POLYPHARMACY: PATTERNS AND POLICY PROPOSITIONS

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ABSTRACT

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Sixty percent of U.S. adults report frequent use of prescription medications, a prevalence that is higher than ever before. Although medications are lifesaving when used properly, they can produce side effects ranging from minor problems like dizziness to severe events such as an increased risk of cancer. Polypharmacy – a phenomenon typically defined as concurrent use of multiple medications – may present unique risks for medication side effects, amplifying the effects of each of the medication in a set. Given the growing medication use across the country, this dissertation examined the causes of polypharmacy and the consequences of concurrent use of medications with side effects on population health and health care use. The first chapter provided background information on polypharmacy and medication side effects. The second chapter used the National Health and Nutrition Examination Survey (NHANES) to investigate whether and how the introduction of Medicare Part D, a large and sudden change to health care financing for Medicare beneficiaries, affected medication use for older adults. While Part D increased the use of lifesaving medications, it also increased polypharmacy. The third chapter used the NHANES to show that concurrent use of three or more medications with cognitive impairment side effects among U.S. older adults increased three-fold in the past two decades. Individuals who used three or more such medications experienced increased risks of cognitive deficits compared to non-users. The fourth chapter used the Medical Expenditure Panel Survey (MEPS) to document a growth of 36% in the concurrent use of at least three medications with mental health side effects among U.S. adults in the past two decades. Concurrent use of these medications was associated with an increase in psychiatric symptoms and the use/costs of mental health services. In the fifth chapter, I discussed how the processes of medicalization and pharmaceuticalization contributed to rising medication use and disparities in such use, which in turn had implications for population-level health disparities. Collectively, these findings shed light on patterns and

disparities in population health associated with polypharmacy and speak directly to the role of broader social, economic, cultural, and institutional inequalities in generating and maintaining health disparities.

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Introduction

Polypharmacy

Almost 60 percent of U.S. adults report frequent use of prescription medications, a prevalence that is higher than ever before (Kantor et al., 2015). The use of medications varies significantly by demographic characteristics. Adults over 65 years of age, non-Hispanic Whites, women, and U.S. born citizens are more likely to consume prescription medications than their counterparts. Much of the increase in medication use between 1999 and 2012 could be attributed to growing use of certain drug classes such as antihyperlipidemic agents (6.9% to 17%), antidepressants (6.8% to 13%), prescription proton-pump inhibitors (3.9% to 7.8%), and muscle relaxants (1.2% to 2.5%) (Kantor et al., 2015). The growth in popularity of these drug classes in part reflected the increasing availability of medications, as well as rising occurrences of disease such as high cholesterol (Superko et al., 2019), depression (Weinberger et al., 2018), gastroesophageal reflux diseases (El–Serag, 2007), and chronic pain (Nahin et al., 2019).

While the use of at least one medication increased by almost 18% between 1999 and 2012 among community-dwelling adults, the use of five or more medications increased by nearly 83% – a phenomenon typically referred to as polypharmacy (Kantor et al., 2015). Although there is no scientific consensus or clinical definition for polypharmacy, this term is typically used interchangeably to describe multiple, concurrent, excessive, unnecessary, or unindicated medication consumption. A handful of studies defined polypharmacy as consuming at least five medications concurrently for older adults and at

least two medications for young adults, because researchers typically detected adverse effects of medications at these thresholds in various health care settings (Mortazavi et al., 2016). Given that the prevalence of polypharmacy is likely to increase even more in the future, it is important to examine the causes of polypharmacy and its potential consequences on health.

Causes of polypharmacy

Causes of polypharmacy are multifactorial. Potential risk factors for polypharmacy include the rise in chronic conditions and comorbidity, failure to consider comorbidity in clinical practice guidelines, health care fragmentation, and the use of medications to treat adverse drug reactions.

Chronic conditions and comorbidity. The rise in chronic conditions in the United States may partly explain for growing prevalence of polypharmacy. In 2010, approximately half of U.S. adults had at least one chronic condition[1] (Ward & Schiller, 2013). When one condition occurs, more conditions await backstage. Therefore, among individuals with at any chronic conditions, half had at least two conditions (Ward & Schiller, 2013). The proportion of U.S. adults having multiple chronic conditions is not only high and alarming, but it has also been increasing over time. The prevalence of having at least two chronic conditions in 2001 was 21.8%, while it was 25% in 2010 (Ward & Schiller,

[1] Chronic conditions in the study by Ward and Schiller (2013) included hypertension, coronary heart disease, stroke, diabetes, cancer, arthritis, hepatitis, weak or failing kidneys, chronic obstructive pulmonary disease, and current asthma.

2013). The growth in comorbidity has also been observed across various demographic subgroups, such as men (19.1% to 24%), women (24.3% to 27.7%), adults aged 45-64 (30.7% to 33.8%), adults aged 65+ (56.2% to 62.1%), and non-Hispanic Whited (23.4% to 28.1%) (Ward & Schiller, 2013). An increase in comorbidity, combined with rapid pharmaceutical advancements and an overconfidence in medicine as a solution to disease, may have given rise to polypharmacy.

Failure to consider comorbidity in clinical practice guidelines. Clinical practice guidelines help manage chronic conditions. However, most guidelines only address a single disease outcome in accordance with modern medicine's practice and fail to acknowledge the presence of comorbidity, especially among older patients. Take an example of a hypothetical patient that has hypertension, diabetes mellitus, osteoporosis, osteoarthritis, and chronic obstructive pulmonary disease. Strict adherence to the national guidelines for these conditions easily results in 12 prescriptions that require 19 doses taken five times per day (Boyd et al., 2005). Under the recent pay-for-performance initiative in the health care system, which rewards physicians who follow interventions that reflect national clinical guidelines, one should expect that polypharmacy may increase as a result.

Health care fragmentation. Medical care delivery in the U.S. often involves multiple providers and organizations, without a single entity that effectively coordinates all aspects of care (Elhauge, 2010). Although the ideal physician-to-patient ratio is one, many patients may see several physicians to manage the same medical condition (Cebul

et al., 2008). Marked variation in physicians' practice styles may contribute to various treatment plans for patients. It has been well-established that health care delivery varies across small geographical areas, or even within the same hospital or health care system (Keating et al., 2006; Zhang et al., 2012). Cutler, Skinner, Stern, & Wennberg (2019) found that although patients' characteristics and preferences fail to explain for the geographical variation in end-of-life care delivery, 35% of the variation is explained by physician beliefs. Similarly, Zhang, Baicker, & Newhouse (2010) found a substantial variation in the quality of prescribing – defined as prescribing medications that are potentially high-risk for older adults – among local hospital markets even after controlling for patients' characteristics. The lack of care coordination across providers who have different beliefs, training, and knowledge about a patient's medical history may result in polypharmacy and adverse outcomes associated with polypharmacy. In fact, Col, Fanale, & Kronholm (1990) found that the number of physicians seen regularly is positively associated with the likelihood of being admitted to hospital for drug-related illnesses.

Adverse drug reactions. All medications have adverse side effects. Although pharmaceutical therapies are typically lifesaving when used correctly, consuming a medication that has adverse side effects may lead to the onset of another condition for which the medication was not intended. Symptoms that are due to adverse drug reactions are often mistakenly diagnosed as a new disease. As a result, 80% of drug adverse reactions are treated with another drug (Tamblyn, 1996).

Consequences of polypharmacy

Although medications are critical for disease management and prevention, growing concerns have emphasized the consequences of polypharmacy on adverse drug reactions, drug-drug interactions, medication nonadherence, and excessive medical interventions that do more harm than good for patients' health. Previous studies have documented adverse medical outcomes of polypharmacy on health in various settings. Among outpatients of all ages, using at least five medications is associated with an increase of 88% in experiencing adverse drug events (Bourgeois et al., 2010). For nursing home residents, the bar is higher. Using at least nine medications is associated with an increased risk of adverse drug reactions by 2.33 times (Nguyen et al., 2006). Concurrent use of medications can also lead to drug-drug interactions when the effectiveness or toxicity of a medication is altered by the other. Lindblad et al. (2005) found that the risk drug-drug interaction increased 4 times and 9 times among elderly veterans who consumed 5-8 medications and at least 9 medications simultaneously, compared to nonusers. Polypharmacy also has direct impacts on health: those who consumed at least five medications are more likely to experience cognitive impairment and falls, and these associations have been observed across all age groups (Huang et al., 2010; Jyrkkä et al., 2011; Kool et al., 2012). Adverse medical outcomes associated with polypharmacy may in turn lead to higher medical costs (Akazawa et al., 2010; Hovstadius & Petersson, 2013).

Limitations

Causes of polypharmacy. While a handful of previous studies has documented medical outcomes associated with polypharmacy, we know little about causes of this phenomenon. Even though the current literature has suggested some potential causes of polypharmacy – such as the rise in chronic conditions and comorbidity, failure to address comorbidity in clinical practice guidelines, health care fragmentation, and adverse drug reactions – many of these causes are suggestive and they lack adequate empirical evidence. Moreover, there are other causes that have not been frequently discussed in the literature, such as the role of health insurance expansion and increased access to medical services. From the late 1990s until the mid-2010s, the U.S. health care system witnessed multiple significant health care expansions. Examples include the Children's Health Insurance Program (CHIP) in 1997 that expanded Medicaid to cover uninsured low-income children; the Medicare Prescription Drug, Improvement and Modernization Act of 2003 that, for the first time, covered outpatient prescription medications for Medicare beneficiaries; and most recently the Affordable Care Act that allowed young adults under the age of 26 to remain as dependents on their parents' insurance plans and expanded Medicaid eligibility to cover more than 15.5 million uninsured low-income adults (Gates et al., 2016). Although these expansions significantly eliminated financial burdens and provided access to medical treatments that were otherwise unaffordable to some of the most vulnerable segments of population (Committee on Child Health Financing, 2014; Engelhardt & Gruber, 2011; Mazurenko et al., 2018), little is known about their unintended impacts on polypharmacy.

Consequences of polypharmacy. Although the literature on adverse consequences of polypharmacy is relatively more extensive than that of the causes of polypharmacy, further investigation of this topic is warranted due to two main reasons. First, studies that investigated the consequences of polypharmacy on health and health care utilization failed to address a possibility that not all medications result in adverse reactions, even when consumed in a set. It is possible that some groups of medications are more harmful when combined with others. For example, Qato, Ozenberger, & Olfson (2018) provided evidence that concurrent consumption of multiple medications with depression as a potential side effect was significantly associated with an increased risk of depressive symptoms. The authors also found a dose-response relationship, such that the association increased for every additional medication consumed that has depression as a potential side effect. In contrast, using medications *without* known depression side effect was not harmful to mental health, even when consuming multiple simultaneously. As such, policies that aim to address polypharmacy should target the simultaneous use of multiple medications with serious side effects, instead of reducing the use of all medications. It is possible that medications without side effects are indeed beneficial for disease management, and that reducing the use of these medications may be harmful to patients.

Second, the literature on polypharmacy typically focuses on older adults because they are at higher risks of adverse drug reactions due to biological and medical reasons, such as decreases in hepatic metabolism and renal clearance (Leon, 2011; Shi & Klotz, 2011), the presence of comorbidity (Ward & Schiller, 2013), and the use of multiple medications simultaneously (Kantor et al., 2015). Regardless, the consequences of polypharmacy

among young adults are also of important policy and clinical concerns. For young and healthy adults, the selection into using multiple medications simultaneously may be attributed to the early onset of chronic conditions that can be more debilitating to health than those that occur at older ages. Moreover, the threshold at which polypharmacy results in negative consequences for young adults may be even lower than that for older adults. Huang et al. (2010) found that using four to five medications simultaneously increased the risk of falls among young adults with diabetes compared to those using one or no medications. For older adults with diabetes, the authors did not observe a significant relationship between polypharmacy and falls until patients consumed six to seven medications. From an economic perspective, experiencing adverse effects of medications at young ages not only have cumulative effects on health, but also on productivity, human capital, and income throughout the lifetime. While the prevalence of polypharmacy among young adults is much lower than that among older adults (3.1% vs. 39% in 2011-2012), the significantly increasing trend in polypharmacy over time among young adults prompts further investigation into this population (Kantor et al., 2015).

