20
3-Visit a doctor's office or emergency room because of this reaction [c]	67	142
4-Doctor cut down or stopped the medication because of this reaction [d]	171	54
5-Take another medication or treatment to treat this reaction [e]	78	143
6-Admitted to a hospital overnight because of this reaction [f]	25	192

This table reports data for those who responded yes, a= 42 missing, b= 20 missing, c= 37 missing, d= 21 missing, e= 25 missing, f= 29 missing

In Table 4.5, we can see that participants called the doctor if they had a severe drug reaction. Their doctors may cut down the medication or stop it, but most of the participants did not need another medicine to treat the reaction or to be admitted to the hospital.

Aim 2-To assess the cross-sectional relationship between polypharmacy and functional status using a large nationally-representative dataset

2-A) Cross-sectional study looking at the association between ADL and polypharmacy at baseline (2004)

In the contingency Table 4.6, demographic and functional status-related factors are grouped by ADL difficulty and no difficulty. There was a significant difference in participants with and without ADL difficulties in the following factors: polypharmacy, marital status, number of people living in the same home, education, total household income, self-reported health status, number of chronic conditions, hypertension, diabetes, heart conditions, stroke, arthritis, psychiatric conditions, depression, drinking alcohol, obesity, and light exercise. The non-significant variables where: age, gender, race, having a lung condition, having cancer, smoking status, cognitive status, and having government health insurance. A detailed bivariate analysis was then conducted to examine the demographic and functional status-related factors, with each outcome (ADL and IADL) in both baseline and endline.

Table 4.6: Demographic and functional status-related factors, grouped by ADL no difficulty and difficulty

Variable	2004		P-value [c]
	ADL no difficulty n [a] (weighted %)[b]	ADL difficulty n [a] (weighted %)[b]	
Age (years)			0.2925
65-74	1035 (71.4%)	124 (66.7%)	
≥75	331 (28.6%)	55 (33.3%)	
Gender			0.1009
Male	569 (41.9%)	59 (34.2%)	
Female	797 (58.1%)	120 (65.8%)	
Race			0.1855
White	1166 (90.6%)	142 (87.2%)	
African American	158 (6.4%)	32 (10.0%)	
Others	42 (3.0%)	5 (2.8%)	

Marital status			0.0025
Married	897 (65.6%)	87 (50.1%)	
Divorced	115 (7.5%)	22 (10.6%)	
Widowed	323 (24.4%)	66 (37.3%)	
Never married	31 (2.5%)	4 (2.0%)	
Education			<0.0001
0-6 years	59 (3.2%)	19 (8.2%)	
7-12 years	766 (55.5%)	120 (67.5%)	
>13 years	541 (41.2%)	40 (24.2%)	
# of people living in same house			0.0300
Alone	344 (27.1%)	54 (32.8%)	
2 persons	816 (58.3%)	89 (46.3%)	
More than 2	206 (14.6%)	36 (20.9%)	
Wealth			<0.0001
Lowest quartile	283 (19.5%)	82 (41.8%)	
Mid-low quartile	322 (23.0%)	45 (24.8%)	
Mid-high quartile	382 (28.5%)	30 (18.7%)	
Highest quartile	379 (29.0%)	22 (14.7%)	
Polypharmacy			0.0053
0-4 medications	1211 (65.2%)	187 (55.5%)	
≥5 medications	689 (34.8%)	146 (44.5%)	
Self-reported health			<0.0001
Excellent	164 (12.0%)	4 (1.8%)	
Very good	461 (35.1%)	15 (9.6%)	
Good	473 (35.5%)	51 (28.6%)	
Fair	223 (14.6%)	67 (40.3%)	
Poor	44 (2.9%)	42 (19.8%)	
# chronic conditions			<0.0001
0	175 (13.6%)	7 (3.3%)	
1	378 (28.3%)	31 (17.0%)	
2	406 (29.7%)	50 (29.2%)	
3	264 (18.4%)	49 (27.6%)	
4	104 1(7.1%)	25 (14.2%)	
5	26 (6.7%)	13 (6.7%)	
6-7	13 (1.0%)	4 (2.1%)	
Hypertension			0.0048
No	604 (45.7%)	58 (33.3%)	
Yes	760 (54.3%)	121 (66.7%)	
Diabetes			0.0001
No	1155 (86.1%)	126 (70.3%)	
Yes	208 (13.9%)	53 (29.7%)	
Heart conditions			0.0401
No	1046 (76.7%)	122 (69.1%)	
Yes	320 (23.3%)	57 (30.9%)	

Lung conditions			0.9285
No	1269 (93.1%)	164 (93.4%)	
yes	96 (6.9%)	15 (6.6%)	
Cancer			0.0855
No	1141 (83.3%)	150 (82.1%)	
Yes	219 (16.7%)	27 (17.9%)	
Stroke			0.0052
No	1284 (94.3%)	159 (86.7%)	
Yes	82 (5.7%)	20 (13.2%)	
Psychiatric conditions			<0.0001
No	1252 (92.1%)	144 (81.2%)	
Yes	113 (7.9%)	35 (18.8%)	
Arthritis			0.0002
No	555 (41.8%)	40 (22.6%)	
Yes	810 (58.2%)	139 (77.4%)	
Cognitive impairment			0.1018
No	1349 (99.0%)	174 (97.8%)	
Yes	17 (1.0%)	5 (2.2%)	
Depression			<0.0001
No	1241 (91.4%)	125 (74.1%)	
Yes	125 (8.6%)	54 (25.9%)	
Governmental health plan			0.6633
No	38 (2.5%)	3 (1.9%)	
Yes	1326 (97.5%)	3176 (98.1%)	
Smoker			0.6321
Current	124 (8.3%)	17 (10.4%)	
Former	597 (44.6%)	83 (46.6%)	
Never	632 (47.1%)	79 (43.1%)	
Alcohol drinking			<0.0001
No	1032 (47.2%)	231 (63.8%)	
Yes	868 (52.8%)	102 (36.2%)	
Obesity			<0.0001
No	1041 (78.5%)	94 (56.9%)	
Yes	313 (21.5%)	84 (43.1%)	
Light exercise			<0.0001
Every day	92 (6.4%)	8 (4.3%)	
>1 week	777 (58.6%)	80 (43.7%)	
1 per week	346 (24.2%)	43 (24.6%)	
1-3 per month	73 (5.3%)	12 (5.3%)	
Never	77 (5.5%)	36 (22.2%)	

a-unweighted n value; b-weighted column percent, PROC SURVEYFREQ to report weighted column % and, c-Rao-Scott Chi-Square test

Bivariate and multivariable analyses were performed to examine the association between ADL and IADL with covariates that showed significance or prior knowledge of their importance from the literature. Looking at the bivariate analysis between ADL and variables at baseline (2004) without adjusting for other variables yielded several observations. Participants who were taking five or more prescribed medications were 1.6 (95% CI = 1.181-2.213) times more likely to have difficulties in ADL than participants who were taking less than five prescribed medications. Also, females were 1.5 (95% CI = 1.044-2.019) times more likely to have difficulties in ADL than males. The odds of having difficulties in ADL for divorced, widowed, and never married participants were 2.0 (95% CI = 1.189-3.273), 2.1 (95% CI = 1.493-2.973), and 1.3 (95% CI = 0.459-3.856) respectively, compared to married couples. Participants with 7-12 years of education were almost 50% (95% CI = 0.280-0.844) as likely to report difficulties in ADL and participants with 13 years or more of education were nearly 23% (95% CI = 0.125-0.422) as likely to report problems in ADL than participants with 6 years or less of education. Participants who were living with at least one person were 70% (95% CI = 0.484-0.997) as likely to have difficulty with ADL than participants who lived alone. For wealth and total household income, participants who were in mid-low income, mid-high income, and highest income quartiles were 50% (95% CI = 0.324-0.717), 27% (95% CI = 0.174-0.423), and 20% (95% CI = 0.122-0.329) as likely to report difficulties in ADL than participants in the lowest quartile. For self-reported health, those who reported good, fair, or poor health status were 4.4 (95% CI = 1.572-12.417), 12.3 (95% CI = 4.403-34.40), and 39.1 (95% CI = 13.312-114.994) times more likely to have difficulties in ADL than those reporting excellent health status. The number of chronic conditions also increased the likelihood of having ADL difficulties. Having any of the following chronic conditions: hypertension, diabetes, heart conditions, stroke, arthritis, and

psychiatric conditions, would result in a higher likelihood of reporting challenges in ADL compared to those who do not have these conditions as presented in Table 4.7. Also, depressed participants were 4.3 (95% CI = 2.967-6.211) times more likely to report challenges with ADL than non-depressed participants. Those who drink alcohol were 50% (95% CI = 0.386-0.740) as likely to have difficulties in ADL than non-drinkers. Obese participants were almost 3.0 (95% CI = 2.158-4.094) times more likely to report problems with ADL than non-obese participants. Participants who never do light exercise were 5.4 (95% CI = 2.360-12.256) times more likely to develop difficulties in ADL than participants who do light exercise daily. (See Table 4.7)

The association between ADL at baseline with age, race, ethnicity, having lung conditions, cancer, having cognition impairment, having government health insurance, having prescription drug coverage, and smoking were not significant.

Table 4.7: Bivariate associations between participants' study variables and ADL at the baseline (2004)

Predictor variable	Unadjusted OR	95% CI	p-value
Polypharmacy	1.617	1.181-2.213	0.0027*
Age (ref=65-74 years)	1.387	0.987-1.950	0.0598
Gender (ref=male)	1.452	1.044-2.019	0.0267*
Race (ref=white)	1.663	1.095-2.526	0.0566
African American	0.978	0.381-2.511	
Others			
Ethnicity (ref=Hispanic)	1.644	0.977-2.767	0.0611
Marital status (ref=married)			0.0001*
Divorced	1.972	1.189-3.273	
Widowed	2.107	1.493-2.973	
Never married	1.330	0.459-3.856	

Education (ref=0-6 years)			< 0.0001*
7-12 years	0.486	0.280-0.844	
>13 years	0.230	0.125-0.422	
# of people living in the home (ref=alone)			0.0345*
2 people	0.695	0.484-0.997	
>2	1.114	0.706-1.756	
Wealth (ref=lowest quartile)			< 0.0001*
Mid-low quartile	0.482	0.324-0.717	
Mid-high quartile	0.271	0.174-0.423	
Highest quartile	0.200	0.122-0.329	
Self-reported health (ref=excellent)			< 0.0001*
Very good	1.334	0.436-4.076	
Good	4.420	1.572-12.417	
Fair	12.316	4.403-34.40	
Poor	39.125	13.312-114.994	
Number of chronic conditions (ref=0)			< 0.0001*
1	2.050	0.886-4.747	
2	3.079	1.396-6.925	
3	4.640	2.055-10.479	
4	6.010	2.551-14.381	
5	12.500	4.567-34.216	
6-7	7.692	1.991-29.717	
Hypertension [a]	1.658	1.191-2.308	0.0027*
Diabetes [a]	2.336	1.641-3.325	< 0.0001*
Heart conditions [a]	1.527	1.089-2.142	0.0142*
Lung conditions [a]	1.209	0.685-2.134	0.5123
Cancer [a]	0.938	0.607-1.448	0.7721
Stroke [a]	1.970	1.176-3.299	0.0100*
Psychiatric conditions [a]	2.693	1.776-4.085	< 0.0001*
Arthritis [a]	2.381	1.648-3.440	< 0.0001*

Cognitive impairment [a]	2.280	0.831-6.258	0.1095
Depression [a]	4.292	2.967-6.211	< 0.0001*
Government health insurance [a]	1.681	0.514-5.504	0.3905
Prescription drug coverage (ref=some by self and rest by insurance)	1.052	0.644-1.716	0.3373
Discounts	0.661	0.405-1.078	
Full price	0.663	0.309-1.296	
Pay nothing	1.126	0.518-2.449	
Other			
Smoking (ref=current)			0.8088
Former	1.014	0.581-1.769	
Never	0.912	0.522-1.593	
Alcohol drinking [a]	0.535	0.386-0.740	0.0002*
Obesity (ref=non-obese)	2.972	2.158-4.094	< 0.0001*
Light exercise (ref=every day)			< 0.0001*
>1 week	1.184	0.555-2.527	
1 per week	1.429	0.649-3.164	
1-3 per month	1.890	0.734-4.868	
Never	5.378	2.360-12.256	
Using Atorvastatin [a]	1.216	0.799-1.852	0.3613

* p-value < 0.05, indicates significant relationship, a= reference group is No

A multivariable logistic regression model was developed with the significant variables in the bivariate analysis and ADL. A backward elimination method (p=0.1) was used, and the least significant variables were removed one at a time until the model had only variables with a p-value of 0.1 or less. Tables 4.8 and 4.9 display the variables remaining in the model. The results of the final model for this cross-sectional analysis showed that polypharmacy, light exercise, self-reported health, depression, and obesity were all significant predictors for reporting ADL difficulties at baseline. Arthritis and psychiatric condition were in the final model because their

p-value was < 0.1 but > 0.05 (p=0.0598 and p=0.0891). Participants with polypharmacy were 1.4 (95% CI = 1.047-1.971) times more likely to report ADL difficulties than participants with non-polypharmacy after controlling for other confounders. Participants reporting good, fair, or poor health status were 4.2 (95% CI = 1.199-14.399), 11.2 (95% CI = 3.336-37.507) and 18.6 (95% CI = 5.194-66.773) times more likely to have ADL difficulties than participants with excellent health status. Those who never exercise lightly are 2.9 (95% CI = 1.073-8.001) times more likely to report ADL difficulties than those who exercise daily controlling for other confounders. Depressed individuals were 1.8 (95% CI = 1.020-3.160) times more likely to report ADL difficulties. Moreover, obese persons were 1.9 (95% CI =1.303-2.782) times more likely to report ADL difficulties. The detailed results are presented in Tables 4.8 and 4.9. According to the Goodness-of-Fit Test (p=0.9793), there was no gross lack of fit in this model.

Table 4.8: The predictor variables in the cross-sectional final model for ADL at baseline

Variables	p-value
Polypharmacy	0.0256
Self-reported health	< 0.0001
Light exercise	0.0170
Arthritis	0.0598
Depression	0.0428
Obesity	0.0013
Psychiatric conditions	0.0891

Table 4.9: The adjusted odds ratio of the predictor variables in the cross-sectional final model for ADL at baseline

Variables	Adjusted OR	95% CI	
Polypharmacy	1.437	1.047	1.971
Self-reported health (ref=excellent)			
Very Good	1.620	0.458	5.728
Good	4.154	1.199	14.399
Fair	11.186	3.336	37.507
Poor	18.623	5.194	66.773
Light exercise (ref= everyday)			
>1 per week	0.897	0.419	1.918
1 per week	0.898	0.370	2.179
1-3 per month	0.780	0.293	2.075
Never	2.930	1.073	8.001
Arthritis (ref= no)	1.602	0.980	2.620
Depression (ref= not depressed)	1.795	1.020	3.160
Obesity (ref= non-obese)	1.903	1.303	2.782
Psychiatric conditions (ref= no)	1.606	0.928	2.779

Goodness-of-Fit Test p= 0.9793, N= 1529, 16 missing observations were deleted

Aim 2-B) Cross-sectional study looking at the association between ADL and polypharmacy at endline (2008)

The bivariate analysis at endline (2008) between ADL and study variables without adjusting for them showed the following observation: Participants who were taking five or more prescription medications were 3.6 (95% CI = 2.723-4.803) times more likely to have difficulties in ADL than participants who were taking less than five prescription medications. Also, participants aged 75 years and older were 1.9 (95% CI = 1.426-2.445) times more likely to have difficulties in ADL than participants aged 65-74 years. The odds of having difficulties in ADL for widowed participants were 1.9 (95% CI = 1.470-2.594) compared to married couples, however, divorced and never married couples did not show a significant association. Participants with 7-12 years of education were almost 50% (95% CI = 0.302-0.838) as likely to report difficulties in ADL, and participants with 13 years or more of education were nearly 33% (95% CI = 0.195-0.571) as likely to report problems in ADL than participants with 6 years or less of education. For wealth and total household income, participants who were in the mid-low income, mid-high income, and highest income quartiles were 56% (95% CI = 0.412-0.831), 40% (95% CI = 0.275-0.569), and 26% (95% CI = 0.174-0.395) as likely to report difficulties in ADL than participants in the lowest household income quartile. For self-reported health, those who reported good, fair, or poor health status were 4.4 (95% CI = 1.345-14.299), 16.5 (95% CI = 5.123-53.252), and 59.3 (95% CI = 17.753-198.238) times more likely to have difficulties in ADL than those with excellent health status. The number of chronic conditions also increases the likelihood of having ADL difficulties. Having one of the following chronic conditions: hypertension, diabetes, heart conditions, stroke, lung conditions, arthritis, and psychiatric conditions results in increased likelihood of reporting difficulties in ADL than those who do not have those conditions

as presented in Table 4.10. Participants with cognitive impairment were 7 (95% CI = 4.110-11.933) times more likely to report ADL difficulties compared to participants with good cognitive status. Also, depressed participants were 4.8 (95% CI = 3.455 -6.742) times more likely to report problems than non-depressed individuals. Those who drink alcohol were 55% (95% CI = 0.413-0.725) as likely to have difficulties in ADL than non-drinkers. Obese participants were almost 1.9 (95% CI = 1.408-2.461) times more likely to report difficulties in ADL than non-obese participants. Participants who never do light exercise or who exercise only one to three time per month were 9.3 (95% CI = 5.304-16.323) and 3.3 (95% CI = 1.655 -6.427) times more likely to develop difficulties in ADL than the participants who do light exercise daily, while other categories of light exercise were not significant. Participants interviewed by proxy were 10.6 (95% CI = 4.888-22.865) times more likely to report ADL difficulties compared to participants who completed the interviews themselves.

The association between ADL at endline with gender, race, ethnicity, number of people living in the same home with the participant, having cancer, having government health insurance, having prescription drug coverage, smoking, and using atorvastatin were not significant. (See Table 4.10)

Table 4.10: Bivariate associations between participants' study variables and ADL at the endline (2008)

Predictor variable	Unadjusted OR	95% CI	p-value
Polypharmacy	3.617	2.723-4.803	< 0.0001*
Age (ref=65-74 years)	1.867	1.426-2.445	< 0.0001*
Gender (ref=male)	1.290	0.979-1.701	0.0709
Race (ref=white)	1.468	1.011-2.131	0.1215
African American	0.905	0.400-2.047	
Others			

Ethnicity (ref=Hispanic)	1.088	0.658-1.800	0.7428
Marital status (ref=married)			< 0.0001*
Divorced	1.088	0.652-1.816	
Widowed	1.952	1.470-2.594	
Never married	1.364	0.553-3.364	
Education (ref=0-6 years)			0.0001*
7-12 years	0.503	0.302-0.838	
>13 years	0.333	0.195-0.571	
# of people living in the home (ref=alone)			0.1485
2 people	0.795	0.582-1.084	
>2	1.083	0.723-1.623	
Wealth (ref=lowest quartile)			< 0.0001*
Mid-low quartile	0.585	0.412-0.831	
Mid-high quartile	0.396	0.275-0.569	
Highest quartile	0.262	0.174-0.395	
Self-reported health (ref=excellent)			< 0.0001*
Very good	2.976	0.898-9.862	
Good	4.401	1.345-14.299	
Fair	16.517	5.123-53.252	
Poor	59.324	17.753-198.238	
Number of chronic conditions (ref=0)			<0.0001*
1	1.108	0.459-2.674	
2	2.124	0.942-4.788	
3	2.818	1.250 -6.354	
4	5.224	2.272-12.013	
5	11.200	4.631-27.089	
6 -7	22.909	7.837-66.966	
Hypertension [a]	1.781	1.310-2.422	0.0002*
Diabetes [a]	2.134	1.590-2.862	<0.0001*
Heart conditions [a]	1.786	1.358-2.348	<0.0001*
Lung conditions [a]	2.215	1.536-3.193	<0.0001*
Cancer [a]	1.118	0.806-1.549	0.5040

Stroke [a]	3.343	2.354-4.748	<0.0001*
Psychiatric conditions [a]	3.396	2.433-4.741	<0.0001*
Arthritis [a]	3.266	2.265-4.711	<0.0001*
Cognitive impairment [a]	7.003	4.110-11.933	< 0.0001*
Depression [a]	4.826	3.455 -6.742	< 0.0001*
Government health insurance [a]	2.145	0.500-9.203	0.3045
Prescribed medication coverage [a]	1.118	0.444-2.813	0.8133
Smoking (ref=current)			0.9851
Former	1.034	0.609-1.757	
Never	1.047	0.717-1.776	
Alcohol drinking (ref=no)	0.547	0.413-0.725	< 0.0001*
Obesity (ref=non-obese)	1.861	1.408-2.461	< 0.0001*
Light exercise (ref=every day)			< 0.0001*
>1 week	1.059	0.614-1.828	
1 per week	1.617	0.922-2.837	
1-3 per month	3.261	1.655 -6.427	
Never	9.305	5.304-16.323	
Using Atorvastatin [a]	1.202	0.836-1.728	0.3202
Proxy interview [a]	10.571	4.888-22.865	< 0.0001*

* p-value < 0.05, indicates significant relationship, a= reference group is No

The 2008 cross-sectional analysis evaluated the association between ADL and the significant variables in the bivariate analysis. Table 4.11 displays the significant variables in the model. Polypharmacy, age, self-reported health, light exercise, arthritis, obesity, depression, and psychiatric conditions were all significant predictors of reporting ADL difficulties at endline. Participants with polypharmacy were 1.9 (95% CI = 1.240 3.009) times more likely to report ADL difficulties than those without polypharmacy after controlling for other confounders. The

adjusted OR of participants aged 75 years or older was 2.1(95% CI = 1.461-3.006) times higher than participants aged 65-74 years. Participants reporting good, fair, or poor health status were 4.8 (95% CI = 1.002-22.647), 11.7 (95% CI = 2.477-55.392), and 28.2 (95% CI = 5.795-137.210) times more likely to have ADL difficulties than participants with excellent health status. Those who never lightly exercise were 3.6 (95% CI = 1.771-7.497) times more likely to report ADL difficulties than those who exercise daily controlling for other confounders. Individuals with arthritis were 2.3 (95% CI =1.322-3.851) times more likely to report ADL difficulties after controlling for other confounders. Moreover, obese persons were 1.6 (95% CI = 1.100-2.246) times more likely to report ADL difficulties than non-obese participants. Depressed individuals were 2.7 (95% CI = 1.711-4.203) times more likely to report ADL difficulties than participants who were not depressed. In addition, individuals with psychiatric conditions were 1.9 (95% CI = 1.221-3.011) times more likely to experience ADL difficulties after controlling for other confounders. The results of this analysis are presented in Tables 4.11 and 4.12. The model had a Goodness-of-Fit Test p= 0.3367, which indicates no gross lack of fit.

Table 4.11: The predictor variables in the cross-sectional final model for ADL at endline

Variables	p-value
Polypharmacy	0.0044
Age	0.0001
Self-reported health	< 0.0001
Light exercise	0.0005
Arthritis	0.0036
Depression	< 0.0001
Obesity	0.0140
Psychiatric conditions	0.0056

Table 4.12: The adjusted odds ratio of the predictor variables in the cross-sectional final model for ADL at endline

Predictor variables	Adjusted OR	95% CI	
Polypharmacy	1.932	1.240	3.009
Age (ref=65-74 years)	2.096	1.461	3.006
Self-reported health (ref=excellent)			
Very Good	3.926	0.900	17.126
Good	4.764	1.002	22.647
Fair	11.707	2.477	55.329
Poor	28.198	5.795	137.210
Light exercise (ref= everyday)			
>1 per week	1.019	0.506	2.053
1 per week	1.208	0.596	2.448
1-3 per month	2.168	0.864	5.444
Never	3.644	1.771	7.497
Arthritis	2.256	1.322	3.851
Depression	2.682	1.711	4.203
Obesity	1.572	1.100	2.246
Psychiatric conditions	1.917	1.221	3.011

Goodness-of-Fit Test p= 0.3367, N= 1502, and 43 missing observations were deleted

Aim 2-C) Cross-sectional study looking at the association between IADL and polypharmacy at endline (2004)

For IADL, the bivariate analysis at baseline (2004) between IADL and study variables without controlling for confounders resulted in the following observation: Participants with polypharmacy did not show a significant association with IADL. Age showed a significant association with IADL; participants aged 75 and older were 1.6 (95% CI = 1.072-2.249) times more likely to have difficulties with IADL than participants aged 65-74 years. African Americans were 1.5 (95% CI = 1.320-3.158) times more likely to have trouble with IADL than white participants, while other races did not show a significant difference. Participants with 7-12 years of education were almost 35% (95% CI = 0.198-0.608) as likely to report difficulties in IADL, and participants with 13 years or more of education were almost 19% (95% CI=0.104-0.360) as likely to report difficulties in IADL than those with 6 years or less of education. Participants living with more than two persons in the same household were 56% (95% CI = 0.359-0.861) as likely to report IADL difficulties than participants living alone. For wealth and total household income, participants who were in the mid-low income, mid-high income, and highest income quartiles were 50% (95% CI = 0.324-0.776), 30% (95% CI = 0.183-0.484) and 19% (95% CI = 0.109-0.338) as likely to report difficulties in IADL than participants with low household income. In self-reported health status, those who reported fair or poor health status were 7.1 (95% CI = 2.785-18.217) and 25.8 (95% CI = 9.624-69.207) times more likely to have difficulties in IADL than those with excellent health status while good and very good health status were not significant. The number of chronic conditions also increased the likelihood of having IADL difficulties. Having one of the following chronic conditions: hypertension, diabetes, heart conditions, lung conditions, stroke, arthritis, and psychiatric conditions would

result in reporting difficulties in IADL more often than those who do not have those conditions as presented in Table 4.13. Participants with cognitive impairment were 3 (95% CI =1.082-8.195) times more likely to report IADL difficulties compared to participants with good cognitive status. Also, depressed participants were 3.7 (95% CI = 2.487-5.556) times more likely to report problems with IADL than non-depressed individuals. Former and never smokers were 57% (95% CI = 0.337-0.976) and 51% (95% CI = 0.297-0.867) as likely to report difficulties in IADL compared to current smokers. Those who drink alcohol were 44% (95% CI = 0.301-0.635) as likely to have difficulties in IADL than non-drinkers. Obese participants were almost 2 (95% C I = 1.385-2.849) times more likely to report IADL difficulties than non-obese participants. Participants who never do light exercise were 11.2 (95% CI = 3.826-32.880) times more likely to develop difficulties in IADL than participants who do light exercise daily while other categories in the light exercise were not significant.