Given the limitations in the literature, this dissertation aims to address the following questions:

<u>Chapter 2:</u>

- What is the impact of expanding the Medicare Part D prescription medication insurance on polypharmacy among older adults?
- Did polypharmacy increase significantly more for some socio-demographic sub-groups compared to others?

Chapter 3:

- What are the trends in the using medications with cognitive impairment side effects from 1999 to 2016 among adults aged 60 and older?
- What is the relationship between cognitive function and concurrent use of medications with and without cognitive side effects for older adults?
- Does the relationship vary by subgroups?

Chapter 4:

- What are the trends in using medications that have insomnia, depression, suicide, and anxiety as potential side effects among U.S. adults?
- What is the association between concurrent use of medications with and without these side effects and nonspecific psychological distress, as well as utilization and costs of mental health services?
- Does the association differ by age?

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CHAPTER 2:

The Impact of Medicare Part D on Polypharmacy

Objective: To investigate whether and how the introduction of Medicare Part D increased polypharmacy – the concurrent use of five or more medications – among older adults.

Data source: Nationally representative sample of adults aged 55-74 from the National Health and Nutrition Examination Survey (NHANES) in 1999-2016 without public health insurance.

Study design: I used a difference-in-differences approach to compare medication use and polypharmacy between Medicare eligible adults (aged 65-74) and Medicare ineligible adults (aged 55-64) before and after Part D was introduced in 2006, while controlling for socio-demographic characteristics, health insurance coverage, health conditions, and secular trends.

Principal findings: Among Medicare-ineligible respondents (aged 55-64), the number of prescription medications consumed was not significantly different before and after Part D took effect (2.30 medications and 16.6% for polypharmacy before 2006 vs. 2.36 medications and 16.1% for polypharmacy after 2006). In contrast, prescription medication use increased considerably among Medicare-eligible respondents (aged 65-74) after Part D (3.24 medications and 26.6% for polypharmacy before 2006 vs. 3.77 medications and 32.4% for polypharmacy after 2006). The implementation of Part D was associated with an increase in the odds of polypharmacy by 1.57 times ($p < 0.01$). In multiple sensitivity and placebo analyses, Part D did not have any effects on the use of dietary supplements or poly-supplementation (the concurrent use of five or more dietary

supplements), which were not covered under standard Part D plans. In addition, Part D did not alter the use of prescription medications among publicly insured respondents who already received some prescription medication benefits prior to Part D. The results were also robust to the unobserved impacts of the Great Recession and different definitions of medication use and polypharmacy.

Conclusion: Although prescription medications are lifesaving when used properly, using five or more medications simultaneously has been linked to adverse medical outcomes for older adults, including mortality, drug-drug interactions, adverse drug events, medical nonadherence, falls, and cognitive impairment. While the benefits of gaining access to life-saving prescription medications as a result of Medicare Part D may outweigh the unintended effects of polypharmacy, efforts that focus on addressing the adverse effects of polypharmacy may generate additional health benefits for Medicare beneficiaries. Using Medicare Part D as a case study, I demonstrated that other health insurance program expansions might have similar effects on polypharmacy (i.e. the Medicaid expansion under the Affordable Care Act or a Medicare-for-All initiative).

Introduction

Understanding the effects of health insurance on health and health behavior is a central question in every debate on the U.S. health care reform. On the one hand, health insurance may improve health by improving access to medical services and financial security (Currie & Gruber, 1996; Engelhardt & Gruber, 2011; Goldin et al., 2019; Hanratty, 1996; F. Lichtenberg, 2002). On the other hand, receiving additional medical care as a result of gaining health insurance may provide few clinical benefits at the margin (Baicker et al., 2013; Brook et al., 1983). One of the most heated public policy debates in recent U.S. presidential elections is whether a Medicare-for-all initiative improves the well-being of Americans. Since its inception, Medicare is a national health insurance program that primarily provides coverage to Americans aged 65 and older, young adults with disability, and individuals with end-stage renal disease. The original Medicare program covered most medical expenditures, such as hospital and doctor costs, but it excluded prescription medications. Public concern about rising medication prices and the potential consequences of medication unaffordability on health of older adults in the U.S. drove efforts to provide prescription medication coverage to Medicare beneficiaries. This resulted in the introduction of Medicare Part D in January 2006, which for the first time expanded the Medicare program to include coverage for outpatient medications.

The current paper revisits the implementation of Part D and examines its effects around a previously understudied margin: whether and how the program resulted in polypharmacy – the use of five or more medications simultaneously – among older adults. Although

there is no scientific consensus or clinical definition for polypharmacy, this term is typically used interchangeably to describe multiple, concurrent, excessive, unnecessary, or unindicated medication consumption (Mortazavi et al., 2016). Previous research has shown that expanding prescription medication coverage under Part D increased access to lifesaving medications that were otherwise unaffordable to older adults (Ayyagari & Shane, 2015; Engelhardt & Gruber, 2011; Ghosh et al., 2019), but coverage expansion might also increase the risk of polypharmacy, which has more ambiguous effects on health. Prior studies have documented the negative health consequences of polypharmacy for older adults, including adverse drug events, drug-drug interactions, medication nonadherence, falls, and cognitive impairment (Bourgeois et al., 2010; Hovstadius & Petersson, 2013; Huang et al., 2010; Jyrkkä et al., 2011; Lindblad et al., 2005; Maher et al., 2014; Marcum & Gellad, 2012; Sergi et al., 2011). The causes of polypharmacy are multifactorial. Potential risk factors for polypharmacy include the rise in chronic conditions and comorbidity (Ward & Schiller, 2013), failure to consider comorbidity in clinical practice guidelines (Boyd et al., 2005), and visiting multiple physicians or filling medications at multiple pharmacies (Col et al., 1990). Regardless, little is known about the role of health insurance expansion in the rising prevalence of polypharmacy.

I add to the existing literature by using the introduction of Medicare Part D in 2006, a large and sudden change to health care financing for Medicare beneficiaries, to study the relationship between health insurance expansion and polypharmacy. Part D benefits are provided by private stand-alone prescription medication plans or Medicare Advantage plans that offer both prescription medication and health care coverage. Although benefits

varied across plans, beneficiaries were typically entitled to the following coverage for prescription medication in 2006: no coverage for the first $250 in medication spending each year, coverage of 75% of the next $2,250, no coverage for the next $3,600, then coverage of 95% of costs above $5,100. Before Part D, Medicare beneficiaries had access to prescription medication coverage through employer-sponsored retirement health benefits, Medicare managed care plans, or through dual eligibility with Medicaid or other public insurance programs. Only two-thirds of Medicare enrollees had prescription drug coverage (Safran et al., 2005; Schneeweiss et al., 2009). While enrollment in Part D was voluntary, any Medicare beneficiaries who enrolled in the program after May 15, 2016 were subjected to a financial penalty to alleviate adverse selection into the program. In the first year after Part D took effect, 67% of Medicare beneficiaries without prescription medication insurance gained coverage through a stand-alone prescription medication plan, a Medicare Advantage plan, or through their current employer's plan provided that the benefits were as generous as those of standard Part D plans (Levy & Weir, 2009). Before Part D, 90% of Medicare beneficiaries reported taking prescription medication and almost half of them used five or more medications concurrently (Safran et al., 2005). Given a high prevalence of medication use, 30% of Medicare enrollees spent over $100 per month on prescription medications in 2003 (Safran et al., 2005). Out-of-pocket medication expenditures also increased with age: individuals aged 50-64 paid on average $237 annually for prescription medication in 1998 while those aged 65-79 paid $456 and those aged 80 and older paid $530 (Ihara, 2002).

Prior research found a modest reduction in out-of-pocket medication spending as a result of gaining Part D benefits (Khan & Kaestner, 2009; Lichtenberg & Sun, 2007; Yin et al., 2008). The cost reduction mainly concentrated among high-spending beneficiaries who often required long-term pharmaceutical therapies (Engelhardt & Gruber, 2011). Other studies demonstrated that Part D increased the consumption of prescription medications (Kaestner & Nasreen Khan, 2012), improved mental health (Ayyagari & Shane, 2015), reduced hospitalization and emergency department visits (Afendulis et al., 2011; Ayyagari et al., 2017), and reduced medication nonadherence (Madden et al., 2008). However, little is known about whether increased access to prescription medications under Medicare Part D gave rise to polypharmacy. While prescription medications are lifesaving when used properly, polypharmacy may increase the risk of adverse medical outcomes and medical costs associated with these outcomes (Sergi et al., 2011). To the extent that the results are generalizable to other health insurance programs, this paper speaks directly to the potentially unintended impact of health insurance expansion on polypharmacy. It also highlights the importance of addressing polypharmacy among older adults.

Methods

I used the 1999-2016 National Health and Nutrition Examination Survey (NHANES), a nationally representative two-year cycle survey of the civilian noninstitutionalized U.S. population. NHANES was obtained using a multistage probability sampling design to represent the general population but with an oversampling of Black, Hispanic, and adults aged 60 and older. The average non-response rate was 22%. All analyses used survey

weight to produce nationally representative estimates and to avoid non-response bias. I removed respondents interviewed in 2005-2006 because this survey cycle overlapped with the introduction of Medicare Part D in January 2006. I also dropped respondents interviewed in the 2013-2014 and 2015-2016 survey cycles to avoid spillover effect of the Medicaid expansion in 2014 onto the analysis. Previous studies suggested that the Medicaid expansion in 2014 influenced physicians' prescribing practice and medication use (Ghosh et al., 2019; Saloner et al., 2018). Since many physicians treat both Medicaid and non-Medicaid patients, changes in prescribing practice as a result of Medicaid expansion may have a spillover effect to Medicare beneficiaries. I selected respondents aged 55 to 74 because their ages were close to the Medicare's age eligibility of 65 (N = 9,319). I classified respondents into two distinct groups based on the likelihood that the introduction of Part D affected their prescription drug coverage. Medicare eligible respondents aged 65-74 qualified for Medicare Part D at the time of the survey interview, while ineligible respondents aged 55-64 did not qualify. I excluded respondents aged 55-64 who received Medicare benefits (N = 529) and respondents who had public health insurance – including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and other state-sponsored or government health plans (N = 1,464). The former mainly consisted of individuals with disability whose unobservable characteristics might be different from those of their peers. The latter included individuals with public insurance who already received some prescription drug coverage before Part D. I excluded respondents who had missing information on medication use and control covariates (N = 1,271). I imputed missing data for control covariates using multiple imputation with chained equations, but the results were similar

to when not using imputation. As such, the results were restricted to a final sample of 6,055 respondents without missing data.

Prescription medications were collected during the prescription medication interviews. Interviewers asked respondents to show the containers of all prescription medications they had taken in the past 30 days. Respondents who could not show a container were asked to verbally report the medication's name. When interviewers entered the medication names into a computer, more than 95% of entries resulted in exact or similar matches with an existing drug. The drug database used for the match was obtained from Lexicon Plus, a proprietary database of Cerner Multum that provided, on an annual basis, a comprehensive list of all prescription and some non-prescription medications available in the U.S. market. Using reported use of medications in the past month, I constructed two main outcomes: the number of medications used last month, and whether a respondent used at least five medications last month (polypharmacy).