The association between IADL at baseline with gender, ethnicity, marital status, having cancer, having government health insurance, and having prescription drug coverage were not significant. (See Table 4.13)

Table 4.13: Bivariate associations between participants' study variables and IADL at the baseline (2004)

Predictor variable	Unadjusted OR	95% CI	p-value
Polypharmacy	1.284	0.904-1.824	0.1632
Age (ref=65-74 years)	1.553	1.072-2.249	0.0198*
Gender (ref=male)	0.930	0.655-1.319	0.6826
Race (ref=white)			0.0029*
African American	1.468	1.320-3.158	
Others	0.484	0.116-2.022	

Ethnicity (ref=Hispanic)	1.216	0.650-2.273	0.5402
Marital status (ref=married)			0.4341
Divorced	1.436	0.814-2.533	
Widowed/Never married	1.225	0.832-1.805	
Education (ref=0-6years)			< 0.0001*
7-12 years	0.347	0.198-0.608	
>13 years	0.193	0.104-0.360	
# of people living in the home (ref=alone)			0.0307*
2 people	0.630	0.381-1.041	
>2	0.556	0.359-0.861	
Wealth (ref=lowest quartile)			< 0.0001*
Mid-low quartile	0.502	0.324-0.776	
Mid-high quartile	0.298	0.183-0.484	
Highest quartile	0.192	0.109-0.338	
Self-reported health (ref=excellent)			< 0.0001*
Very good	1.430	0.528-3.872	
Good	1.771	0.671-4.674	
Fair	7.123	2.785-18.217	
Poor	25.808	9.624-69.207	
Number of chronic conditions (ref=0)			< 0.0001*
1	1.151	0.472-2.806	
2	2.014	0.876-4.630	
3	3.768	1.654 -8.588	
4	5.140	2.124-12.441	
5	11.111	4.021-30.703	
6 -7	21.875	6.175--66.966	
Hypertension [a]	1.802	1.240-2.618	0.0020*
Diabetes [a]	2.138	1.442-3.169	0.0002*
Heart conditions [a]	2.270	1.587-3.246	<0.0001*
Lung conditions [a]	2.913	1.773-4.784	<0.0001*
Cancer [a]	1.146	0.727-1.807	0.5579

Stroke [a]	3.032	1825-5.036	< 0.0001*
Psychiatric conditions [a]	3.067	1.947-4.767	< 0.0001*
Arthritis [a]	2.307	1.534-3.648	< 0.0001*
Cognitive impairment [a]	2.978	1.082-8.195	0.0346*
Depression [a]	3.717	2.487-5.556	< 0.0001*
Government health insurance [a]	0.581	0.240-1.405	0.2282
Prescription drug coverage			0.4174
Discounts	0.933	0.536-1.624	
Full price	0.783	0.472-1.299	
Pay nothing	0.422	0.167-1.068	
Other	1.013	0.421-2.436	
Smoking (ref=current)			0.0044*
Former	0.573	0.337-0.976	
Never	0.508	0.297-0.867	
Alcohol drinking (ref=no)	0.437	0.301-0.635	< 0.0001*
Obesity [a]	1.987	1.385-2.849	0.0002*
Light exercise (ref=every day)			< 0.0001*
>1 week	1.741	0.619-4.902	
1 per week	2.673	0.932-7.665	
1-3 per month	1.499	0.390-5.771	
Never	11.217	3.826-32.880	
Using Atorvastatin [a]	1.026	0.631-1.669	0.9173

* p-value < 0.05 indicates a significant relationship

The association between IADL in 2004 and the significant variables in the bivariate analysis was then evaluated using a multivariable model. Table 4.14 displays the significant variables in the model. Polypharmacy did not significant association after controlling for other confounders. Self-reported health, light exercise, having heart conditions, drinking alcohol and total household income were all significant predictors of reporting IADL difficulties at baseline.

Participants reporting poor health status were 5.7 (95% CI = 1.440-22.552) times more likely to have IADL difficulties than participants with excellent hath status. Those who never lightly exercise were 5 (95% CI = 1.442-17.205) times more likely to report IADL difficulties than those who exercise daily controlling for other confounders. Individuals with heart conditions were 1.8 (95% CI = 1.156-2.957) times more likely to report IADL difficulties after controlling for other confounders. For wealth and total household income, participants who were in the mid-low income and highest income quartiles were 66% (95% CI = 0.438-0.989) and 36% (95% CI = 0.170-0.764) as likely to report difficulties in IADL than participants in the low household income quartile. Results of the multivariable analysis are presented in Tables 4.14 and 4.15. The model had a Goodness-of-Fit Test p= 0.8325, which indicates no gross lack of fit.

Table 4.14: The predictor variables in the cross-sectional final model for IADL at baseline

Variable	p-value
Polypharmacy	0.5080
Self-reported health	<0.0001
Light exercise	0.0010
Heart condition	0.0114
Psychiatric conditions	0.0629
Alcohol drinking	0.0657
Wealth	0.0342

Table 4.15: The adjusted odds ratio of the predictor variables cross-sectional final model for IADL at baseline

Predictor variable	Adjusted OR	95%CI	
Polypharmacy	1.153	0.751	1.771
Self-reported health (ref=excellent)			
Very Good	0.991	0.279	3.525
Good	0.689	0.194	2.447
Fair	2.388	0.693	8.225
Poor	5.699	1.440	22.552
Light exercise (ref= everyday)			
>1 per week	1.195	0.387	3.694
1 per week	1.446	0.463	4.514
1-3 per month	0.753	0.160	3.542
Never	4.982	1.442	17.205
Heart condition	1.849	1.156	2.957
Psychiatric condition	1.561	0.975	2.500
Alcohol drinking (ref=no)	0.700	0.479	1.024
Wealth (ref=lowest quartile)			
Mid-low quartile	0.658	0.438	0.989
Mid-high quartile	0.551	0.300	1.013
Highest quartile	0.360	0.170	0.764

Goodness-of-Fit Test p= 0.8325, N= 1543 and 2 missing observations were deleted

Aim 2-D) Cross-sectional study evaluating the association between IADL and polypharmacy at endline (2008)

The endline (2008) bivariate analysis to examine the association between IADL and covariates yielded the following results: participants with polypharmacy were 2.6 (95% CI = 1.968-3.555) times more likely to report IADL difficulties than the group without polypharmacy. Age significantly associated with IADL difficulty, and participants aged 75 and older were1.8 (95% CI = 1.354-2.416) times more likely to have difficulties in IADL than participants aged 65-74 years. Females were 1.6 (95% CI = 1.195-2.205) times more likely to report IADL difficulties than males. The odds of having difficulties in IADL for widowed were 2.2 compared to married couples (95% CI = 1.604-2.965), however, divorced and never married couples did not show a significant association. Participants with 7-12 years of education were almost 60% (95% CI=0.349-0.692) as likely to report difficulties in IADL and participants with 13 years or more of education were almost 33% (95% CI = 0.184-0.595) as likely to report difficulties in IADL compared to participants with 0-6 years of education. Participants living with more than two persons in the same household were 41% (95% CI = 0.411-0.0.886) as likely to report IADL difficulties than participants living alone. Regarding wealth and total household income, participants who were mid-low income, mid-high income, and highest income quartiles were 48% (95% CI = 0.327-0.692), 34% (95% CI = 0.229-0.498) and 20% (95% CI = 0.128-0.320) as likely to report difficulties in IADL than participants with low household income. For self-reported health status, those who reported fair or poor health status were 5.6 (95% CI = 2.346-13.156) and 17.5 (95% CI = 7.130-43.150) times more likely to experience difficulties in IADL than individuals with excellent health status, while good and very good health status were not significant. Having four or more chronic conditions increases the chances of reporting IADL

difficulties. Having one of the following chronic conditions: hypertension, diabetes, heart conditions, lung conditions, stroke, arthritis, and psychiatric conditions resulted in reporting difficulties in IADL than those who do not have those conditions as presented in Table 4.16. Participants with cognitive impairment were 10.3 (95% CI = 6.000-17.735) times more likely to have IADL difficulties compared to participants with good cognitive status. Depressed participants were 4.5 (95% CI = 3.184-6.437) times more likely to experience difficulty in IADL than non-depressed individuals. Alcohol drinkers were 47% (95% CI = 0.342-0.636). as likely to have difficulties in IADL than non-drinkers. Participants who never do light exercise or exercise only 1-3 times per month were 9.0 (95% CI = 4.988-16.092) and 3.1 (95% CI = 1.513-6.306) times more likely to develop difficulties in IADL than the participants who do light exercise daily while other categories in the light exercise were not significant. Participants interviewed by proxy were 18.4 (95% CI = 8.080-41.896) times more likely to report ADL difficulties compared to participants who completed the interviews themselves. The association between IADL at baseline with race, ethnicity, having cancer, having government health insurance, having prescription drug coverage, smoking, and obesity were not significant.

Table 4.16: Bivariate associations between participants' characteristics and IADL at the endline (2008)

Predictor variable	Unadjusted OR	95% CI	p-value
Polypharmacy	2.645	1.968-3.555	< 0.0001*
Age (ref=65-74 years)	1.809	1.354-2.416	< 0.0001*
Gender (ref=male)	1.623	1.195-2.205	0.0019*
Race (ref=white)			0.1960
African American	1.443	0.968-2.152	
Others	1.118	0.493-2.535	

Ethnicity (ref=Hispanic)	0.865	0.485-1.545	0.6246
Marital status (ref=married)			< 0.0001*
Divorced	1.627	0.983-2.694	
Widowed	2.181	1.604-2.965	
Never married	1.134	0.391-3.291	
Education (ref=0-6years)			< 0.0001*
7-12 years	0.603	0.349-1.041	
>13 years	0.331	0.184-0.595	
# of people living in the home (ref=alone)			0.0068*
2 people	0.927	0.610-1.408	
>2	0.603	0.411-0.886	
Wealth (ref=lowest quartile)			< 0.0001*
Mid-low quartile	0.476	0.327-0.692	
Mid-high quartile	0.338	0.229-0.498	
Highest quartile	0.203	0.128-0.320	
Self-reported health (ref=excellent)			< 0.0001*
Very good	1.496	0.614-3.648	
Good	1.772	0.740-4.246	
Fair	5.555	2.346-13.156	
Poor	17.540	7.130-43.150	
Number of chronic conditions (ref=0)			< 0.0001*
1	1.328	0.559-3.158	
2	1.848	0.816-4.187	
3	2.049	0.898 -4.673	
4	3.644	1.564-8.490	
5	7.000	2.860-17.135	
6 -7	17.231	5.970-49.733	
Hypertension [a]	1.483	1.076-2.044	0.0161*
Diabetes [a]	1.460	1.053-2.026	0.0234*
Heart conditions [a]	1.485	1.104-1.996	0.0089*
Lung conditions [a]	1.879	1.263-2.796	0.0019*
Cancer [a]	1.069	0.752-1.520	0.7108

Stroke [a]	3.574	2.484-5.141	< 0.0001*
Psychiatric conditions [a]	3.851	2.726-5.440	< 0.0001*
Arthritis [a]	2.213	1.547-3.166	< 0.0001*
Cognitive impairment [a]	10.316	6.000-17.735	< 0.0001*
Depression [a]	4.527	3.184-6.437	< 0.0001*
Government health insurance [a]	0.778	0.262-2.308	0.6504
Prescription drug coverage [a]	0.929	0.345-2.497	0.8833
Smoking (ref=current)			0.2150
Former	0.661	0.392-1.113	
Never	0.801	0.479-1.341	
Alcohol drinking (ref=no)	0.466	0.342-0.636	< 0.0001*
Obesity [a]	1.258	0.924-1.715	0.1453
Light exercise (ref=every day)			< 0.0001*
>1 week	0.884	0.493-1.587	
1 per week	1.395	0.765-2.544	
1-3 per month	3.089	1.513-6.306	
Never	8.959	4.988-16.092	
Using Atorvastatin [a]	1.144	0.773-1.695	0.5012
Proxy interview [a]	18.398	8.080-41.896	< 0.0001*

* p-value < 0.05 indicates a significant relationship

After adding the variables in the bivariate analyses into a multivariable model to examine their association with endline IADL, the following results were obtained: gender, age, polypharmacy, light exercise, self-reported health status, having a psychiatric condition, depression, and wealth were all significant predictors of reporting IADL difficulties in 2008. Participants with polypharmacy were 1.7 (95% CI = 1.080-2.525) times more likely to report

IADL difficulties than those without polypharmacy, after controlling for other confounders. Participants aged 75 years and older were1.7 (95% CI = 1.044-2.673) times more likely to have difficulties in IADL than participants aged 65-74 years, after controlling for other confounders. Females were 1.8 (95% CI = 1.128-2.777) times more likely to develop IADL difficulties than males, controlling for other confounders. Participants reporting poor health status were 5.4 (95% CI = 1.595-18.041) times more likely to have IADL difficulties than participants with excellent health status. Those who never lightly exercise were 5 (95% CI = 2.482-10.248) times more likely to report IADL difficulties than those who exercise daily, controlling for other confounders. Individuals with psychiatric conditions were 2.4 (95% CI = 1.407-4.015) times more likely to report IADL difficulties after controlling for other confounders. Depressed participants were 2.1 (95% CI = 1.268-3.534) times more likely to develop IADL difficulties than non-depressed individuals. For wealth and total household income, participants who were mid-high income and highest income quartiles were 50% (95% CI = 0.303-.819) and 47% (95% CI = 0.231-0.962) as likely to report difficulties in IADL than participants in the low household income quartile. The results of the analysis are reported in Tables 4.16 and 4.18. The Goodness-of-Fit Test had a p= 0.8568, which indicate no gross lack of fit.

Table 4.17 The predictor variables in the cross-sectional final model for IADL at endline

Variable	p-value
Polypharmacy	0.0216
Age	0.0330
Gender	0.0140
Self-reported health	0.0005
Light exercise	< 0.0001
Psychiatric conditions	0.0017
Depression	0.0049
Wealth	0.0421

Table 4.18 The adjusted odd ratios of the predictor variables in the cross-sectional final model for IADL at endline

Predictor variable	Adjusted OR	95% CI	
Polypharmacy	1.651	1.080	2.525
Gender (ref=male)	1.770	1.128	2.777
Age (ref=65-74 years)	1.671	1.044	2.673
Self-reported health (ref=excellent)			
Very Good	1.281	0.401	4.093
Good	1.326	0.415	4.243
Fair	2.571	0.827	7.998
Poor	5.364	1.595	18.041
Light exercise (ref= everyday)			
>1 per week	0.749	0.380	1.475
1 per week	0.860	0.462	1.603
1-3 per month	2.165	0.892	5.254
Never	5.044	2.482	10.248
Psychiatric conditions	2.376	1.407	4.015
Depression	2.117	1.268	3.534
Wealth (ref=lowest quartile)			
Mid-low quartile	0.730	0.423	1.261
Mid-high quartile	0.498	0.303	0.819
Highest quartile	0.471	0.231	0.962
Goodness-of-Fit Test p= 0.8568, N= 1508 and 37 missing observations were deleted			

Aim 3 To assess the longitudinal relationship between polypharmacy and functional status using a large nationally-representative dataset

Aim 3-A) To evaluate the relationship between polypharmacy status and functional status in community-dwelling older adults after 4 years

Multiple models were developed to assess the relationship between polypharmacy status and functional status over time (4 years). The first longitudinal model adjusted for the baseline (2004) functional status-related variables and polypharmacy. The second model was the same with the addition of polypharmacy status at the endline (2008). These two models were assessed for the two outcomes, ADL and IADL. There were a total of four models (see Table 4.19). PROC SURVEYLOGISTIC was used to run the models.

Table 4.19: Different models used to evaluate the relationship between polypharmacy status and functional status after 4 years

Model 1	ADL at endline = Baseline functional-related variables + polypharmacy at baseline
Model 2	ADL at endline = Baseline functional-related variables + polypharmacy at baseline + polypharmacy at endline
Model 3	IADL at endline = Baseline functional-related variables + polypharmacy at baseline
Model 4	IADL at endline = Baseline functional-related variables + polypharmacy at baseline + polypharmacy at endline

All of the significant risk predictor variables examined previously in the cross-sectional model were added to the longitudinal model, and backward elimination was performed. Polypharmacy status was retained even if it was not significant. Table 4.19 displays the predictors evaluated in the model between ADL (2008), the baseline polypharmacy status

(2004), and the baseline (2004) function-related variables. Multiple interactions were added to the model between self-reported health and polypharmacy, self-reported health and each chronic condition, and each chronic condition and polypharmacy, but none was significant. Interactions were checked to make sure none had a modifying role in the relationship between polypharmacy and functional status.

In the first model, polypharmacy status at baseline was not a significant predictor of difficulties in ADL after 4 years. Taking ≥ 5 prescribed medications at the beginning of the study did not predict ADL difficulties at the end of the study. The important variables in the first model to assess developing ADL difficulties in 2008 were the following baseline (2004) variables: age, self-reported health status, arthritis, psychiatric conditions, obesity, and cognitive impairment. Participants aged 75 years and older were 2 (95% CI = 1.348-2.987) times more likely to have difficulties in ADL after 4 years than participants aged 65-74 years, controlling for confounders. Participants reporting good, fair, or poor health status were 3.2 (95% CI = 1.339-7.456), 8.4 (95% CI = 3.577-19.581), and 17.5 (95% CI = 7.136-42.838) times more likely to have ADL difficulties than participants with excellent health status. Participants with arthritis were 2.1 (95% CI = 1.381-3.306) times more likely to report ADL difficulties after 4 years than participants without arthritis. The odds of having ADL difficulties after 4 years was 1.9 (95% CI = 1.209-2.913) for those who have baseline psychiatric conditions, controlling for other confounders. Obese participants at baseline were 1.7 (95% CI = 1.141-2.643) times more likely to develop ADL difficulties after 4 years after adjusting for confounders. Participants with cognitive impairment at baseline were 4.1(95% CI = 1.255-13.630) times more likely to develop ADL difficulties after 4 years than participants with good cognition, after adjusting for confounders. See Table 4.20.

Table 4.20: Final model 1 for longitudinal analysis of ADL at endline and controlling for baseline functional-related variables and polypharmacy at baseline

Baseline Predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2004	1.115	0.850	1.463	0.4236
Age (ref=65-74 years)	2.007	1.348	2.987	0.0009
Self-reported health (ref=excellent)				< 0.0001
Very Good	1.609	0.733	3.534	
Good	3.229	1.399	7.456	
Fair	8.370	3.577	19.581	
Poor	17.484	7.136	42.838	
Arthritis	2.136	1.381	3.306	0.0010
Psychiatric conditions	1.876	1.209	2.913	0.0059
Obesity	1.737	1.141	2.643	0.0110
Cognitive impairment	4.135	1.255	13.630	0.0206
Goodness-of-Fit Test p= 0.2894, N= 1529 and 16 missing observations were deleted				

Similar results to model 1 were obtained (Table 4.21) when adding polypharmacy status in 2008 to form model 2. This addition resulted in a significant effect for polypharmacy status in 2008. Participants with polypharmacy in 2008 were 2.4 (95% CI = 1.666-3.570) times more likely to report ADL difficulties than participants without polypharmacy, adjusting for all other confounders. Polypharmacy status is important in the same year rather than 4 years earlier.

Table 4.21: Final model 2 for longitudinal analysis of ADL at endline and controlling for baseline functional-related variables and polypharmacy at both baseline and endline

Baseline predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2004	1.139	0.869	1.493	0.3389
Polypharmacy 2008	2.439	1.666	3.570	< 0.0001
Age (ref=65-74 years)	1.979	1.340	2.921	0.0009
Self-reported health status (ref=excellent)				< 0.0001
Very Good	1.439	0.662	3.130	
Good	2.624	1.152	5.979	
Fair	6.246	2.710	14.394	
Poor	12.191	4.958	29.975	
Arthritis	2.085	1.347	3.228	0.0014
Psychiatric conditions	1.823	1.172	2.835	0.0087
Obesity	1.566	1.014	2.419	0.0434
Cognitive impairment	4.498	1.386	14.595	0.0133
Goodness-of-Fit Test p= 0.8730, N= 1525 and 20 missing observations were deleted				

In Table 4.22, IADL in 2008 could be predicted by the following baseline variables: age, self-reported health status, arthritis, stroke, depression, and alcohol drinking. Participants aged 75 years and older were 2.7 (95% CI = 1.870-3.914) times more likely to have difficulties in IADL after 4 years than participants aged 65-74 years, controlling for confounders. Participants reporting fair or poor health status were 3.1 (95% CI = 1.232-7.656) or 6.1 (95% CI = 2.465-15.079) times more likely to have IADL difficulties in 2008 than participants with excellent health status. Participants with arthritis were 1.7 (95% CI = 1.100-2.523) times more likely to report IADL difficulties after 4 years than participants without arthritis. The odds of having IADL difficulties after 4 years was 2.3 (95% CI = 1.393-3.905) for those who had baseline stroke history, controlling for other confounders. Depressed participants at baseline were 1.7 (95% CI = 1049-2.760) times more likely to develop IADL difficulties after 4 years than non-depressed participants, after adjusting for confounders. Participants who drink alcohol at baseline

were 54% (95% CI = 0.543-0.760) as likely to develop IADL difficulties after 4 years than participants who didn't drink, after adjusting for confounders. Polypharmacy status at baseline was not a significant predictor for IADL difficulties. Taking ≥ 5 prescribed medications at the beginning of the study did not predict IADL difficulties at the end of the study.

Table 4.22: Final model 3 for longitudinal analysis of IADL at endline and controlling for baseline functional-related variables and polypharmacy at baseline

Baseline predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2004	1.232	0.862	1.762	0.2468
Age (ref=65-74 years)	2.705	1.870	3.914	< 0.0001
Self-reported health status (ref=excellent)				< 0.0001
Very Good	1.174	0.465	2.966	
Good	1.299	0.468	3.603	
Fair	3.071	1.232	7.656	
Poor	6.097	2.465	15.079	
Arthritis	1.666	1.100	2.523	0.0170
Stroke	2.333	1.393	3.905	0.0018
Depression	1.702	1.049	2.760	0.0318
Alcohol drinking	0.543	0.387	0.760	0.0006
Goodness-of-Fit Test p= 0.6880, N= 1543 and 2 missing observations were deleted				

A similar observation was seen when adding polypharmacy status in 2008 to form model 4. This addition also resulted in a significant effect for polypharmacy status in 2008. Participants with polypharmacy in 2008 were 2.1 (95% CI = 1.460-2.872) times more likely to have IADL difficulties than participants without polypharmacy, adjusting for all other confounders. See Table 4.23.

Table 4.23: Final model 4 for longitudinal analysis of IADL at endline and controlling for baseline functional-related variables and polypharmacy at both baseline and endline

Baseline predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2004	1.264	0.890	1.797	0.1859
Polypharmacy 2008	2.048	1.460	2.872	< 0.0001
Age (ref=65-74 years)	2.721	1.871	3.959	< 0.0001
Self-reported health (ref=excellent)				< 0.0001
Very Good	1.076	0.428	2.705	
Good	1.094	0.403	2.968	
Fair	2.420	0.985	5.944	
Poor	4.541	1.864	11.062	
Arthritis	1.601	1.045	2.452	0.0312
Stroke	2.046	1.232	3.398	0.0066
Depression	1.629	0.993	2.671	0.0532
Alcohol drinking	0.548	0.394	0.761	0.0742
Goodness-of-Fit Test p= 0.5019, N= 1539 and 6 missing observations were deleted				

Aim 3-B) To assess the relationship between polypharmacy at midline and changes in functional status after 2 years

For this specific aim, the relationship between functional status and polypharmacy was examined after 2 years, controlling for variables in 2006. Similar models to aim 3-A have been assessed and documented in Table 4.24. These four models were evaluated to better understand the relationship between polypharmacy and functional decline over time.

Table 4.24: Different models to evaluate the relationship between polypharmacy status and functional status after 2 years

Model 5	ADL at endline = Midline functional-related variables + polypharmacy at midline
Model 6	ADL at endline = Midline functional-related variables + polypharmacy at midline + polypharmacy at endline
Model 7	IADL at endline = Midline functional-related variables + polypharmacy at midline
Model 8	IADL at endline = Midline functional-related variables + polypharmacy at midline + polypharmacy at endline

The important variables in the model 5 to predict developing ADL difficulties in 2008 were the following midline (2006) variables: polypharmacy, age, self-reported health, light exercise, arthritis, psychiatric conditions, obesity, and cognitive impairment. Participants taking ≥ 5 prescribed medications in 2006 were 1.8 (95% CI = 1.135-2.883) times more likely to develop ADL problems at the end of the study than participant taking < 5 prescribed medications. Participants aged 75 years and older were 1.7 (95% CI = 1.205-2.883) times more likely to have difficulties in ADL after 2 years than participants aged 65-74 years, controlling for confounders. Those who never lightly exercise were 2 times more likely to report ADL problems after 2 years than those who exercise daily controlling for other confounders. Participants reporting good, fair, or poor health status were 3.5 (95% CI =1.277-9.783), 5.4 (95% CI = 1.692-17.144) and 12.0 (95% CI = 3.837-37.349) times more likely to have ADL difficulties after 2 years than participants with excellent health status. Participants with arthritis were 2.5 (95% CI =

1.530-4.184) times more likely to report ADL difficulties after 2 years than participants without arthritis. The odds of having ADL difficulties after 2 years was 2.1 (95% CI = 1.177-3.870) for those who had psychiatric conditions, controlling for other confounders. Obese participants in 2006 were 1.9 (95% CI = 1.174-2.998) times more likely to develop ADL difficulties after 2 years, after adjusting for confounders. See Table 4.25

Table 4.25: Final model 5 for longitudinal analysis of ADL at endline and controlling for midline functional-related variables and polypharmacy at midline

Midline predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2006	1.809	1.135	2.883	0.0138
Age (ref=65-74 years)	1.728	1.205	2.478	0.0037
Self-reported health status (ref=excellent)				< 0.0001
Very Good	1.747	0.565	5.406	
Good	3.534	1.277	9.783	
Fair	5.386	1.692	17.144	
Poor	11.971	3.837	37.349	
Light exercise (ref= everyday)				0.0633
>1 per week	0.704	0.363	1.364	
1 per week	0.804	0.470	1.377	
13 per month	0.972	0.455	2.077	
Never	2.027	0.897	4.582	
Arthritis	2.530	1.530	4.184	0.0005
Psychiatric conditions	2.134	1.177	3.870	0.0135
Obesity	1.873	1.174	2.988	0.0095
Goodness-of-Fit Test p= 0.6893, N= 1289 and 256 missing observations were deleted				

In model 6, when adding polypharmacy status in 2008, the relationship between polypharmacy status in 2006 and ADL changed from significant to non-significant (p=0.5731). This addition also resulted in a significant effect for polypharmacy status in 2008 (p=0.0035). Participants with polypharmacy in 2008 were 2.2 (95% CI = 1.304-3.566) times more likely to

have ADL difficulties than participants without polypharmacy, adjusting for all other confounders (Table 4.26).

Table 4.26: Final model 6 for longitudinal analysis of ADL at endline and controlling for midline functional-related variables and polypharmacy at both midline and endline

Midline predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2006	1.160	0.685	1.964	0.5731
Polypharmacy 2008	2.156	1.304	3.566	0.0035
Age (ref=65-74 years)	1.677	1.170	2.404	0.0057
Self-reported health status (ref=excellent)				< 0.0001
Very Good	1.584	0.504	4.978	
Good	3.156	1.121	8.882	
Fair	4.732	1.487	15.057	
Poor	9.861	3.164	30.736	
Light exercise (ref= everyday)				0.0405
>1 per week	0.688	0.357	1.328	
1 per week	0.761	0.438	1.321	
1-3 per month	0.914	0.428	1.953	
Never	2.093	0.924	4.740	
Arthritis	2.564	1.546	4.252	0.0005
Psychiatric conditions	2.086	1.137	3.829	0.0186
Obesity	1.837	1.145	2.947	0.0127
Goodness-of-Fit Test p= 0.4436, N= 1286 and 259 missing observations were deleted				

The relationship between IADL and polypharmacy after 2 years was also examined by similar methods used above. The important variables in model 7 to develop IADL difficulties in 2008 while controlling for the midline (2006) variables were: age, self-reported health, light exercise, arthritis, psychiatric conditions, stroke, and wealth. Polypharmacy in this model was not significant, however the p-value was close to significant (p=0.0636). Participants aged 75 years and older at midline were 2.3 (95% CI = 1.448-3.542) times more likely to have difficulties in IADL after 2 years than participants aged 65-74 years, controlling for confounders.

Participants reporting fair or poor health status were 3.4 (95% CI = 1.069-10.598) and 4.1 (95% CI = 1.061-16.058) times more likely to have IADL difficulties after 2 years than participants with excellent health status. Those who never lightly exercise were 3.6 (95% CI = 1.567-8.220) times more likely to report IADL problems after 2 years than those who exercise daily, controlling for other confounders. Participants with arthritis at midline were 1.9 (95% CI = 1.049-3.264) times more likely to report IADL difficulties after 2 years than participants without arthritis. Participants with stroke history in 2006 were 2.1 (95% CI = 1.121-4.084) times more likely to have IADL difficulties after 2 years, after adjusting for confounders.