Covariates in this paper included demographic characteristics, health insurance, income, and health conditions. Demographic covariates were age, age squared, race (non-Hispanic Whites: reference category, non-Hispanic Blacks, non-Hispanic others, Hispanic), gender, marital status (married or cohabiting: reference category, widowed/divorced/separated, never married), education (less than high school graduate: reference category, high school graduate, some college, college graduate or above), and nativity/citizenship status (U.S. citizen born in the U.S. or its territories: reference category, U.S. citizen born abroad, not a citizen). Health insurance covariate indicated

whether a person had any type of health insurance. Income covariates included household poverty level as a series of dummy variables (less than 100%: reference category, 100-199%, 200-299%, 300-399%, 400-499%, 500% or more). Health covariates included the number of chronic conditions (none: reference category, one or two, three or more conditions), whether a person was overweight or obese (BMI of at least 25), and self-reported health status (excellent: reference category, very good, good, fair, poor). Chronic conditions in this study included a series of self-reported diagnoses of asthma, arthritis, cancer, congestive health failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, hypertension, and diabetes.

I assessed the impact of Medicare Part D on medication use using a difference-in-differences approach:

$$\mathbf{RxUse_{it} = \alpha_0 + \alpha_1 Eligible_{it} * Post2006_{it} + \alpha_2 Eligible_{it} + \alpha_3 Post2006_{it} + \alpha_4 X_{it} + \varepsilon_{it}}$$

where $RxUse_{it}$ was either the number of prescription medications consumed in the last 30 days by person i at time t, or whether the person used at least five medications in the last 30 days (polypharmacy). $Eligible_{it}$ took the value of 1 if the person qualified for Medicare (ages 65-74), and 0 if the person was 55-64 years of age. $Post2006_{it}$ indicated if the person was interviewed after Part D took effect. $Eligible_{it}*Post2006_{it}$ is the variable of interest, and α_1 reflected the reduced-form effect of Part D on medication use. X_{it} included a set of demographic characteristics, health insurance, income, and health covariates, as described earlier. I controlled for time trends in the outcomes by including

the year fixed effect. The main assumption of the difference-in-differences method, referred to as the parallel assumption, is that any differences in medication use between Medicare eligible and ineligible adults are constant over time prior to Part D. This assumption is empirically tested and presented in the result section.

I conducted multiple additional sensitivity analyses. *First*, I assessed the impact of Part D on the number of dietary supplements consumed and whether a respondent used at least five supplements ("poly-supplementation" hereafter) last month. Part D did not subsidize dietary supplements, thus there should be no impact of Part D on such use. Similar to the prescription medications interview section, respondents reported all dietary supplements[2] and non-prescription antacids[3] that they consumed in the past 30 days. *Second*, I investigated whether Part D affected the use of prescription medication for publicly insured individuals. Most public insurance programs provided their beneficiaries with some prescription medication benefits prior to Part D. Therefore, there should be no impact of Part D on medication use among the publicly insured population (Basu et al., 2010; Millett et al., 2010). *Third*, I included in the analysis survey cycles from 2013 to 2016 that were previously removed because they overlapped with the Medicaid

[2] Dietary supplements included vitamins or minerals (i.e. Calcium, Vitamin C, Calcium and Iron, Vitamin E, Magnesium, Zinc, Calcium plus Vitamin D), multi-vitamins or multi-minerals (i.e. Flintstones, One a Day, Prenatals, Tri-Vi-Flor, B-Complex, Centrum), herbs and botanicals (i.e. Echinacea, garlic, Saw Palmetto, Ginkgo, Ginseng), fiber (i.e. Metamucil, Fibercon, Benefiber), amino acids (i.e. Lysine, Methionine, Tryptophan), and others (i.e. fish oil, Chondrotin, Glucosamine).

[3] Only non-prescription antacids containing calcium or magnesium were included in the dietary supplement files.

expansion in 2014. *Fourth*, the post-Part-D period coincided with the recession from 2007 to 2009, which might have affected Medicare eligible and ineligible respondents in systematic ways. While Medicare eligible adults were relatively insulated from the recession due to their access to Social Security benefits, Medicare ineligible adults were heavily affected by unemployment and the loss of private health insurance associated with their jobs. The lack of health insurance in turn affected medication use among Medicare ineligible adults. To address this possibility, I propose two sets of sensitivity analyses, including (1) removing survey cycles in 2007-2008 and 2009-2010 that overlapped with the recession and (2) excluding all uninsured individuals who might have lost health insurance due to the recession. The interpretation of the results should be similar to that of the main analysis if the use of medication was not driven by unobserved heterogeneity during the recession. *Fifth*, I propose a stricter definition of polypharmacy. In previous analyses, I counted all prescription medications that a person used in the past month. Nevertheless, although a respondent reported taking at least five medications last month, the simultaneous consumption of these medications might not have occurred daily, as the definition of polypharmacy implies. I reconstructed the outcome variables and only included prescription medications that a person consumed every day in the last month and repeated the analysis in equation (1). I also repeated the same analysis for daily use of dietary supplements. *Finally*, I relaxed the numerical threshold of polypharmacy. While there is no clinical definition of polypharmacy, previous studies typically defined polypharmacy as concurrent use of five or more medications. In a set of sensitivity analyses, I created ten outcome variables, ranging from whether a respondent used at least one prescription medication in the last month to whether a respondent used

at least ten prescription medications. I repeated the same analyses for dietary supplements.

Results

Figure 1 presents the gender and age adjusted average number of outpatient prescription medications (Panel A) and dietary supplements (Panel B) consumed by Medicare eligible and ineligible adults from 1999 to 2016. Prior to Part D, Medicare eligible adults consumed more prescription medications than ineligible adults (Panel A). Regardless, the difference in medication consumption of two groups was relatively constant over time before Part D. After Part D took effect, prescription medication use increased significantly among Medicare eligible adults, although it leveled off and declined during the 2007-2009 recession. In contrast, the trend in prescription medication use among Medicare ineligible adults was relatively stable after Part D took effect. Medication use slightly declined during the recession for the ineligible group, possibly because they were affected by unemployment and the loss of health insurance during this period. In Panel B, the use of dietary supplements was not significantly different between Medicare eligible and ineligible adults in all survey cycles. There was no evidence that Part D affected the use of dietary supplements for Medicare eligible adults, mainly because Part D did not subsidize dietary supplements.

-Insert Figure 1 About Here-

Figure 2 demonstrates the gender and age adjusted prevalence of polypharmacy (Panel A) and poly-supplementation (Panel B). The results mirror those observed in Figure 1. In

Panel A, the prevalence of polypharmacy was relatively parallel between two groups before 2006, then diverged after Part D took effect. In contrast, Part D did not have any effect on poly-supplementation (Panel B).

-Insert Figure 2 About Here-

Table 1 compares descriptive statistics of medication use and control variables between Medicare eligible and ineligible respondents, before and after Part D. Among ineligible respondents (aged 55-64), prescription medications consumed was not significantly different before and after Part D (2.30 medications and 16.6% for polypharmacy before 2006 vs. 2.36 medications and 16.1% for polypharmacy after 2006). In contrast, prescription medication use increased considerably among eligible respondents (aged 65-74) after Part D (3.24 medications and 26.6% for polypharmacy before 2006 vs. 3.77 medications and 32.4% for polypharmacy after 2006). In contrast, the use of dietary supplements among Medicare eligible and ineligible adults remained relatively unchanged before and after Part D.

Overall, Medicare ineligible respondents tend to be more racially and ethnically diverse, less likely to be female, more likely to be married, are more educated, less likely to have been born in the U.S., less likely to have health insurance, have higher household income, have fewer chronic conditions, less likely to be overweight or obese, and more likely to report excellent or very good health than Medicare eligible respondents. This is potentially due to the cohort effect and mortality selection in older ages. Regardless, I did

not detect any significant differences between Medicare eligible and ineligible respondents before and after Part D for all control variables after controlling for age.

-Insert Table 1 About Here-

Panel A of Table 2 presents difference-in-difference results for the impact of Part D on medication use and polypharmacy. In the unadjusted model 1, being eligible for Part D after the program took effect resulted in an increase of 0.467 medications used in the last 30 days, compared to Medicare ineligible adults before and after Part D and Medicare eligible adults before Part D ($p<0.05$). Adjusted for socio-demographic characteristics, health insurance, income, health conditions, and time trends (model 5) did not significantly alter the impact of Part D on medication use (coefficient = 0.460, $p < 0.01$). I observed similar patterns for polypharmacy. Medicare Part D resulted in an increase of 1.368 times the odds of polypharmacy in the past month ($p < 0.05$, model 1). Adjusting for all covariates in model 5 increased the estimate (OR = 1.572, $p < 0.01$), although two estimates were not significantly different from one another.

In Panel B of Table 2, I presented the difference-in-differences results with year fixed-effect interactions. Results in models 1 to 5 indicate that the number of medications used did not increase until 2007 after Part D was introduced. There were no statistically significant differences in medication use between eligible and ineligible respondents before 2006, implying that the parallel assumption for the difference-in-difference model was valid. Any changes in medication use in 2006 onward were potentially due to the introduction of Part D. The results for polypharmacy were quite similar. However, the

difference-in-difference models with year fixed-effect did not detect significant differences in polypharmacy between Medicare eligible and ineligible adults in each year, both before and after the implementation of Part D. Regardless, when pooling all years before and after Part D, I detected an increase in polypharmacy as a result of the program implementation.

-Insert Table 2 About Here-

Figures 3 to 11 present the heterogeneous effects of Part D on polypharmacy by race/ethnicity, gender, marital status, educational attainment, nativity and citizenship status, household income, comorbidity, obesity status, and self-reported health status. Overall, the effect of Part D on polypharmacy was particularly large for subgroups that had limited access to prescription drug insurance prior to Part D. The introduction of Part D was associated with an increase in polypharmacy for non-Hispanic Whites, non-Hispanic Blacks, and Hispanic respondents (Figure 3). Regardless, the effect of Part D was larger for non-Hispanic Black and Hispanic respondents compared to that of non-Hispanic Whites, potentially because racial/ethnic minorities were less likely to have access to prescription medication insurance prior to Part D, such as employer-sponsored coverage or Medicare Advantage plans (Briesacher et al., 2003). Similarly, married and widowed/divorced/separated respondents were more likely to experience polypharmacy than their non-married peers as a result of Part D (Figure 5), in part because they were less likely to have prescription medication insurance prior to Part D (Poisal et al., 1999). I found that the effects of Part D on polypharmacy were particularly large and statistically significant among respondents who were college educated (Figure 6), native-born

citizens (Figure 7), and middle-class (Figure 8), compared to their peers. While high-income respondents may purchase private prescription medication insurance and non-college-educated individuals, naturalized citizens, migrants, and low-income respondents may qualify for government programs that help pay for prescription medication costs such as Medicaid or Low-Income Subsidy[4] (Stuart et al., 2012), college educated, native-born, and middle-class respondents typically did not qualify for low-income government programs before Part D. This lack of coverage in part explained why gaining Part D benefits had a particularly large impact on polypharmacy among college educated, native-born, and middle-class respondents. Finally, respondents who had at least three chronic conditions (Figure 9), who were not obese (Figure 10), and who reported excellent or very good health (Figure 11) were more likely to experience polypharmacy due to the implementation of Part D. Respondents who were obese or who reported poor or fair health often required extensive pharmaceutical treatments and had high out-of-pocket medication expenditures (Jackson et al., 2004; Kit et al., 2012, pp. 2005–2008), and might have already had prescription medication coverage through public insurance or the Low-Income Subsidy program before Part D, which explained why Part D did not significantly affect their prevalence of polypharmacy.

-Insert Figures 3 to 11 About Here-

[4] Although I excluded respondents with public health insurance because they already had some prescription medication benefits prior to Part D, I wasn't able exclude respondents who received other forms of prescription medication assistance such as the Low-Income Subsidy due to the lack of data in the NHANES.

I conducted multiple additional sensitivity analyses. First, I assessed the impact of Part D on the use of dietary supplements and poly-supplementation. Since Medicare did not cover non-prescription medications, there should be no impact of Part D on the use of dietary supplements. In Table 3, results from unadjusted and adjust models indicated that there was no impact of Medicare Part D on the number of dietary supplements used and poly-supplementation. This sensitivity analysis reinforced my findings in Table 2: that Medicare Part D only affected the use of prescription medications.

-Insert Table 3 About Here-

Second, I repeated the analyses in Table 2 for publicly insured respondents who already received some prescription medication benefits prior to Part D. I hypothesized that Part D did not affect prescription medication use among this population. As demonstrated in Table 4, there was no effect of Part D on prescription medication use, and in some cases, medication use and polypharmacy even declined for Medicare eligible respondents after Part D compared to the control group.

-Insert Table 4 About Here-

Third, I included in my analysis the 2013-2016 survey cycles that were previously excluded to avoid the spillover effect of the Medicaid expansion in 2014 onto the analyses. In Panel A of Table 5, I replicated results in Table 2 using all survey cycles (1999-2016). The inclusion of data in 2013 onward did not significantly alter the results.

-Insert Table 5 About Here-

Fourth, I assessed whether the 2007-2009 Great Recession affected the results. The recession might have had differential consequences for Medicare eligible and ineligible adults that in turn influenced their use of prescription medications in systematic ways that confounded the effects of Part D. For instance, Medicare ineligible adults might have been more affected by unemployment during the recession than Medicare eligible adults, which reduced their ability to obtain health insurance and to purchase prescription medications. Thus, an increase in medication use after 2006 among Medicare eligible adults compared to those who were ineligible might have been attributed to the loss of health insurance among Medicare ineligible adults, rather than Part D per se. In Panel B of Table 5, I included in the analysis all survey cycles, except for those in 2007-2008 and 2009-2010 that overlapped with the recession. Exclusion of such survey cycles did not significantly alter the interpretation of the results. In Panel C of Table 5, I repeated the main analysis in Table 2 for all survey cycles in 1999-2016, but I excluded all uninsured individuals who might have lost their health insurance due to the recession. I found that the interpretation of the results remained relatively unchanged. Collectively, while the Great Recession might have affected Medicare eligible and ineligible adults differently, it did not affect the results in this paper.

Fifth, I proposed a stricter definition of polypharmacy. In previous analyses, I defined polypharmacy as the use of five or more medications in the past month. However, even though respondents consumed at least five medications, it was unclear whether they consumed those medications simultaneously. I repeated the analyses using a revised measure of polypharmacy that indicated polypharmacy on a daily rather than monthly

basis. I did the same for poly-supplementation. In Table 6, I found that Part D significantly increased the number of medications consumed daily and polypharmacy for Medicare eligible adults, compared to control groups (Panel A). In contrast, I did not detect any effects of Part D on the use of dietary supplements (Panel B).

-Insert Table 6 About Here-

Finally, I estimated the impact of Part D on polypharmacy using different numerical thresholds for polypharmacy. I created ten outcome variables, ranging from whether a respondent used at least one prescription medication in the last month to whether a respondent used at least ten prescription medications. Results in Panel A of Table 7 suggested that Part D affected the use of multiple medications more than single medications, starting at four or more prescription medications to at least ten medications in the past month. As before, I did not find any significant impacts of Part D on the use of dietary supplements, regardless of which cutoff points that were used to define poly-supplementation (Panel B).

-Insert Table 7 About Here-

Discussion

Medicare Part D was one of the most expensive health insurance expansion programs in the United States since the inception of Medicare. Federal spending in 2019 on the program is expected to be more than $95 billion (Centers for Medicare and Medicaid Services, 2019). However, evidence as to the extent to which Part D improves health tends to be ambiguous.

To my knowledge, this paper is the first to provide evidence that health insurance expansion is associated with an increase in polypharmacy. While Part D might have increased the use of prescription medications that were otherwise unaffordable to older adults, it had a more substantial impact on polypharmacy. In various placebo analyses, I found that Part D did not have any effects on the use of dietary supplements, which were not covered under standard Part D plans. In addition, Part D did not alter the use of prescription medications among publicly insured respondents who already received some prescription medication benefits before Part D. The results were also robust to the unobserved impacts of the Great Recession and different definitions of medication use and polypharmacy.

Results in this paper are within the range of estimates from prior studies. In Table 2, I found that Part D was associated with an increase of 16.3% in the number of prescription medication consumed last month. Using Walgreen's 2004-2007 claims data and a similar difference-in-differences approach, prior studies found that Part D led to an increase of 6%-13% in prescription fills (F. R. Lichtenberg & Sun, 2007; Yin et al., 2008). Using pharmacy data in 2005-2006, another study suggested an increase of 11%-37% in medication use as a result of Part D (Schneeweiss et al., 2009). In contrast to these studies, I used a nationally representative sample of older adults and a longer post-Part-D period. Although claims data provide detailed information on medication fills and alleviate recall bias, they are not representative of the population and typically exclude uninsured individuals – one of the population segments that benefited the most from the

introduction of Part D. In addition, the effect of Part D on medication use was likely accumulated over time as more Medicare beneficiaries gained coverage and Part D coverage became more generous over time (Cubanski et al., 2018), which might explain why the estimate in this study was slightly higher than some estimates in prior studies.

Although the benefits of gaining access to life-saving prescription medications as a result of Part D may outweigh the unintended effects on polypharmacy, efforts that focus on addressing polypharmacy may improve health for Medicare beneficiaries. In 2006, the Center for Medicare and Medicaid Services required that all Part D plans included Medication Therapy Management (MTM) services. The MTM program is free for Part D beneficiaries who meet three eligibility criteria: enrollees must have at least two chronic conditions, they must use multiple medications covered under their Part D plan, and they must be at risk at spending more on annual Part D covered medication costs than a certain cost threshold. Through the MTM program, eligible beneficiaries meet with a health professional annually to conduct a comprehensive review of their medications. Health professionals then inform beneficiaries if their medications have any potential side effects, if there are any potentially serious drug-drug interactions among their medications, and if their medication costs can be lowered. The program can potentially address the issue of polypharmacy, but it is significantly underused. A study in Maryland and Delaware found that 60% of Medicare respondents were unaware of the MTM program, and 80% had never received a medication therapy review (Truong et al., 2009). In addition, program eligibility is not universal, but rather varies across plans (Touchette et al., 2006). Private Part D plans can select their own MTM criteria within the general

guidelines from the government: they can select the types of chronic conditions on which they want to focus, the number of chronic conditions that a beneficiary has, or the number of Part D medications required for the beneficiary to be eligible for the program. In 2008, half of Part D plans opened enrollment to their MTM program for beneficiaries who had two chronic conditions, while the other half restricted enrollment to beneficiaries with a minimum of three to five chronic conditions (Wang et al., 2015). In 2010 and onward, approximately 80% of Part D plans required beneficiaries to have three or more chronic conditions to enroll in the MTM program (Wang et al., 2015). Such variation across plans can prevent beneficiaries who are at risk of polypharmacy from receiving a comprehensive review of their medications. Given the benefits of MTM programs on reducing drug-related adverse outcomes (Perlroth et al., 2013; Welch et al., 2009), more efforts should focus on increasing enrollment in the MTM program in order to address the adverse consequences of polypharmacy.

Other program expansions might have similar effects. For example, the Medicaid expansion in 2014 expanded enrollment eligibility to nonelderly adults with family incomes at or below 138% of the federal poverty level. The expansion resulted in an increase of 15.5 million new enrollees two years following its implementation (Gates et al., 2016). Prior research found that Medicaid expansion improved access to medical care, medical affordability, and health outcomes (Mazurenko et al., 2018; Mulcahy et al., 2016). Since Medicaid covers most major pharmacological therapy, expanding coverage may have had similar effects on polypharmacy.

Although this paper has several strengths, including the use of Medicare ineligible group to control for secular trends and a longer post-Part-D period, it faces some limitations. First, Medicare ineligible adults may differ from eligible adults in terms of employment, health, health insurance's coverage generosity, and preferences toward medical care. Such unobserved heterogeneity may result in marked differences in medication use between Medicare ineligible and eligible adults, which can bias the estimates towards the null. Regardless, Table 1 provides evidence that there were no significant differences in medication use and other characteristics between two groups before and after Part D. Second, I may underreport the prevalence of polypharmacy since NHANES lacks information on medications administered to inpatients. However, many inpatient medications were already covered under the traditional Medicare program prior to Part D. Thus, missing data on inpatient medications was unlikely to affect the estimates of the impact of Part D on polypharmacy.

Conclusion

This study presents a strong relationship between expanding public health insurance and polypharmacy among older adults. Despite the well-documented negative consequences of polypharmacy, little is known about the role of health insurance programs in overusing prescription medications. Efforts that address polypharmacy among Medicare beneficiaries can potentially generate additional health benefits by promoting proper prescribing practices.

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Figure 1: Gender and Age Adjusted Weighted Average Number of Prescription Medications and Dietary Supplements Consumed Last Month by Medicare Eligible (Aged 65-74) and Ineligible (Aged 55-64) Adults, with 95% Confidence Intervals. Data Source: NHANES 1999-2000 to 2015-2016.