The odds of having IADL difficulties after 2 years were 2.1 (95% CI = 1.230-3.471) for those who have psychiatric conditions, controlling for other confounders. Participants who were mid-low, mid-high and highest income quartiles were 50% (95% CI = 0.285-0.880), 44% (95% CI = 0.250-0.769), and 40% (95% CI = 0.174-0.914) as likely to report difficulties in IADL than participants in the low household income quartile. (See Table 4.27)

Table 4.27: Final model 7 for longitudinal analysis of IADL at endline and controlling for midline functional-related variables and polypharmacy at midline

Midline predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2006	1.644	0.971	2.785	0.0636
Age (ref=65-74 years)	2.265	1.448	3.542	0.0006
Light exercise (ref= everyday)				<0.0001
>1 per week	0.687	0.377	1.252	
1 per week	1.183	0.611	2.292	
1-3 per month	1.180	0.427	3.263	
Never	3.589	1.567	8.220	
Self-reported health status (ref=excellent)				0.0045
Very Good	1.409	0.476	4.171	
Good	1.191	0.383	3.703	
Fair	3.365	1.069	10.598	
Poor	4.129	1.061	16.058	

Midline predictor variable	Adjusted OR	95% CI		p-value
Arthritis	1.850	1.049	3.264	0.0342
Stroke	2.140	1.121	4.084	0.0220
Psychiatric conditions	2.066	1.230	3.471	0.0070
Wealth (ref=lowest quartile)				0.0160
Mid-low quartile	0.501	0.285	0.880	
Mid-high quartile	0.438	0.250	0.769	
Highest quartile	0.399	0.174	0.914	
Goodness-of-Fit Test p= 0.8081, N= 1298 and 247 missing observations were deleted				

In model 8, adding polypharmacy status in 2008 to the model for the relationship between polypharmacy status in 2006 and IADL resulted in a significant effect for polypharmacy status in 2008 (p = 0.0199) while polypharmacy status in 2006 remained insignificant (p = 0.6029). Participants with polypharmacy in 2008 were 1.8 (95% CI = 1.105-3.046). times more likely to report IADL problems than participants without polypharmacy, adjusting for all other confounders, as seen in Table 4.28

Table 4.28: Final model 8 for longitudinal analysis of IADL at endline and controlling for midline functional-related variables and polypharmacy at both midline and endline

Midline predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2006	1.177	0.630	2.197	0.6029
Polypharmacy 2008	1.835	1.105	3.046	0.0199
Age (ref=65-74 years)	2.212	1.420	3.446	0.0007
Self-reported health status (ref=excellent)				0.0084
Very Good	1.279	0.422	3.874	
Good	1.063	0.331	3.416	
Fair	2.959	0.921	9.504	

Midline predictor variable	Adjusted OR	95% CI		p-value
Poor	3.248	1.056	9.990	
Light exercise (ref= everyday)				< 0.0001
> 1 per week	0.674	0.371	1.226	
1 per week	1.139	0.587	2.208	
1-3 per month	1.108	0.387	3.175	
Never	3.715	1.614	8.549	
Arthritis	1.877	1.043	3.379	0.0362
Stroke	2.091	1.114	3.924	0.0225
Psychiatric conditions	2.003	1.184	3.389	0.0106
Wealth (ref=lowest quartile)				0.0136
Mid-low quartile	0.486	0.277	0.853	
Mid-high quartile	0.436	0.247	0.771	
Highest quartile	0.383	0.167	0.877	
Goodness-of-Fit Test p= 0.6044, N= 1295 and 250 missing observations were deleted				

Sensitivity analysis (1)

In the following section, a sensitivity analysis was performed. The sensitivity analysis is a method used to determine how different values of the exposure change the impact on the outcome. Polypharmacy definition in this analysis was:

1) non-polypharmacy: using <5 prescribed medications
2) polypharmacy: using 5-9 prescribed medications
3) excessive polypharmacy: using 10 or more prescribed medications

At baseline, non-polypharmacy group had 986 (64.1%) participants, polypharmacy group had 470 (30.4%) participants, and excessive polypharmacy had 89 (5.5%) participants. At endline, non-polypharmacy group had 897 (59.1%) participants, polypharmacy group had 514 (32.6%) participants, and excessive polypharmacy had 130 (8.3%) participants. The sensitivity analysis was done to evaluate the relationship between polypharmacy status and functional status in

community-dwelling older adults after 4 years using different polypharmacy cut-offs. Similar approaches to previous analyses for building different models were conducted.

Table 4.29: Different models to evaluate the relationship between polypharmacy status and functional status after 4 years using different polypharmacy cut-offs

Model 9	ADL at endline = Baseline functional-related variables + polypharmacy and excessive polypharmacy at baseline
Model 10	ADL at endline = Baseline functional-related variables + polypharmacy and excessive polypharmacy at baseline + polypharmacy and excessive polypharmacy at endline
Model 11	IADL at endline = Baseline functional-related variables + polypharmacy and excessive polypharmacy at baseline
Model 12	IADL at endline = Baseline functional-related variables + polypharmacy and excessive polypharmacy at baseline + polypharmacy and excessive polypharmacy at endline

In model 9, polypharmacy at baseline was not a significant predictor of difficulties in ADL after 4 years as seen in model 1. Taking 5-9 prescribed medications at the beginning of the study did not predict ADL difficulties at the end of the study. Also, taking 10 or more prescribed medications at the beginning of the study did not predict ADL difficulties at the end of the study. The important variables in this model to assess developing ADL difficulties in 2008 were the same as model 1 except for obesity. Refer to Table 4.30.

Table 4.30: Final model 9 for longitudinal analysis of ADL at endline and controlling for baseline functional-related variables and polypharmacy and excessive polypharmacy at baseline

Baseline Predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2004 (ref= 0-4 Rx)				0.7136
Polypharmacy (5-9 Rx)	1.133	0.838	1.534	
Excessive Polypharmacy (≥10 Rx)	0.980	0.467	2.055	
Age (ref=65-74 years)	1.853	1.312	2.617	0.0007
Self-reported health (ref=excellent)				< 0.0001
Very Good	1.667	0.761	3.651	
Good	3.417	1.492	7.823	
Fair	9.161	3.961	21.185	
Poor	20.368	8.283	50.083	
Arthritis	2.241	1.427	3.521	0.0007
Psychiatric conditions	1.848	1.186	2.878	0.0076
Cognitive impairment	3.788	1.183	12.127	0.0257

Goodness-of-Fit Test p= 0.5127, N= 1543 and 3 missing observations were deleted, Rx=prescription medications

A similar observation was noted when adding polypharmacy and excessive polypharmacy in 2008 to model 10 (Table 4.31). This addition resulted in a significant effect for polypharmacy and excessive polypharmacy in 2008. Participants with polypharmacy in 2008 were 2.6 (95% CI = 1.663-3.909) times more likely to have ADL difficulties than participants without polypharmacy, adjusting for all other confounders. Participants with excessive polypharmacy at endline were 4.7 (95% CI = 2.704-8.096) times more likely to have ADL difficulties than participants without excessive polypharmacy, adjusting for all other confounders. Model 10 was similar to model 2.

Table 4.31: Final model 10 for longitudinal analysis of ADL at endline and controlling for baseline functional-related variables and polypharmacy and excessive polypharmacy at baseline and at endline

Baseline predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2004 (ref= 0-4 Rx)				0.7924
Polypharmacy (5-9 Rx)	1.101	0.787	1.539	
Excessive Polypharmacy (≥10 Rx)	1.174	0.517	2.662	
Polypharmacy 2008 (ref= 0-4 Rx)				< 0.0001
Polypharmacy (5-9 Rx)	2.550	1.663	3.909	
Excessive Polypharmacy (≥10 Rx)	4.679	2.704	8.096	
Age (ref=65-74 years)	1.547	1.024	2.339	0.0387
Self-reported health (ref=excellent)				< 0.0001
Very Good	1.930	0.714	5.219	
Good	3.573	1.336	9.558	
Fair	8.286	3.040	22.586	
Poor	13.690	4.266	43.932	
Arthritis	2.147	1.328	3.468	0.0024
Psychiatric conditions	2.247	1.444	3.496	0.0006
Cognitive impairment	3.452	1.174	10.146	0.0251

Goodness-of-Fit Test p= 0.7038, N= 1359 and 186 missing observations were deleted

In model 11 and 12, similar observations were also noted. Polypharmacy and excessive polypharmacy at baseline were not significant predictors for IADL difficulties with p=0.461 (Table 4.32). While when adding them at endline, they became significant as seen in Table 4.33. Participants with excessive polypharmacy at endline were 3.7 (95% CI = 2.401-6.608) times more likely to have IADL difficulties than participants without excessive polypharmacy, adjusting for all other confounders.

Table 4.32: Final model 11 for longitudinal analysis of IADL at endline and controlling for baseline functional-related variables and polypharmacy and excessive polypharmacy at baseline

Baseline predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2004 (ref= 0-4 Rx)				0.4160
Polypharmacy (5-9 Rx)	1.280	0.877	1.868	
Excessive Polypharmacy(≥10 Rx)	0.945	0.430	2.077	
Age (ref=65-74 years)	2.710	1.871	3.926	< 0.0001
Self-reported health (ref=excellent)				< 0.0001
Very Good	1.162	0.457	2.954	
Good	1.284	0.458	3.600	
Fair	3.043	1.215	7.620	
Poor	6.043	2.435	14.999	
Arthritis	1.667	1.099	2.527	0.0171
Stroke	2.312	1.383	3.866	0.0019
Depression	1.694	1.039	2.762	0.0351
Alcohol drinking	0.547	0.391	0.766	0.0007
Goodness-of-Fit Test p=0.6563, N= 1543 and 2 missing observations were deleted				

Table 4.33: Final model 12 for longitudinal analysis of IADL at endline and controlling for baseline functional-related variables and polypharmacy and excessive polypharmacy at baseline and at endline

Baseline predictor variable	Adjusted OR	95% CI		p-value
Polypharmacy 2004 (ref= 0-4 Rx)				0.2021
Polypharmacy (5-9 Rx)	1.400	0.959	2.042	
Excessive Polypharmacy(≥10 Rx)	1.267	0.621	2.584	
Polypharmacy 2008 (ref= 0-4 Rx)				< 0.0001
Polypharmacy (5-9 Rx)	2.123	1.458	3.091	
Excessive Polypharmacy(≥10 Rx)	3.673	2.041	6.608	
Age (ref=65-74 years)	2.448	1.679	3.570	< 0.0001
Self-reported health (ref=excellent)				< 0.0001
Very Good	1.484	0.466	4.724	
Good	1.440	0.431	4.816	
Fair	3.187	1.096	9.268	
Poor	6.659	2.192	20.226	

Baseline predictor variable	Adjusted OR	95% CI		p-value
Arthritis	1.606	1.037	2.489	0.0344
Stroke	1.945	1.072	3.528	0.0293
Alcohol drinking	0.534	0.357	0.799	0.0029
Goodness-of-Fit Test p= 0.5119, N= 1360 and 185 missing observations were deleted				

Sensitivity Analysis (2)

In this analysis, the continuous form of ADL and IADL score were used. Also, number of medications was used as a continuous measure. Collinearity check was done for all continuous variables. Multiple linear regression model was used in this analysis. The first regression model will adjust for the baseline (2004) functional-related variables and number of medications at baseline. The second model will be the same with the addition of number of medication at the endline (2008). Each of the two models was done to each of the continuous ADL and IADL scores at endline.

The weighted mean for ADL at baseline was 0.186 ± 0.637, and at endline 0.294 ± 0.875. The weighted mean for IADL at baseline was 0.129 ± 0.475, and at endline 0.249 ± 0.793. Higher score indicates greater disabilities. The weighted mean for number of prescription medications at baseline was 3.979 ± 3.256, and at endline 4.340 ± 3.572.

Table 4.34: Final model 13 for linear regression model of ADL at endline and controlling for baseline functional-related variables and number of medications at baseline

Baseline predictor variable	Estimate	Standard Error	p-value
Age			
65-74 years	Ref.	Ref.	
75+ years	0.2553	0.0483	<0.0001
Number of medications (2004)	0.0033	0.0063	0.6041
Light exercise			0.0023
Everyday	Ref.	Ref.	
> 1 per week	0.1469	0.0848	0.0831
1 per week	0.1122	0.0899	0.2118
1-3 per month	0.1221	0.1187	0.3036
Never	0.4210	0.1120	0.0002
Self-reported health			<0.0001
Excellent	Ref.	Ref.	
Very Good	-0.0155	0.0729	0.8317
Good	0.0773	0.0729	0.2885
Fair	0.3362	0.0816	<0.0001
Poor	1.1755	0.1145	<0.0001
Obese	0.1390	0.0482	0.0039
Depress	0.1416	0.0678	0.0367
Arthritis	0.1300	0.0434	0.0027
Goodness-of-Fit Test p= 0.6361			

Number of medications at baseline was not significant (p=0.6041) in final regression model for ADL as an outcome (Table 4.34). Baseline characteristic: age, SRH, light exercise, obesity, depression, and arthritis were all significant predictor for ADL difficulties at endline. Adding the number of medications at endline resulted in significant outcomes, for each unit increases in number of medications at endline the ADL score increases by 0.0432. (Table 4.35)

Table 4.35: Final model 14 for linear regression model of ADL at endline and controlling for baseline functional-related variables and number of medications at baseline and endline

Baseline predictor variable	Estimate	Standard Error	p-value
Age			
65-74 years	Ref.	Ref.	
75+ years	0.2549	0.0475	<0.0001
Number of medications (2004)	0.0038	0.0062	0.5386
Number of medications (2008)	0.0432	0.0060	<0.0001
Light exercise			0.0088
Everyday	Ref.	Ref.	
> 1 per week	0.1356	0.0834	0.1040
1 per week	0.1039	0.0884	0.2402
1-3 per month	0.0954	0.1168	0.4141
Never	0.3746	0.1104	0.0007
Self-reported health			<0.0001
Excellent	Ref.	Ref.	
Very Good	-0.0451	0.0718	0.5299
Good	0.0113	0.0722	0.8755
Fair	0.2300	0.0816	0.0048
Poor	1.0320	0.1143	<0.0001
Obese	0.0926	0.0479	0.0530
Depress	0.1272	0.0667	0.0565
Arthritis	0.1030	0.0428	0.0162
Goodness-of-Fit Test p= 0.6155			

Table 4.36: Final model 15 for linear regression model of IADL at endline and controlling for baseline functional-related variables and number of medications at baseline

Baseline predictor variable	Estimate	Standard Error	p-value
Age			
65-74 years	Ref.	Ref.	
75+ years	0.3064	0.0439	<0.0001
Number of medications (2004)	0.0077	0.0058	0.1830
Self-reported health			<0.0001
Excellent	Ref.	Ref.	
Very Good	-0.0048	0.0670	0.9426
Good	0.0126	0.0669	0.8511
Fair	0.1910	0.0741	0.0099
Poor	0.7495	0.1021	<0.0001
Arthritis	0.0967	0.0398	0.0152
Cognitive impairment	0.7074	0.1641	<0.0001
Stroke	0.3182	0.0777	<0.0001
Alcohol drinking	0.1026	0.0389	0.0083
Goodness-of-Fit Test p= 0.5465			

Table 4.37: Final model 16 for linear regression model of IADL at endline and controlling for baseline functional-related variables and number of medications at baseline and endline

Baseline predictor variable	Estimate	Standard Error	p-value
Age			
65-74 years	Ref.	Ref.	
75+ years	0.3127	0.0435	<0.0001
Number of medications (2004)	0.0078	0.0058	0.1742
Number of medications (2008)	0.0313	0.0056	<0.0001
Self-reported health			<0.0001
Excellent	Ref.	Ref.	
Very Good	-0.0251	0.0664	0.7058
Good	-0.0368	0.0668	0.5817
Fair	0.1119	0.0747	0.1339
Poor	0.6418	0.1030	<0.0001
Arthritis	0.0741	0.0396	0.0616

Baseline predictor variable	Estimate	Standard Error	p-value
Cognitive impairment	0.7320	0.1626	<0.0001
Stroke	0.2553	0.0778	0.0010
Alcohol drinking	0.0955	0.0385	0.0132
Goodness-of-Fit Test p= 0.5359			

In the final regression model, the number of medications at baseline was not significant (p=0.1830) for IADL as an outcome (Table 4.36). Baseline characteristic: age, SRH, arthritis, cognitive impermanent, stroke, and alcohol drinking were all significant predictor for IADL difficulties at endline. Adding the number of medications at endline resulted in significant outcomes, for each unit increases in number of medications at endline the IADL score increases by 0.0313. (Table 4.37).