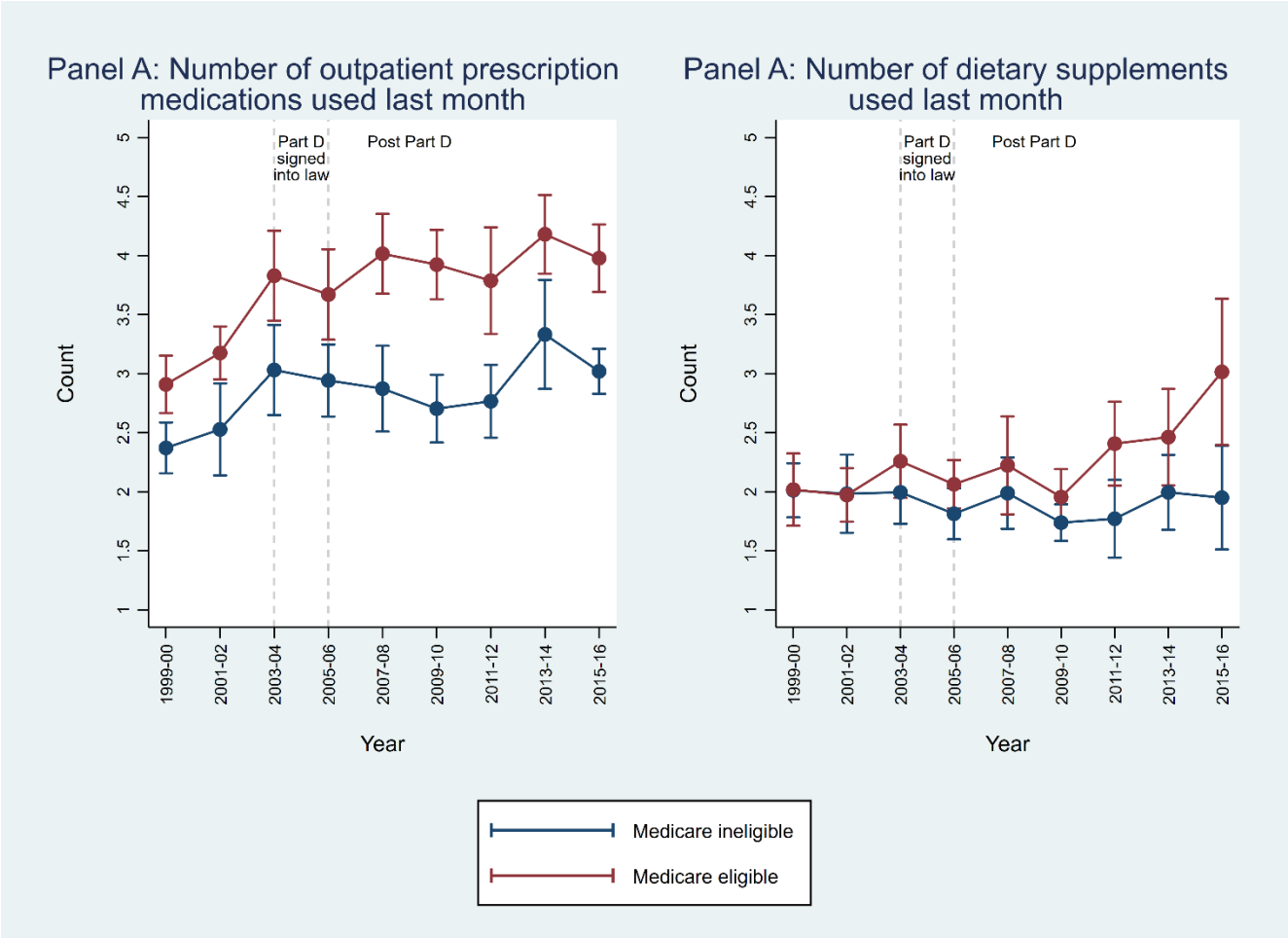


Figure 2: Gender and Age Adjusted Weighted Prevalence of Medicare Eligible (Aged 65-74) and Ineligible (Aged 55-64) Adults Consuming At Least Five Prescription Medications and Dietary Supplements Last Month, with 95% Confidence Intervals. Data Source: NHANES 1999-2000 to 2015-2016.

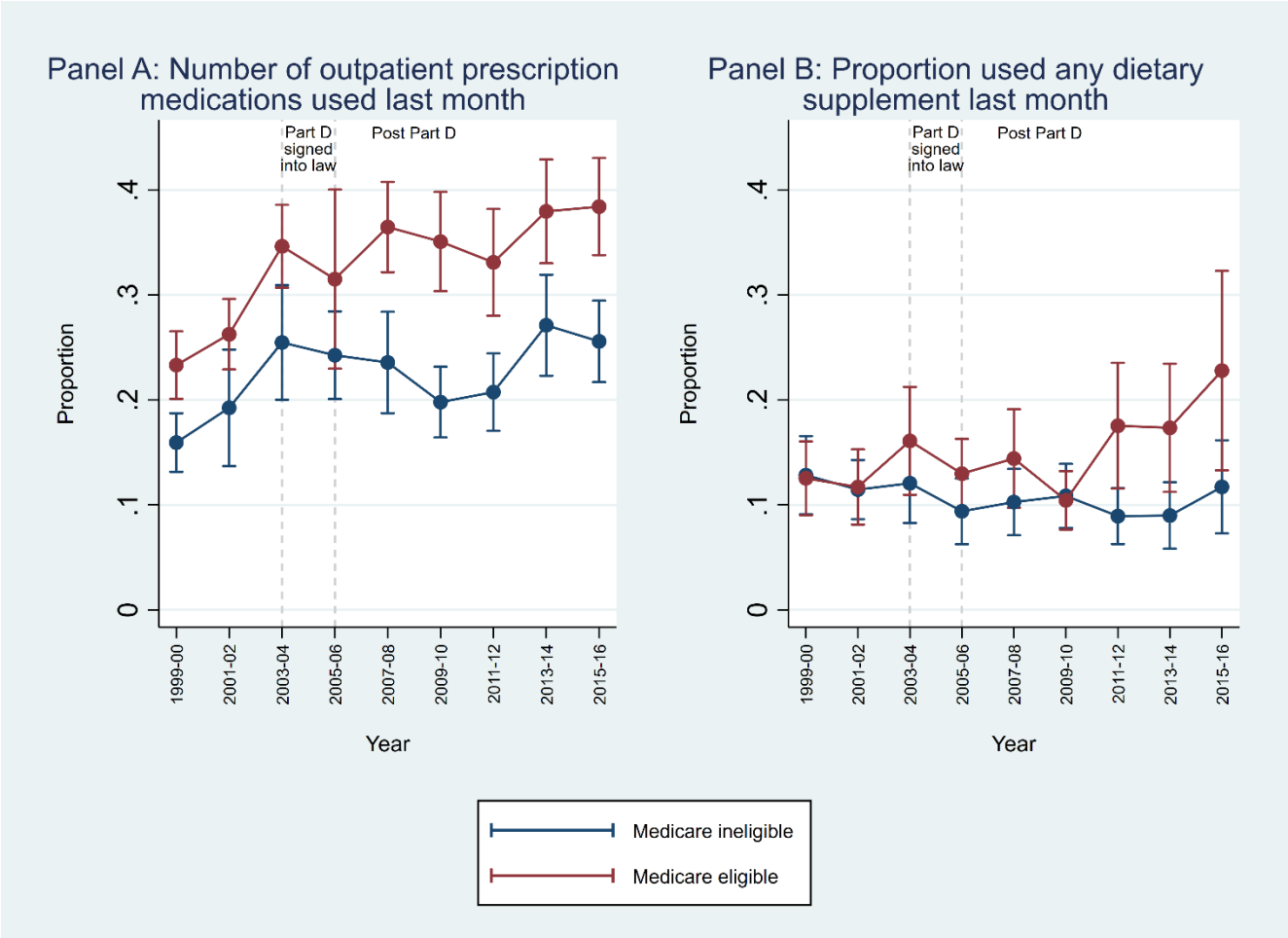


Table 1: Descriptive Statistics of Medication Use and Characteristics of Medicare Eligible (Aged 65-74) and Ineligible (Aged 55-64) Adults Before and After Medicare Part D Took Effect. Data Source: NHANES 1999-2012.

	Medicare ineligible (ages 55-64)				Medicare eligible (ages 65-74)				
	Before Part D (1999-2004)		After Part D (2007-2012)		Before Part D (1999-2004)		After Part D (2007-2012)		p-value [a]
Outcomes									
Number of prescription medications used last 30 days, mean[b] (SE)	2.30	(0.08)	2.36	(0.09)	3.24	(0.11)	3.77	(0.12)	p = 0.012
Used >= 5 prescription medications last 30 days, N[c] (%[d])	196	(16.6)	307	(16.1)	332	(26.6)	534	(32.4)	p = 0.031
Number of dietary supplements used last 30 days, mean[b] (SE)	1.97	(0.13)	1.80	(0.10)	2.07	(0.10)	2.11	(0.12)	p = 0.252
Used >= 5 dietary supplements last 30 days, N[c] (%[d])	128	(13.4)	168	(10.6)	144	(15.1)	175	(15.3)	p = 0.149
Socio-demographic characteristics									
Race, N[c] (%[d])									
Non-Hispanic White	645	(78.4)	793	(78.4)	741	(82.9)	846	(81.6)	p = 0.595
Non-Hispanic Black	231	(8.4)	439	(8.4)	216	(7.4)	343	(8.2)	p = 0.578
Hispanic	339	(8.5)	494	(7.1)	347	(6.6)	307	(5.9)	p = 0.724
Non-Hispanic others	50	(4.7)	144	(6.0)	32	(3.1)	88	(4.3)	p = 0.880
Age (in years), mean[b] (SE)	59.01	(0.11)	59.12	(0.09)	69.18	(0.10)	69.04	(0.10)	N/A
Female, N[c] (%[d])	671	(53.9)	942	(52.5)	663	(54.5)	801	(53.7)	p = 0.779
Marital status, N[c] (%[d])									
Married	926	(75.6)	1254	(72.6)	903	(70.4)	975	(67.8)	p = 0.792
Widowed, divorced, separated	290	(20.5)	482	(21.2)	395	(27.6)	531	(29.1)	p = 0.810
Never married	49	(3.8)	134	(6.2)	38	(2.0)	78	(3.1)	p = 0.820
Educational attainment, N[c] (%[d])									
Less than high school	413	(18.8)	445	(11.8)	530	(25.1)	507	(20.3)	p = 0.122
High school graduate	266	(23.5)	429	(23.9)	322	(30.3)	390	(24.7)	p = 0.049
Some college	297	(27.3)	502	(28.9)	272	(23.7)	374	(28.2)	p = 0.325
College graduate or above	289	(30.4)	494	(35.3)	212	(20.9)	313	(26.8)	p = 0.555
Nativity and citizenship, N[c] (%[d])									
Citizen, born in the U.S.	982	(86.9)	1338	(87.2)	1089	(89.6)	1240	(89.6)	p = 0.873
Citizen, born abroad	160	(9.0)	310	(7.8)	160	(7.6)	236	(7.6)	p = 0.461

Not a citizen	123	(4.1)	222	(5.0)	87	(2.8)	108	(2.9)	p = 0.482
Insurance coverage									
Has any health insurance, N[c] (%[d])	962	(84.8)	1328	(83.8)	1281	(98.6)	1506	(97.7)	p = 0.148
Income									
Household poverty thresholds, N[c] (%[d])									
< 100%	117	(4.9)	257	(6.2)	173	(7.0)	238	(7.5)	p = 0.465
100-199%	254	(12.7)	383	(11.7)	411	(26.6)	482	(23.8)	p = 0.839
200-299%	189	(13.9)	301	(16.0)	273	(22.5)	304	(19.3)	p = 0.103
300-399%	185	(16.1)	173	(11.0)	147	(13.7)	174	(12.9)	p = 0.130
400-499%	154	(15.4)	194	(13.6)	128	(11.6)	121	(11.1)	p = 0.709
500% or higher	366	(37.1)	562	(41.5)	204	(18.5)	265	(25.5)	p = 0.297
Health									
Number of chronic conditions, N[c] (%[d])									
None	345	(29.4)	557	(28.9)	215	(15.5)	203	(13.7)	p = 0.434
One or two	702	(53.5)	993	(53.8)	718	(53.0)	832	(52.2)	p = 0.801
Three or more	218	(17.1)	320	(17.2)	403	(31.5)	549	(34.1)	p = 0.466
Whether overweight or obese, N[c] (%[d])	963	(73.4)	1441	(74.6)	1003	(74.2)	1196	(74.7)	p = 0.837
Self-reported health status, N[c] (%[d])									
Excellent	219	(21.6)	239	(17.1)	177	(16.1)	167	(14.4)	p = 0.439
Very good	343	(32.9)	511	(34.3)	329	(28.8)	393	(31.1)	p = 0.726
Good	389	(28.7)	670	(33.2)	437	(32.1)	564	(34.5)	p = 0.454
Fair	252	(13.3)	366	(13.2)	303	(17.6)	365	(15.7)	p = 0.472
Poor	62	(3.5)	84	(2.3)	90	(5.4)	95	(4.2)	p = 0.626
No. respondents	1,265		1,870		1,336		1,584		

[a]: p-value for the difference between eligible and ineligible groups before and after Part D was introduced, controlling for age.