The sensitivity analyses showed similar results to logistic models done in the previous section. Polypharmacy or number of medications were important predictors in all models looking at the relationship over time and which had polypharmacy at the endline. Categorizing the number of medications was more clinically applicable. Also, categorizing ADL and IADL were easier to interpret the result for clinical sittings. However, continuous measures gives more information, and it is more sensitive to changes. It needs a smaller sample size and it give variety of analysis options.

Aim 4: To identify potential confounders of the relationship between polypharmacy and functional status

Aim 4-A): To assess the role of chronic conditions in the relationship between polypharmacy and functional status

Each of the chronic conditions and the number of chronic conditions was examined in both cross-sectional and longitudinal models and were adjusted. The number of chronic conditions was significant in bivariate analyses. However, it was not significant in the multivariable models. Regarding each chronic condition, some of them, like arthritis and psychiatric conditions, were significant in most of the multivariable models. Other chronic conditions, like cancer, were not significant. In conclusion, some chronic conditions were considered important confounders to the relationship between functional status and polypharmacy.

Aim 4-B) To identify potential confounders or modifiers of the relationship between polypharmacy and functional status

All of the previous analyses in Aims 2 and 3 were performed to identify potential confounders and/or modifiers. Multiple interaction terms were included to identify effect modifiers. Those interactions included interactions between: self-reported health and polypharmacy, self-reported health and each chronic condition, and each chronic condition and polypharmacy. However, none of the interactions were significant. All of the significant study variables are confounders, and they change the relationship between polypharmacy and functional status in community-dwelling older adults.

Correlation between ADL and IADL

The Pearson Correlation Coefficients was 0.569 at baseline and 0.653 at endline. This means there is moderate correlation between ADL and IADL and it may measure similar thing but not exactly the same. It is known that ADL focus more on the physical activities of daily living and IADL focus in more complex aspects of instrumental activities of daily living. This explains the moderate correlation we see between ADL and IADL. We need both to get a better understanding of functional decline.

Chapter 5 Discussion

5.1 Descriptive data discussion

This study showed that polypharmacy was significantly associated with functional decline in cross-sectional and longitudinal analyses. A stronger association was found at the end of the study. Our results are similar to others studies that examined the association between functional status and polypharmacy (Jay Magaziner et al. 1989; Jyrkkä et al. 2011b; Lau et al. 2011). Other confounders were also important such as self-related health, age, and arthritis in the longitudinal analyses. In all cross-sectional analyses self-reported health and light exercise were also associated with functional status. The baseline demographics reported in this study are similar to those reported in other studies using the same HRS and PDS files (Zivin et al. 2009; An and Lu 2015). In Table 4.1, we can recognize that 16.2% of participants reported ADL difficulties and 13.8% of participants reported IADL difficulties in 2008. Both percentages increased 4.7% from 2004 to 2008. ADL difficulties were slightly more common than IADL difficulties. A similar trend was observed in a study using the same HRS dataset waves, and showed that ADL difficulties were reported slightly higher than IADL difficulties (An & Lu 2015). Overall, the proportion of the population reporting functional limitations was low in our study population compared to other studies like the National Health and Aging Trends Study which reported that 48.3% of participants experienced difficulty and received help from another person with ADL (Freedman & Spillman 2014). Under-reporting of functional limitations is common in community-dwelling older adults until it is no longer tolerable, , and it may be

attributable to the threat of loss of independence (Guccione et al. 1994; Fried and Guralnik 1997). Other explanations for under-reporting are participants may limit the frequency of doing a duty to the minimum essential effort, or sometimes increase the frequency of a task but do less work at any one time. Also, they could change the way they do the task to minimize the effort, for example, lean on the shopping cart and report no difficulties (Fried and Guralnik 1997; Saliba et al. 2000). Our study population was also relatively healthy, as most of them reported very good to good health status. It is interesting to mention that older adults often interpret self-reported health (SRH) in general as their health compared to other people of similar age, which means that they might have some health issues but considering their age they think they are healthy (Chen et al. 2016). Also, a non-polypharmacy group is three times more likely to report good SRH than a polypharmacy group (Agbor et al. 2013). In our study, we have more non-polypharmacy than polypharmacy participants compared to this study.

The prevalence of polypharmacy was similar to what was reported in the literature. It was reported in previous studies that the prevalence of older adults taking more than five medications is 36% to 39% (Charlesworth et al. 2015; Levy 2017). In our study, 35.9% reported polypharmacy status, and it increased to 40.7%. One potential reason for this increase in our study population was that Medicare Part D for prescription drug coverage had been implemented. Atorvastatin was the most common medication used in the study. It is also the most commonly used statin worldwide (Patel et al. 2013). Statins are prescribed to prevent cardiovascular diseases and lowering cholesterol levels. Statins side effects can include muscle weakness and fatigue. A randomized control study showed a relation between statin usage and fatigue which could lead to functional decline (Golomb et al. 2012). In our study, we only tested one medication from the statins class, which was Atorvastatin, as a confounder, but the results

were not significant. One study in Australia reported a low statin–drug interactions and that statins do not interact with many other medications which could explain the non-significant results we had in our results (Thai et al. 2015). However, we cannot rule out that there is no association between all statins as a class of drug and functional decline and further studies to look at the relation between statins and functional status is recomended. The HRS does not have enough information about drug classes and each participant was asked to write a list of all the medications prescribed, including those taken occasionally. And if they were more than ten medications, then participants choose what he/she consider the most important. So, we cannot tell if the participants were taking statins or not. Another explanation might be that the relationship between polypharmacy and functional status is not simply due to the use of drugs like statins whose side effects (muscle weakness, fatigue) in older adults but due to using a large number of medications together.

About 70% of participants used drug chain stores, mail orders pharmacies, and independent pharmacies as the source of getting their prescribed medications. One study reported that drug chains and independent pharmacies accounted for 40% and 35% of all pharmacies in the US (75% in total), which is consistent with the most common source identified in this study. Different types of insurances were also used, and 55% of participants paid some of the costs of their prescribed medications and the insurance paid the rest. Having governmental insurance or prescription drug coverage were not significant as variables affecting the relationship between polypharmacy and functional outcomes in all the bivariate analysis and longitudinal models.

Our study showed we had 13 non-responses in the endline, which were deleted from the study. All the non-responses were code 4, meaning that the participants were alive as far as we know but did not respond. It is important to look at non-responders, especially if they were

deceased because the results might then be attenuated. Since our non-responders were alive and their sample size is very low, then deleting them should not affect our results significantly.

5.2 Functional status and polypharmacy in cross-sectional analyses

Looking at the cross-sectional models, we can conclude that polypharmacy was an important predictor for ADL in both bivariate and multivariable analyses. After controlling for confounders, the odd ratio between polypharmacy and ADL increased from 2004 to 2008, $OR_{2004} = 1.4$ ($p = 0.0256$) and $OR_{2008} = 1.9$ ($p = 0.0044$). After 4 years, participants with polypharmacy were almost 90% more likely to report ADL difficulties than non-polypharmacy participants, compared to the beginning of the study where the participants with polypharmacy were 40% more likely to report ADL difficulties than non-polypharmacy participants. For IADL, both the adjusted and unadjusted analyses at the baseline did not show an association between IADL and polypharmacy status (adjusted $OR_{2004} = 1.2$; $p = 0.5080$). However, in 2008 the association became significant ($p = 0.0216$), and the OR increased to $OR_{2008} = 1.7$. Similar results for IADL decline after 3 years were also described in Jyrkka et al (Jyrkkä et al. 2011b). The change in the association from not significant to significant and the rise in the OR might be due to Medicare Part D implementation and the availability of prescription drug coverage. In 2006, Medicare Part D was implemented and provided prescription drug coverage for older adults through private health plans. This coverage could lead to increased polypharmacy status leading to a decline in IADL. One study reported similar results demonstrating a stronger association between ADL decline and polypharmacy and significant but a weaker association between IADL and polypharmacy (Jay Magaziner et al. 1989). Marital status could be another explanation, as we noticed 7.6% of married people in 2004 became widowed by 2008. IADL

include food preparation, shopping, medication administration, using the telephone, and managing money. Those listed items in IADL could be performed with the help of a caregiver. However, the number of people living in the same house, and marital status were not a significant predictor for functional decline in the adjusted analyses. Our results are similar to the cross-sectional study discussed in the literature review chapter. Connolly et al. reported a stronger relationship between ADL and polypharmacy than IADL and polypharmacy (Connolly et al. 2017).

5.3 Confounders in cross-sectional analyses

The confounder is a variable that influences both the outcome (functional status) and the exposure (polypharmacy) causing a false association. In order to be a confounder, it needs to be a risk factor for both exposure and outcome and not to be in the causal pathway. We can identify potential confounders from previous knowledge, common sense, or meeting the three criteria listed above.

In the adjusted cross-sectional analyses, self-reported health (SRH) and light exercise were the two variables that were present in all cross-sectional models for both outcomes ADL and IADL. Self-reported health was also recognized in the literature to be a significant predictor of negative outcomes including functional decline and mortality (Fonta et al. 2017; Cesari et al. 2008). The poorer the SRH, the more medications are prescribed. Therefore, it influences both number of medications and functional decline. Regular exercise, ranging from light to vigorous, has been shown to decrease the risk of mortality and negative health outcomes including disability (Fonta et al. 2017). Interaction terms between SRH and polypharmacy and other chronic conditions were conducted, and none were significant. For exercise, it is well established that a sedentary lifestyle can increase the risk of heart disease, stroke, and functional limitations.

Increasing the number of comorbid conditions will also increase the number of prescribed medications and thus polypharmacy status. It is important to mention that exercise can reverse some of the health consequences when individuals start to exercise regularly (Rosenkranz et al. 2013).

Also, in the ADL and IADL cross-sectional analyses we can realize that psychiatric conditions were included in the final model in 2004; however, the p-value was < 0.10 and higher than our significance level of 0.05. The psychiatric conditions in 2004 for ADL and IADL had a $p = 0.0891$ and $p = 0.0629$ respectively. While in 2008, the psychiatric disorders for ADL and IADL had a $p = 0.0056$ and $p = 0.0017$ respectively. The psychiatric condition is a mental illness diagnosed by a mental health professional, and it affects mood, behavior, and thinking abilities. It can cause great harm to the person's life leading to disability and death. Since functional status needs both physical and mental ability, the presence of psychiatric problems could disturb a person's ADL and IADL. It has been shown that there is a relationship between psychiatric disorders and decline in both ADL and IADL (Kivelá & Pahkala, 2001; Mograbi et al. 2017). Likewise, persons with psychiatric conditions tend to have more prescribed medications than those who have not been diagnosed with a psychiatric condition (Lau et al. 2011). Since depression is often a part of psychiatric disorder, an interaction term between psychiatric conditions and depression was evaluated, and it was not significant.

We observed that the final models for ADL in 2004 and 2008 were similar and had similar predictors. In addition to polypharmacy, SRH, and light exercise (and psychiatric conditions in 2008), we noticed that obesity and depression were present in all cross-sectional analyses with ADL difficulties as an outcome. There are many longitudinal and cross-sectional studies that reported the association between ADL disabilities and obesity, and a limited number

of studies reported the association between IADL disabilities and obesity (Okamoto et al. 2018; Cesari et al. 2008; Himes 2000). A study that used HRS as the data source also showed that obesity, defined as BMI ≥ 30 kg/m^2, was associated with ADL decline (Sturm et al. 2004). Obesity prevalence in older adults is increasing, and is linked to many factors including sedentary lifestyle, change in metabolic rate, and change in diet (Arteburn 2004). Obesity is linked to many comorbid conditions including heart disease and cancers. It has been hypothesized that obesity and big body size could be linked to a decline in functional status by limiting mobility. The excess weight can also affect joint flexibility, decrease muscle strength, and reduce the capacity to exercise. Another study hypothesized that obesity would increase the risk of chronic conditions and thus it will increase both the number of prescribed medications and functional decline (Gibbs et al 2005). For depression, it has been reported that there is an association between depression and functional decline, but it is not clear whether the depression leads to functional decline, or if the functional decline leads to depression (Zivin et al. 2009; Mograbi et al. 2017; Kivelá and Pahkala 2001). Depression also increases the number of prescribed medications. The long term use of antidepressant medications is also associated with functional decline (An & Lu 2016).

In the final model for IADL at 2004 and 2008, wealth was an important confounder. It is well documented that low socioeconomic status is associated with poor health, disability, and premature mortality (Torres et al. 2016). Higher economic status allows individuals to have better access to healthcare facilities and medications. Moreover, individuals with a higher economic status are more likely to have good social support, spouses, and more friends. Torres et al. showed a negative relationship between wealth and difficulties in ADL and IADL.

Some additional confounders were found in the IADL or ADL final model. Arthritis was an important risk factor in the final model of ADL difficulties in 2008. Arthritis was also in the final model of ADL difficulties in 2004; however, it was not significant ($p = 0.0598$). Patients with arthritis are more likely to have functional disabilities (Marques et al. 2016). Arthritis is also associated with polypharmacy in long-term care facilities (Jokanovic et al. 2015). Gender was also included in our final model for IADL in 2008. Many studies have identified that females are more likely to have polypharmacy and are at higher risk of polypharmacy consequences since body fat increases as a part of aging in females to a greater extent than males (Jay Magaziner et al. 1989). Also, females are more likely to take prescribed medications. They are also more likely to report poor SRH and disability (Fonta et al. 2017).

Alcohol drinking also appeared in the final cross-sectional model for IADL in 2004. Those who drink alcohol were 70 % as likely to report IADL difficulties than nondrinkers. Similar results were also found in a systematic review. Many studies in the review found that nondrinkers are at higher risk for functional difficulties compared to moderate drinkers (Stuck et al. 1999). In addition, individuals with poor health might stop drinking, and that might explain these results. Heavy drinkers, on the other hand, are at greater risk of functional decline and drinking increases the risk of drug interactions. Alcohol concentration is higher in older adults for the same amount consumed in younger adults because of the change of body composition with more body fat and less body water (Delafuente 2008). Additionally, heart conditions appeared in the final cross-sectional model for IADL in 2004, and they are a well-known risk factor for polypharmacy. Patients with angina and myocardial infarction will be automatically on at least 5 prescribed medications according to practice guidelines (Schwinger 2018; Jokanovic et

al. 2015). Heart conditions are also a risk factor for functional decline as reported in Stuck et al. 1999.

5.4 Functional status and polypharmacy in longitudinal analyses

In the adjusted models looking at the four-years (2004-2008) relationship between polypharmacy and our main outcomes ADL and IADL, we noted that polypharmacy status at baseline (2004) was not an important predictor for functional decline (model 1 and 3); however, adding polypharmacy status for the endline (2008) was an important predictor (model 2 and 4). The odds for reporting ADL and IADL decline in 2008 were 2.4 (95% CI = 1.666-3.570) and 2.1 (95% CI = 1.460-2.872) times more likely in participants with a 2008 polypharmacy status.

Looking at the two-year (2006-2008) relationship between polypharmacy and functional status, we recognized that polypharmacy status before 2 years was important (ADL p = 0.0138, IADL p = 0.0636 [borderline significance]) (model 5 and 7). When adding polypharmacy status for the endline (2008) to model 6 and 8, polypharmacy status at 2006 was no longer significant (ADL p = 0.5731, IADL p = 0.6029). This means that polypharmacy status of the same period was more important than two years prior. This result is similar to that observed in another study that concluded that polypharmacy cannot predict functionality over a three-years period (Jyrkkä et al. 2011b). Polypharmacy of the same year was significant in almost all cross-sectional models with one exception (discussed above), and in all longitudinal models which had polypharmacy at the endline as a predictor. As a result, we can conclude that polypharmacy is an important predictor of functional decline and it might not have the long-term relationship (4 years) but rather two years or less. It interrupts participant's functional status around the same period rather than contributing to future decline. This might be due to the acute effects of drug-drug interactions, or PIMs. Patient could have been in poor health or experienced a health event that

led to an increase in prescribed medications and eventually functional decline. Also, the low number of prescribed medications used by most participants in HRS (participants with polypharmacy were fewer than participants with no polypharmacy) could contribute to the lack observation of a long-term relationship. We also had a low percentage of participants who reported functional decline and our population were mostly healthy, which could also contribute to not seeing a long-term relationship. Previous studies that showed long-term relationships had more participants with polypharmacy than in our study and they included OTC medications to determine polypharmacy status. Our study did not include OTC medications, which is an important factor for the number of medications, especially if they are being taken regularly. Not including OTCs is one of our study limitations. Also, the populations of previous studies had more health conditions with more participants reporting poor SRH. In addition, we did not exclude participants with functional decline at the baseline, this gave us different starting points for our participants and might influence the results.

In the observed association between polypharmacy and functional decline after 2 and 4 years the number of medication itself may not be the cause, but rather it is a contributing cause where the benefits may outweigh the risks for some patients and vice versa. Functional decline also occurs in the absence of polypharmacy. This suggests that polypharmacy may be a good predictor or indicator for early detection of functional decline.

5.5 Confounders in longitudinal analyses

Age, SRH, and arthritis were confounders in all the adjusted longitudinal analyses for both outcomes ADL and IADL. Age is a well-known risk factor for both functional decline and polypharmacy. 19.4% of our participants had a shift in age categories from 65-74 years to 75+ years during the 4 years (Table 4.1). Aging is associated with physiological changes that include

decreased hepatic and renal function, changes in body composition, decline in baseline performance and decreased homeostatic reserve. These physiological changes can cause changes in drug pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (receptor and drug action on the body) often resulting in increased drug exposure and exaggerated drug (Bushardt et al. 2008; Jokanovic et al. 2015). SRH is the only confounder that was present in all models (cross-sectional and longitudinal). This supports the idea that functional status reflects the health status and independency of people. SRH seems to be a very important predictor, and this means that we should pay attention to participants reporting fair or poor health and having polypharmacy because they are at higher risk of reporting functional decline. In this case, we can see polypharmacy as a risk factor, and managing prescribed medications for patients who report fair to poor health as mandatory. On the other hand, for patients reporting excellent and good health status, polypharmacy might be appropriate with no need for modification. Multiple medications do not always have to be problematic (Levy 2017). Some older adults are on multiple medications, and they are healthy, while others would be in better health if their medications were fewer. Regardless, it is important to ensure that for all medications the benefits outweigh the risks for the individual patient.

Regarding the longitudinal models with ADL as the main outcome, obesity and psychiatric conditions were the additional confounders that presented in all longitudinal models, whereas the IADL model had stroke as a confounder. Stroke affects the neuromuscular system and could affect the functional status depending on the prognosis and severity. Stroke was found in the Framingham study to be the most strongly associated with grocery shopping dependence (Guccione et al. 1994). Shopping is one of the items in IADL, and so this could be the explanation of the IADL decline associated with stroke observed in our study. Lastly, cognitive

impairment was a confounder for the association between ADL and polypharmacy in Models 1 and 2 (4 years association). In our study, cognitive impairment was associated with ADL decline. Cognitive impairment has been shown to be related to polypharmacy (Silay et al. 2017). Also, functional decline is associated with cognitive impairment (Ho et al. 2018).

Since functional decline is reversible in some cases and polypharmacy could be adjusted and monitored to give better outcomes, then we should pay attention to the modifiable risk factors we found in our study (alcohol use, exercise, BMI) along with a prescribed medication checkup. Monitoring risks factors for functional decline could change patient status from dependent to independent or at least slow the progression of functional decline.

5.6 Strength and limitation

Using a nationally representative dataset not previously evaluated was a strength to our study. Another strength was controlling for some chronic conditions and the number of chronic conditions. Both cross-sectional and longitudinal analyses were conducted in our study to better understand the relationship. Looking at multiple time points and providing a sensitivity analysis which looked at excessive polypharmacy strengthened our study.

One major limitation of this study is the use of self-reported data. The accuracy of self-reported information is dependent on a variety of factors including participants' understanding of the questions, willingness to be honest with the interviewer about potentially embarrassing topics, bias towards providing socially-desirable responses, and mood and mental status at the time of interview. Despite controlling for many confounders in our observational study, we cannot eliminate the confounding bias due to non-randomized design of our observational study, and thus our result is association rather than causation.

Another limitation is the inclusion of only those participants with complete functional and medication data at both baseline and endline, which limited our study population. Other limitations of this study include a lack of data on health conditions other than the eight chronic diseases included in the HRS, the severity of the chronic conditions mentioned in the "Measures" section and a lack of information about over-the-counter medication use. It is also not possible to examine the use of potentially inappropriate medication because this would require an individual assessment of each participant's prescription list and health history. The generalizability of this study is limited to community-dwelling adults in the United States, and findings may not apply to institutionalized adults or adults in other countries.

Finally, an important limitation is the time when the data was collected, more than 10 years ago. Prevalence of polypharmacy, access to healthcare and other factors may have changed during the past ten years. This dataset remains a valuable resource to assess the relationships between polypharmacy and functional status however.

5.7 Conclusion

Polypharmacy is a good predictor or indicator for early detection of functional decline. Polypharmacy status of the same year showed a significant association with functional decline in cross-sectional, and in all longitudinal models which had polypharmacy at the endline as a predictor. Many confounders were found to be significant. SRH and light exercise were associated with functional decline in all cross-sectional analyses. SRH, age and arthritis were important confounders for the longitudinal analyses.

5.8 Future directions

Since both polypharmacy and functional decline are modifiable and preventable, then it would appropriate to conduct additional observational studies (prospective cohort) and look for possible reasons behind the observed association, confirm the observed association, and try to overcome the limitations in the studies to date. Future studies should enroll participants with no functional decline at the beginning of the study, follow them over time, gather information regarding prescribed and OTC medications taken regularly, and record detailed information regarding dosage, frequency, indication of prescriptions, side effects, and any special instruction. The medications should be checked by pharmacists for PIM including medications on the Beer's list, drug-drug interactions, drug-disease interactions, duplications, inappropriate dosing, and unnecessary medication (no indication for usage). Also, access to participants' medical records to check for an appropriate indication of the medications would be valuable. The severity of participants' chronic illness should be accounted for as well.

Our study would help health care providers and policy makers target at risk populations for interventions and help older adults maintain independence. Future studies examining specific medication classes and their relationship to functional decline could help in designing interventions. Also, implementing an intervention study for de-prescribing, or intensive medication review to evaluate functional status as an outcome would help to better understand this relationship.

Our study may also have implications for the annual Medicare Wellness Visit that is part of Medicare Part B. During the first Medicare Annual Wellness Visit (AWV) (medicareinteractive.org), the following should be assessed:

1) Height, weight, blood pressure, and other routine measures.

2) Health risk assessments about health status, injury risks, behavioral risks, and urgent health needs.
3) Functional ability of ADL and level of safety (includes risk of falling, and level of safety)
4) Medical and family history
5) Current prescription medications, as well as vitamins and supplements, and durable medical equipment (DME) suppliers.
6) Cognitive impairment, including diseases such as Alzheimer's and other forms of dementia
7) Depression

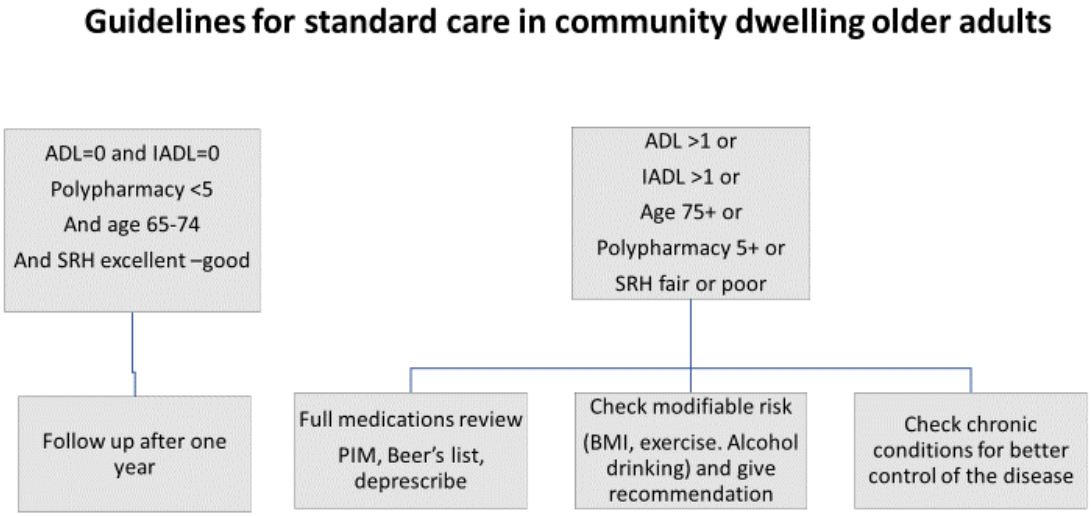
Based on this assessment, the provider should create a written 5-10 year screening schedule or check-list as well as provide appropriate health advice and referrals to health education and/or preventive counseling services aimed at reducing identified risk factors and promoting wellness which includes: weight loss, physical activity, smoking cessation, fall prevention, nutrition, and more.

The following visit will be conducted according to patients' needs and written plan. The annual visit is very good opportunity to address issues around polypharmacy and functional status in older adults. Based on our study, considering polypharmacy, functional status, and other confounders I propose the following approach to incorporate our findings into patient care (Figure 5.1):

1) If the patient is between 65 and 74 years of age, has no difficulty in both ADL and IADL, no polypharmacy, or SRH is excellent-good, then there is no need for intervention, and follow up can occur after one year.
2) If the patient is 75 years or older, has difficulty in ADL, has difficulty in IADL, has polypharmacy, or SRH is fair-poor, then full medication review is recommended, along with assessing for modifiable risk factors and controlling chronic conditions, and individualize an appropriate intervention to reduce risk.

This could be incorporated into the annual visit by identifying participants who need immediate attention, and others who can be seen in the following year. Also, once identifying the risk group, a full medication review is recommended to identify PIMs, medications to avoid in Beer's list and drug-interactions. Moreover, a full medical history and lab work for chronic conditions should be performed to guide better management of chronic disease.