[b]: weighted mean [c]: unweighted frequency [d]: weighted percentage

Table 2: Linear and Logit Regressions of The Impact of Medicare Part D on Medication Use and Polypharmacy Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.

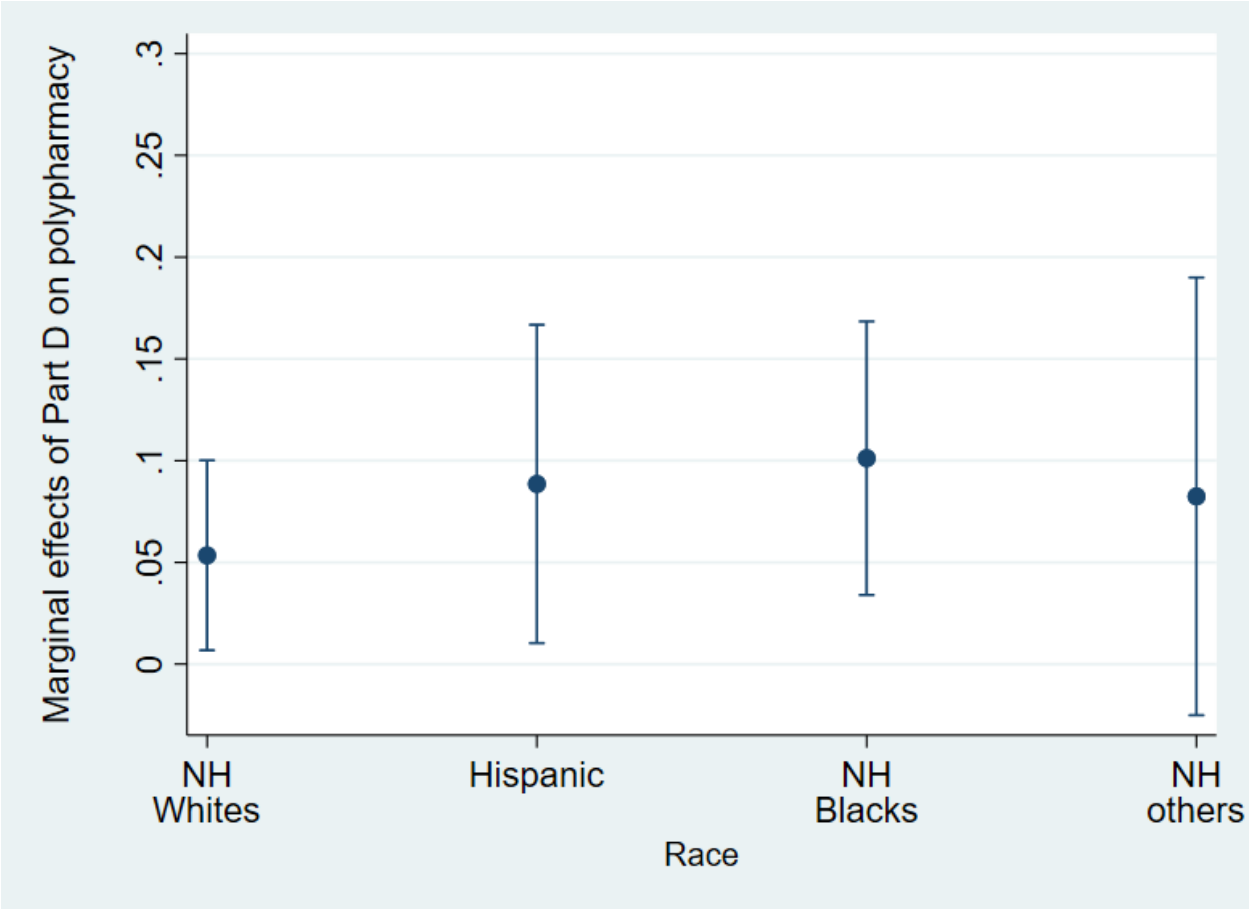
	Model 1: no covariates		Model 2: Model 1 + demographic covariates		Model 3: Model 2 + health insurance		Model 4: Model 3 + income		Model 5: Model 4 + health conditions	
Outcomes: Use of prescription medications	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx
	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)
Panel A: Difference-in-differences										
Ages 65-74 (vs. 55-64)	0.937*** (0.123)	1.823*** (0.188)	0.102 (0.223)	1.063 (0.200)	0.002 (0.225)	1.000 (0.187)	-0.027 (0.225)	0.965 (0.180)	-0.172 (0.179)	0.834 (0.163)
Post 2006	0.058 (0.119)	0.966 (0.129)	0.367* (0.160)	1.435* (0.241)	0.374* (0.152)	1.440* (0.239)	0.371* (0.154)	1.433* (0.242)	0.299+ (0.167)	1.399 (0.308)
Ages 65-74 * post 2006	0.467* (0.190)	1.368* (0.202)	0.497** (0.186)	1.389* (0.205)	0.497** (0.185)	1.389* (0.207)	0.501** (0.181)	1.408* (0.207)	0.460** (0.156)	1.572** (0.250)
Panel B: Difference-in-differences with year fixed-effect										
Ages 65-74	0.794*** (0.171)	2.177*** (0.437)	-0.008 (0.246)	1.287 (0.336)	-0.157 (0.266)	1.184 (0.320)	-0.187 (0.265)	1.145 (0.306)	-0.198 (0.231)	1.196 (0.369)
Ages 65-74 * years 1999-2000 (reference)										
Ages 65-74 * years 2001-2002	0.011 (0.249)	0.772 (0.200)	0.000 (0.254)	0.762 (0.198)	0.073 (0.264)	0.789 (0.214)	0.077 (0.265)	0.779 (0.210)	-0.042 (0.243)	0.619 (0.199)
Ages 65-74 * years 2003-2004	0.304 (0.299)	0.815 (0.211)	0.279 (0.306)	0.796 (0.210)	0.343 (0.318)	0.818 (0.223)	0.342 (0.318)	0.819 (0.224)	0.090 (0.260)	0.624 (0.188)
Ages 65-74 * years 2005-2006 (dropped)										
Ages 65-74 * years 2007-2008	0.564* (0.248)	1.073 (0.267)	0.589* (0.250)	1.086 (0.272)	0.648* (0.262)	1.118 (0.291)	0.653* (0.261)	1.122 (0.291)	0.421+ (0.249)	0.973 (0.306)
Ages 65-74 * years 2009-2010	0.704* (0.276)	1.197 (0.342)	0.667* (0.281)	1.175 (0.339)	0.716* (0.293)	1.203 (0.360)	0.718* (0.294)	1.215 (0.362)	0.450+ (0.258)	1.035 (0.351)
Ages 65-74 * years 2011-2012	0.551 (0.363)	1.157 (0.320)	0.568 (0.352)	1.166 (0.331)	0.609+ (0.357)	1.191 (0.347)	0.618+ (0.349)	1.210 (0.350)	0.563+ (0.306)	1.264 (0.416)

p-value for F-test of null hypothesis H_0: Ages 65-74 * (years 2001-2002 + years 2003-2004) = Ages 65-74 * (years 2007-2008 + years 2009-2010 + years 2011-2012):

	p < 0.01	p = 0.05	p < 0.01	p < 0.05	p < 0.01	p < 0.05	p < 0.01	p < 0.05	p < 0.01	p < 0.05
Mean outcome	2.822	0.218	2.822	0.218	2.822	0.218	2.822	0.218	2.822	0.218
No. respondents	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055

Notes: + p < 0.1, * p < 0.05, ** p < 0.01, *** p<0.001. All analyses excluded survey cycle in 2005-2006 that overlapped with the introduction of Part D.
[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.
Demographic covariates include age, age squared, race (non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic others, and Hispanic), gender, marital status (married or cohabiting, widowed/divorced/separated, never married), education (less than high school graduate, high school graduate, some college, college graduate or above), and nativity/citizenship status (citizen born in the US, citizen born abroad, not a citizen). Health insurance indicates whether a person has any type of health insurance. Income covariates include household poverty level (less than 100%, 100-199%, 200-299%, 300-399%, 400-499%, 500% or more). Health condition covariates include the number of chronic conditions (none, one or two, and three or more conditions), whether a person is overweight or obese (BMI of at least 25), and self-reported health status (excellent, very good, good, fair, and poor).

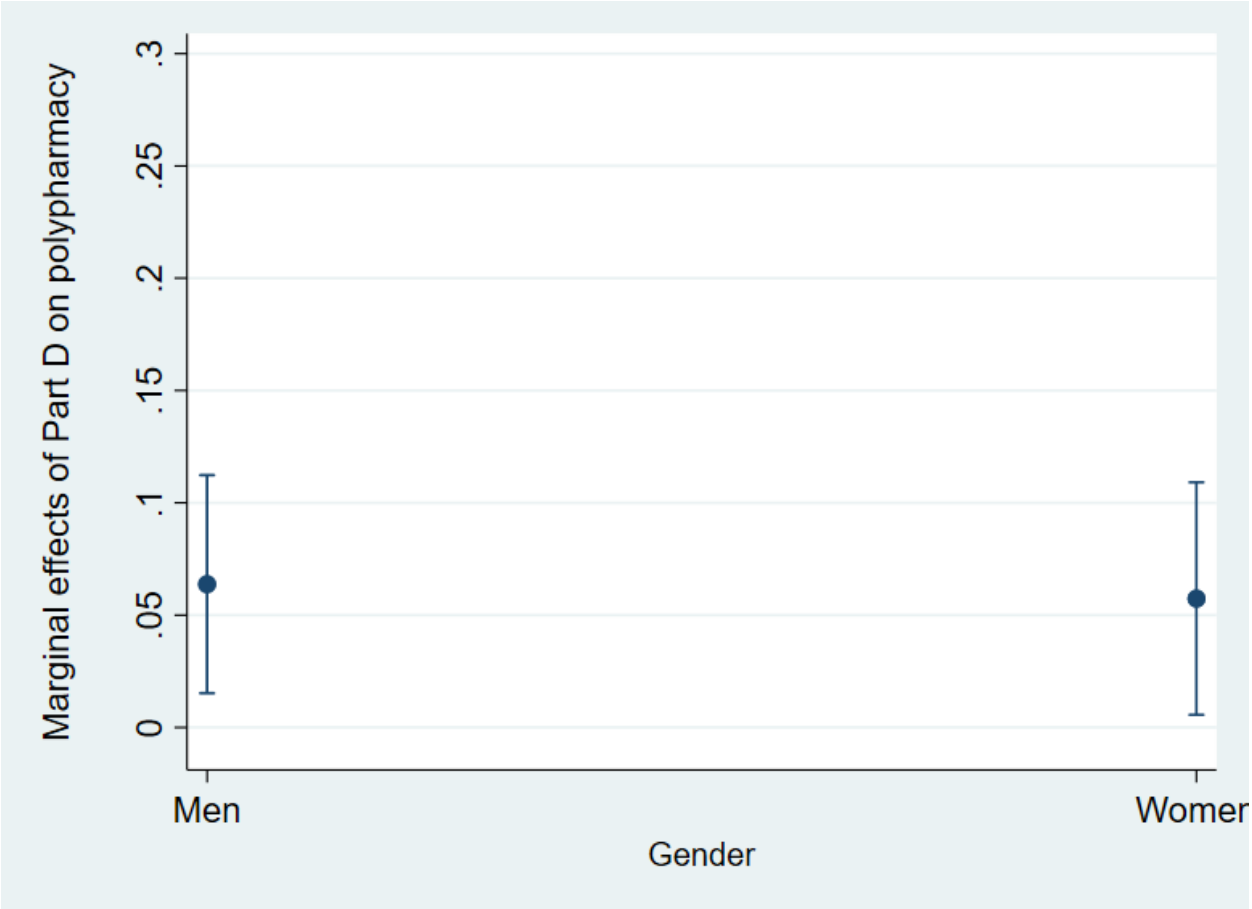
Figure 3: Marginal Effects (with 95% Confidence Intervals) of Medicare Part D on Polypharmacy by Race/Ethnicity Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.



[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

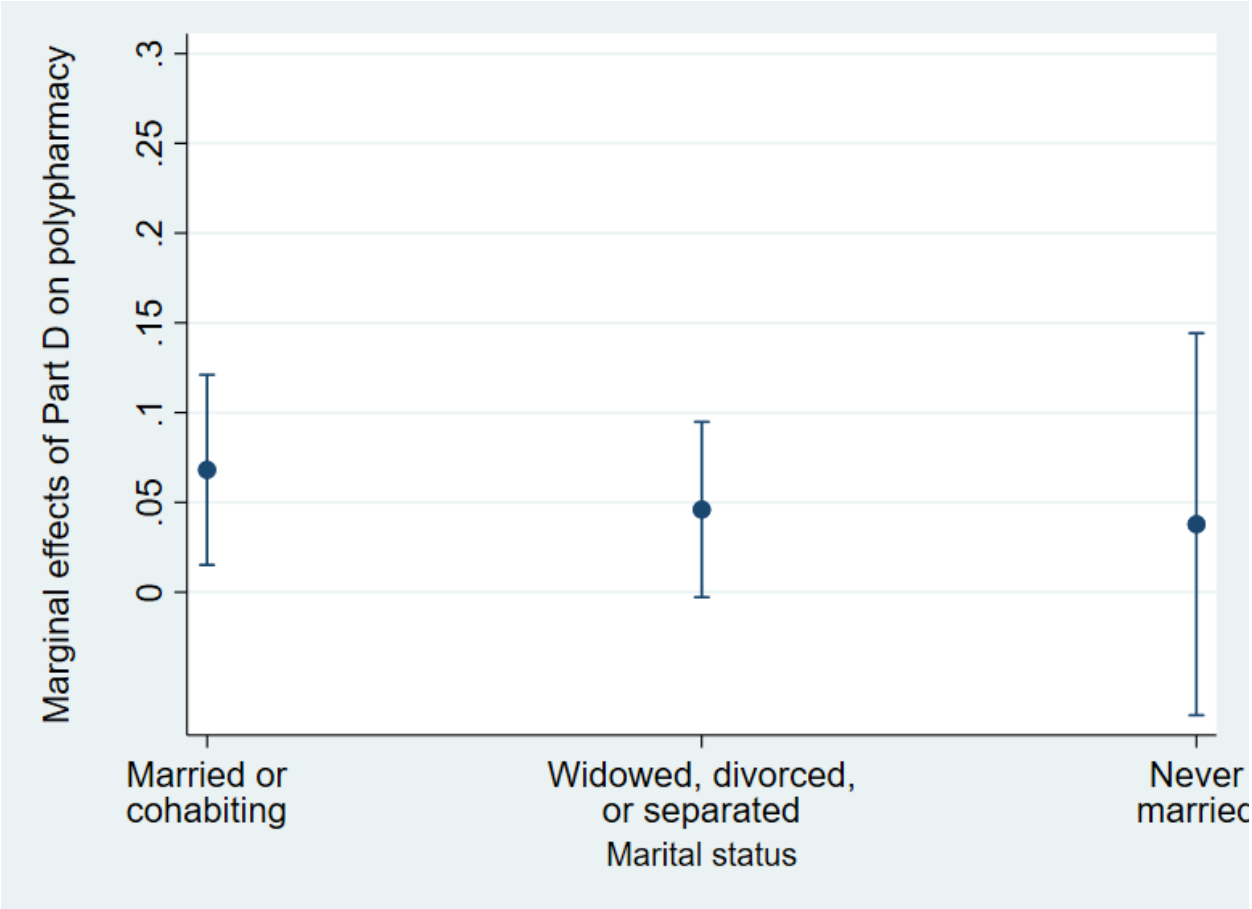
NH: Non-Hispanic

Figure 4: Marginal Effects (with 95% Confidence Intervals) of Medicare Part D on Polypharmacy by Gender Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.



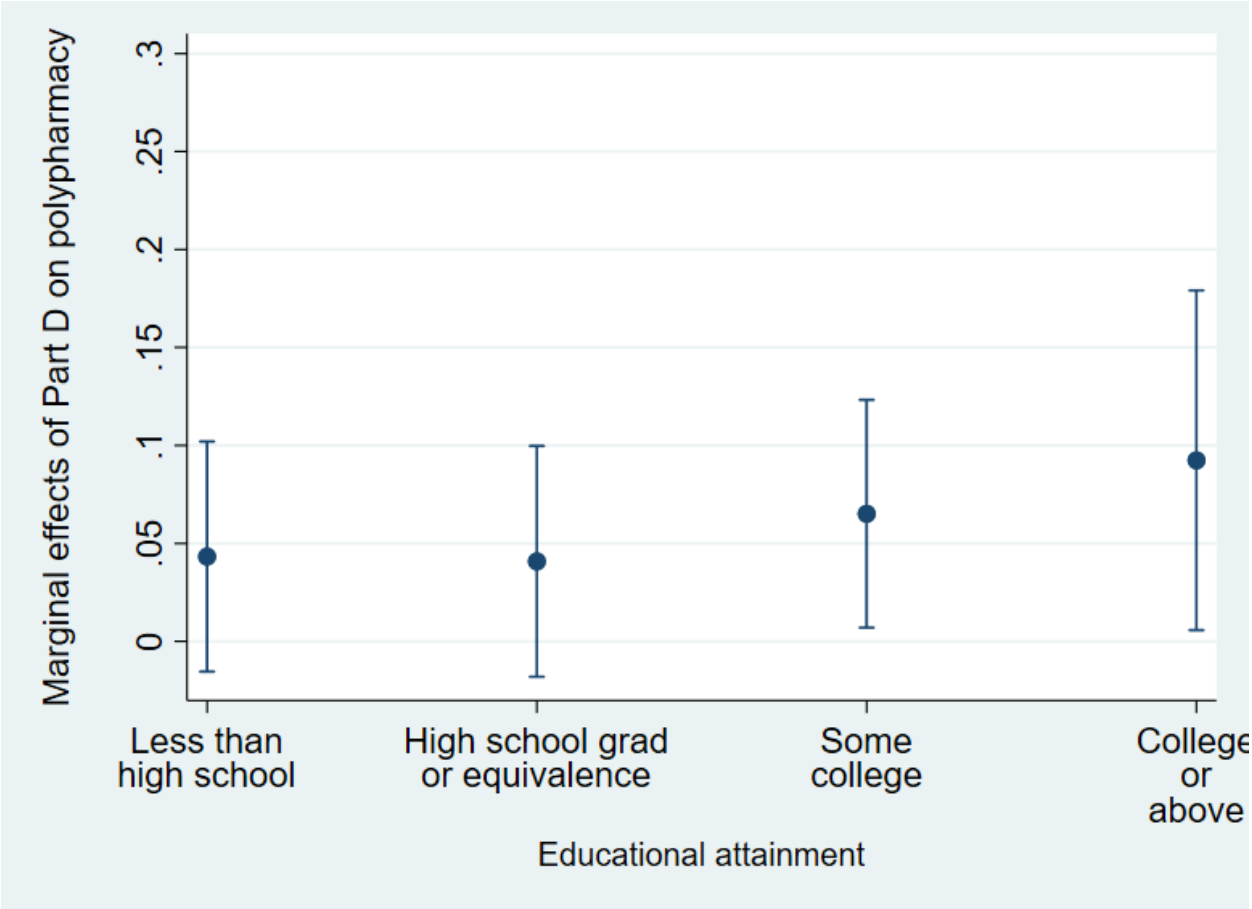
[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Figure 5: Marginal Effects (with 95% Confidence Intervals) of Medicare Part D on Polypharmacy by Marital Status Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.



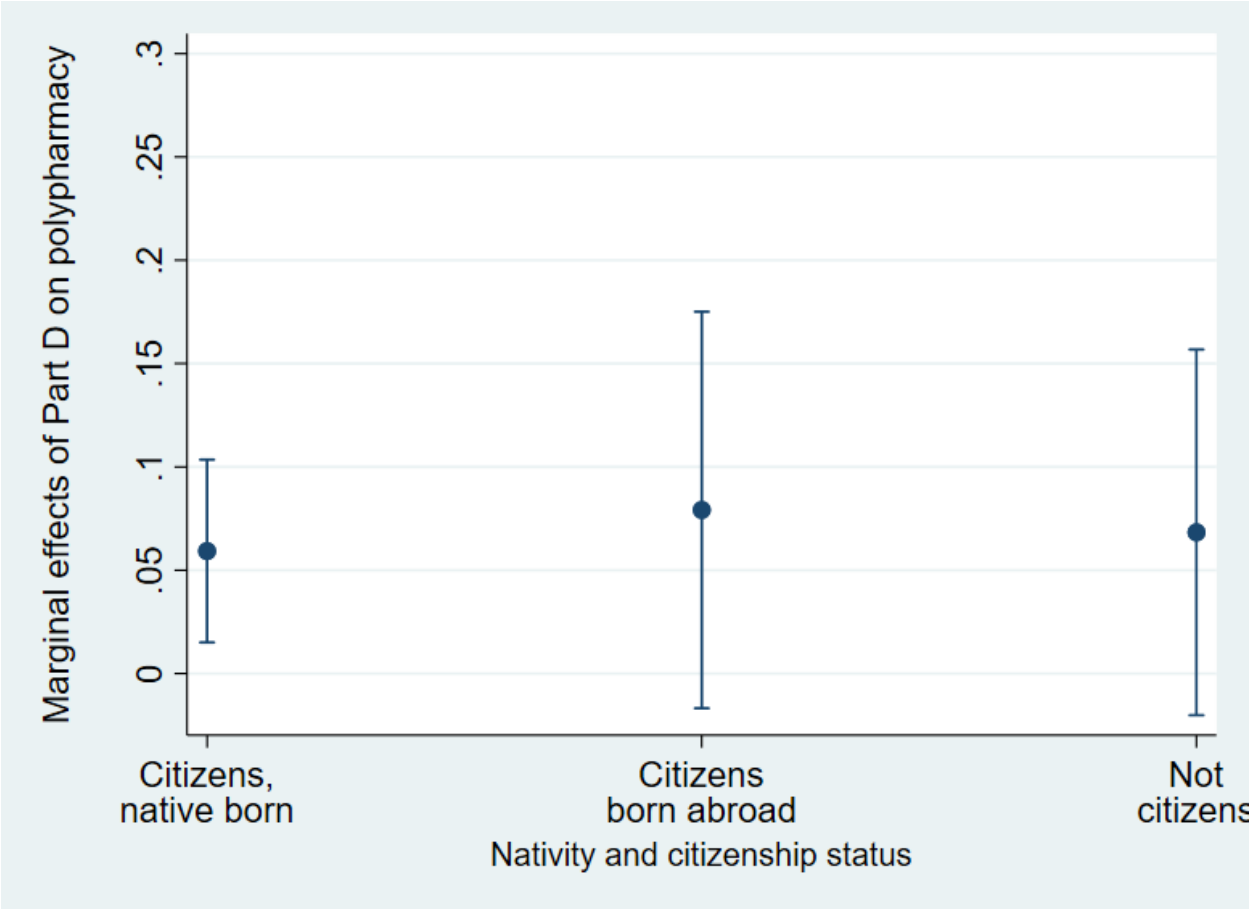
[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Figure 6: Marginal Effects (with 95% Confidence Intervals) of Medicare Part D on Polypharmacy by Educational Attainment Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.