Figure 5.1 Guidelines for standard care in community-dwelling older adults



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Appendix

Table A: Medications drug survey data variables (2005 and 2007 PDS, and 2009 HWB) and SAS code

Variable/ Name before merge	Name after merge	Notes	Dataset PDS05
Merge variables	HHID, PN, POSITION		HHID and PN all sections, position section E
Number of medications	Pds05_medsintable	Number scripts in table provided in the questionnaire	Not in data, built during merge from section E. MAX(position)
Name of medications	Pds05_P1DRUGNAME1	Drug name from 1 to 10	Not in data, built during merge from section E
Medication brand name	Pds05_1BRANDNAME	Brand name from1-10	Not in data, built during merge from section E
Medication: How long taking /P1E2	Ppds05_duration	Duration of use for each drug from 1to 10	Section E
# Prescribed medications in last month/P1A3	Pds05_P1A3		Section A
# Prescribed medications regularly /P1A4	Pd05_P1A4/ Polybase	Categorized into Polypharmacy baseline <5 prescribed medications, ≥5 prescribed medications	Section A
What type of pharmacy	Pds05_P1A7A	From A-J	Section A
Prescription drug coverage P1B1	Pds05_P1B1	1.I pay some of the price and insurance 2. I get a small discount 3. I pay full price for all medications 4. I don't pay anything. 5. Other	Section A

Source of prescription insurance (yes/no by category)/P1b8a-g	Pds05_p1b8	Pds05_p1b8a -g	Section A
Any side effects	Pds05_P1C2	SKIP=0	Section A
Action in response to side effects (yes/no by category)	Pds05_P1C3A-F		Section A
Questionnaire by proxy/P1H1	Pds05_P1H1		Section A
Sample weights and completion status	P1QX, P1MED, P1QXWT, P1QXMED		Section S
Merge variables for PDS07	HHID, PN, POSITION, POSITION_F		All sections (position only in section E and F) *
# Prescribed medications regularly/ P2A4	Pds07_P2A4/polymed	Categorized into Polypharmacy middle <5 prescribed medications, ≥5 prescribed medications	Section A*
Prescription drug coverage /P2B1	Pds07_ P2B1	1.I pay some of the price and insurance 2. I get a small discount 3. I pay full price for all medications 4. I don't pay anything. 5. Other	Section A*
Merge variables	HHID, PN		All sections (A and S) **
# Prescribed medications regularly /P3A4	Hwb09_P3A4/polyend	Categorized into Polypharmacy end line <5 prescribed medications, ≥5 prescribed medications	Section A**
Prescription Drug coverage/P3A1B	hwb09_P3A1B	Yes, no	Section A**

* PDS07 dataset ** HWB09 dataset

Table B: Functional status variables and SAS codes

Variable	Name	Name after merge and coding	Notes	Dataset
ADL			Summary score were recoded into (yes, no) for having functional limitations and adlbase/adlmed/ adlend	
Summary score	RwADLA	R7ADLA/R8ADLA/R9ADLA		
Bathing	RwBATHA	R7BATHA/R8BATHA/R9BATHA		RAND
Dressing	RwDRESSA	R7DRESSA/R8DRESSA/R9DRESSA		RAND
Eating	RwEATA	R7ETA/R78EATA/R9EATA		RAND
Getting in or out of bed	RwBEDA	R7BEDA/R8BEDA/R9BEDA		RAND
Walking	RwWALKRA	R7WALKRA/R8WALKRA/R9WALKRA		RAND
IADL			Summary score were recoded into (yes, no) for having functional limitations and Iadlbase/ Iadlmed/ Iadlend	
Summary score	RwIADLA	R7IADLA/R8IADLA/R9IADLA		RAND
Phone	RwPHONEA	R7PHONEA/R8PHONEA/R9PHONEA		RAND
Money	RwMONEYA	R7MONEYA/R8MONEYA/R9MONEYA		RAND
Medication Administration	RwMEDSA	R7MEDSA/R8MEDSA/R9MEDSA		RAND
Shopping	RwSHOPA	R7SHOPA/R8SHOPA/R9SHOPA		RAND
Meals	RwMEAL	R7MEAL/R8MEAL/R9MEAL		RAND

Table C: HRS study variables and SAS code

Variable	Name	2004/2006/2008		Dataset
Age	RwAGEY_B	Age /age2_/age3_	Converted into categorical (65-74Y, 75+Y)	RAND
Sex (male, female)	RAGENDER	RAGENDER		RAND
Race (white, black, other)	RARACEM	Race	Non-Hispanic white Non-Hispanic black Others Hispanics	RAND
Hispanic (yes, no)	RAHISPAN	Race		RAND
Education (years)	RAEDYRS	Edu		RAND
Household income	HwITOT	Wealth/wealth2_/wealth3_	Converted into categorical by quartiles	RAND
Number of people in house including respondent and spouse	HwHHRES	People/people2_/people3_	Converted into (alone, 2 persons, more than 2)	RAND
Self -reported Health status (poor, good, excellent)	RwSHLT	R7SHLT/R8SHLT/R9SHLT		RAND
Marital status (Married, divorced, widowed, never)	RwMSTAT	Mstat/mstat2_/mstat3_	I had to make a new recategorize for mstat4_ because never had 0 participants	RAND
# household residents, including respondent and spouse	HwHHRES			RAND
Insurance status				
Government	RwHIGOV	R7HIGOV/R8HIGOV/R9HIGOV		RAND
Employer	RwCOVR	R7COVR/R7COVR/R8COVR		RAND
Spouse's employer	RwCOVS	R7COVS/R8COVS/R9COVS		RAND
Other	RwHIOTHP	R7HIOTHP/R8HIOTHP/R9HIOTHP		RAND
# Health ins plans	RwHENUM	R7HENUM/R8HENUM/R9HENUM		RAND

Depression (yes, no)	RwCESD	Depress/depress2_/depress3_	Recoded to no if score ≤3 or yes if >4	RAND
Cognitive impairment (yes, no)	RwCOGTOT	Cog/cog2_/cog3_	Recoded to no if score >10 or yes if ≤10	
Obesity (yes.no)	RwBMI	Obese/obese2_/obese3_	Recoded to no if score <30 and yes if score≥30	RAND
Exercise				
Frequency vigorous 1.Every day 2.>1 per week 3.1 per week 4.-3 per month 5.Never	RwVGACTX	R7VGACTX/R8VGACTX/R9VGACTX		RAND
Frequency light 1.Every day 2.>1 per week 3.1 per week 4.-3 per month	RwLTACTX			RAND
Smoking		SOMKER/SOKER2_/SMOKER3_	It was recategorized into 1-current smoker 2-former smoker 3-never smoker	
Ever	RwSMOKEV			RAND
Current	RwSMOKEN			RAND
Alcohol (Yes, no)	RwDRINK	R7DRINK/R8DRINK/R9DRINK		RAND
Chronic diseases				
Total number	RwCONDE	R7CONDE/R8CONDE/R9CONDE		RAND
Hypertension	RwHIBPE	R7HIBPE/R8HIBPE/R9HIBPE		RAND
Diabetes	RwDIABE	R7DIABE/R8DIABE/R9DIABE		RAND
Cancer	RwCANCRE	R7CANCRE/R8CANCRE/R9CANCRE		RAND
Lung disease	RwLUNGE	R7LUNGE/R8LUNGE/R9LUNGE		RAND
Heart disease	RwHEARTE	R7HEARTE/R8HEARTE/R9HEARTE		RAND
Stroke	RwSTROKE	R7STROKE/R8STROKE/R9STROKE		RAND
Psychiatric	RwPSYCHE	R7PSYCHE/R8PSYCHE/R9PSYCHE		RAND
Arthritis	RwARTHRE	R7ARTHRE/R8ARTHRE/R9ARTHRE		RAND
Proxy interview	RwPROXY	R7ROXY/R8PROXY/R9PROXY		RAND
Institutionalization status (living in nursing home or	RwNHMLIV	R7NHMLIV/R8NHMLIV/R9NHMLIV		RAND

health care facility)				

VITA

DUAA MOHAMED BAKHSHWIN
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Education:

PhD candidate May 2018
Virginia Commonwealth University (VCU) School of pharmacy Richmond, VA, USA

Master of Science in pharmacology May 2014
Virginia Commonwealth University (VCU) School of medicine Richmond, VA, USA

- Thesis: autophagy inhibition by Chloroquine in HN30 head and nick cancer cell is the cause of radio sensitization, advisor: Dr. David Gewirtz, Professor of Pharmacology up to date GPA **4.0**.

Bachelor degree of Medicine & surgery June 2009
King Abdul Aziz University, Jeddah, Saudi Arabia

- with 2nd honor degree 83.2% (B+) **GPA 4.16** out **of 5.0**.

High school Diploma June 2003
Altheker High school, Jeddah ,Saudi Arabia.

- with an excellent score, 99.89..% **(A+) ,** gained the **5th** highest score upon Saudi Arabia students & the **2nd** highest score upon Jeddah students.

Current Position:

PhD student at pharmacotherapy department
School of Pharmacy
Virginia Commonwealth University

Internship:

One year rotation in multiple hospitals and specialties. July 2009-July 2010
Summer training at King Feisal Specialist Hospital. July 2006
Summer training student at King Abdulaziz University Hospital. July 2004

Post graduate certificates:

SLE (Saudi licenses exam) and earned score of 69% (average score was 59.22%). October 2009
Certified Basic Life Support (BLS), King Abdulaziz University, Jeddah, Saudi Arabia 2010

Academic projects (Researches):

Participated and contributed in several academic projects as;

Diabetes epidemiology as a part of Community Medicine Course

- Collected data about awarnace & knowledge of diabetes among population in Saudi Arabia.
- Checked the fasting blood sugar for estimation of epidemiology
- Found solutions & recommendations to improve health services for geriatrics.

Obesity : (on going research) apart of my elective training in King Fahad Research Center, in Nov 2009 to see the effect of some natural herbs in decreasing the weight of the patients with no side effects

Assisting on the following researches

1. A randomized controlled clinical trial Using flax seeds for women having menopause symptoms in comparison to hormonal therapy.
2. A randomized controlled clinical trial comparing between Aromatase inhibitor and **Clomiphene Citrate** in patient with polycystic ovary regarding ovulation and pregnancy outcome.
3. A randomized controlled clinical trial comparing the effectiveness and safety of 18 month of treatment with nicotinamide Adenine Dinucleotide (NADH) as compared with placebo in patients with mild to moderately Alzheimer's disease.

My research duties was as follow:

- Helped in designing the study and interviewing the patients to include or exclude from the study
- Felling the case report form for each patient
- Conducted literature reviews for publications and projects, reviewing other data for quality assurance.

Academic Appointments(teaching):

As part of being a lecturer in the Department of Pharmacology and Clinical Research unit at King Abdulaziz University

- Gave laboratory lectures
- Provided guidance and additional support to students during laboratory and office hours.
- Scheduled additional study hours based on student request, teaching to different learning styles
- Graded lab quizzes, tests and observed and graded lab experiment exams
- Prepared class materials and quizzes for students, coordinated group discussion in class and grade exams and quizzes

Publications:

1- Yet another function of p53--the switch that determines whether radiation-induced autophagy will be cytoprotective or nonprotective: implications for autophagy inhibition as a therapeutic strategy 2015

Abstracts and presentations:

- Poster presentation at the annual American Association for Cancer Research (AACR) 2014
- Poster presentation at public health department meeting 2015

Honors and Awards:

- Selected too enter the summer program as one of the gifted student in Saudi Arabia
- Certificate for ranking the 2nd among home city Jeddah and 5th among the country during high school
- Full time scholarship to USA to continue my graduate studies
- Nominated for membership in Phi Kappa Phi Honor Society (the nation's oldest, largest, and most selective collegiate honor society for all academic disciplines. Aimed to recognize and promote academic excellence in all fields of higher education) and still waiting for the results

Courses and workshops:

I have attended several courses, orientation and seminar courses as follows:

- Preparing future Facility
- Annual conference for American Association for Cancer Research (AACR) April 2014
- Participated in Pediatric Neurology Forum Epilepsy syndromes December 2007
- Jointed Rheumatology course November 2007
- Update Food Allergy Management Course June 2007

- The 5th Annual Symposium of Neurology for Non-Neurologist — April 2007
- Summer clinical training program at KAUH — July 2004
- Nominated to attend the Higher Education Forum for the Gifted Students. — 2002

Certificates of Appreciations:

I have also organized & participated in several courses & symposiums & received appreciations letter for the following:

- My positive and value participation in health education about H1N1 in Jeddah schools. — October 2009
- For being the chairman and organizer for the Second medical student volunteer day. — February 2008
- For my contribution in (How to pass the university Entrance exam) workshop which was a course to teach the student the tricks of passing the exam. — 2005,2006,2007 & 2008
- On my participation in orphan party. — 2007 & 2008
- For my positive participation in (ABCs of Medical School) workshop, this was an introduction course for medical students and I was the head of project, helped in designing the curriculum & assisted in teaching. — 2005, 2006 & 2007
- For organizing the First Medical Career Day, as the head of onsite committee. — March 2007
- For organizing the 6th GCC medical education conference "Student day", as the head of Onsite committee. — November 2007
- Selected to attend the annual event held on UK as an activity of International Federations of Medical Student Association IFMSA — November 2007
- For my efforts during Diabetes Awareness Campaign. — December 2006
- My participation in Communication skills & Job perfection workshop. — July 2006
- For joining the video conference with Bare Sense for HIV participated in update of HIV with Pasture institute Paris. I was selected by college administrative to choose & Invited the audiences from other medical school in Saudi Arabia & Secured housing for residence for external audiences, participated in the Presentation. — April 2005

Memberships:

I have several medical related memberships as follows:

- A member in the Saudi Scientific club 2004-2008.
- A member in the student counseling committee.
- A secretary general in the **International Federation of Medical Students' Associations (IFMSA)** –Saudi Arabia 2007.
- A member of Phi kappa Phi honor society

Skills:

- Familiar with Windows XP & Vista environment & Microsoft office (Word, Excel, PowerPoint) &Internet Searching.
- Fluent in English and Arabic, both written and spoken
- Familiar with the SPSS and SAS
- Familiar with database research

Hobbies:

- Symposium and celebration organization
- Community Health Program volunteering activities
- Photographing
- Cooking