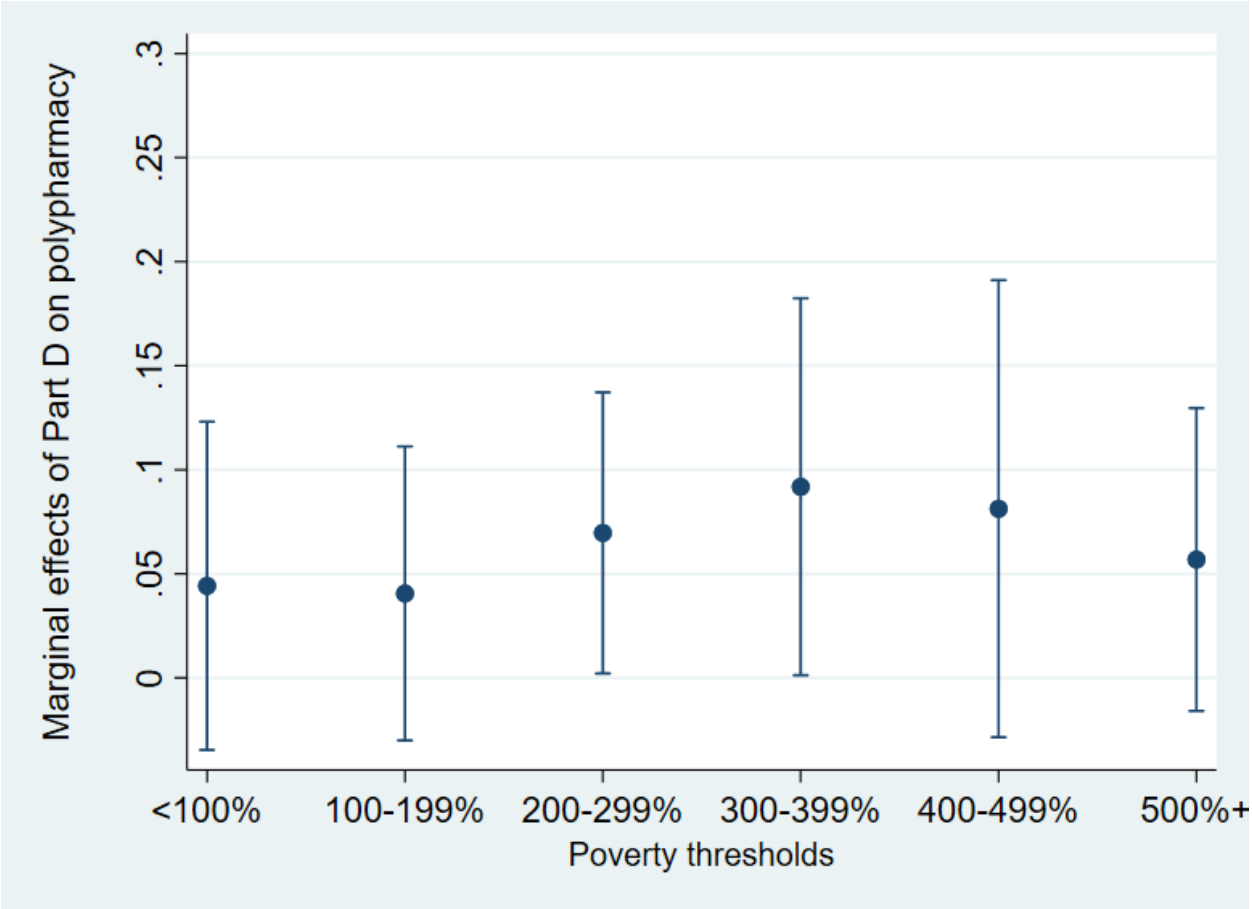
[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Figure 7: Marginal Effects (with 95% Confidence Intervals) of Medicare Part D on Polypharmacy by Nativity/Citizenship Status Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.



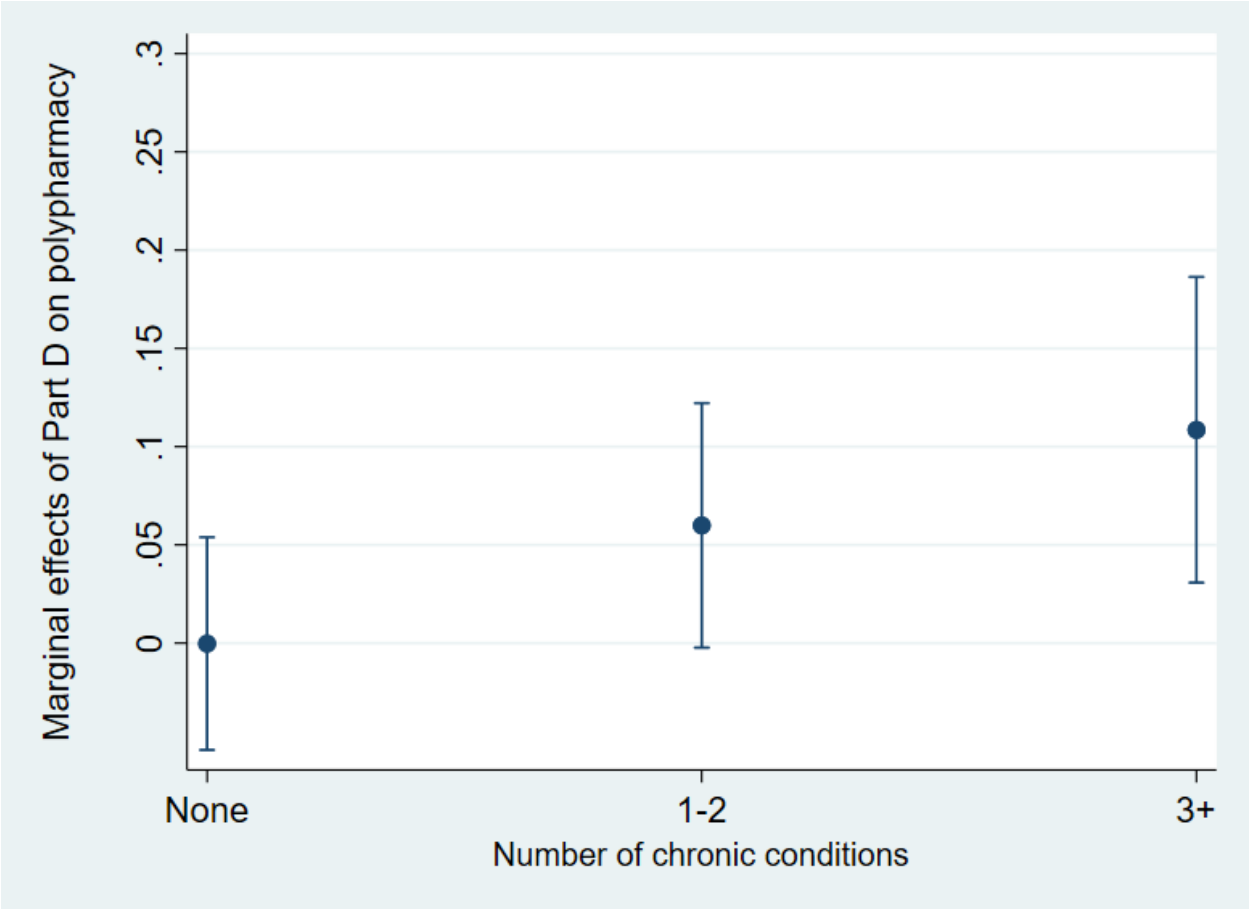
[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Figure 8: Marginal Effects (with 95% Confidence Intervals) of Medicare Part D on Polypharmacy by Household Poverty Thresholds Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.



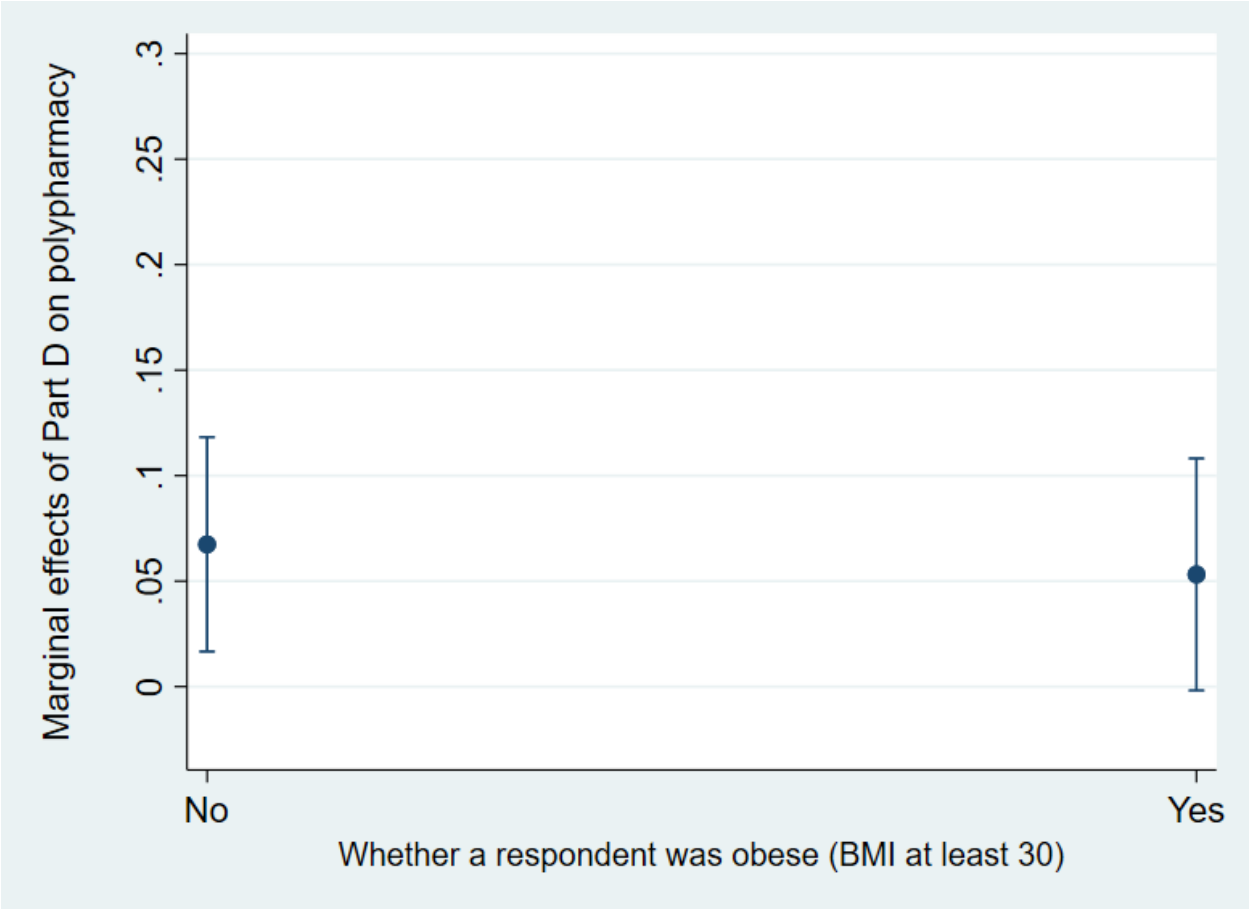
[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Figure 9: Marginal Effects (with 95% Confidence Intervals) of Medicare Part D on Polypharmacy by Number of Chronic Conditions Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.



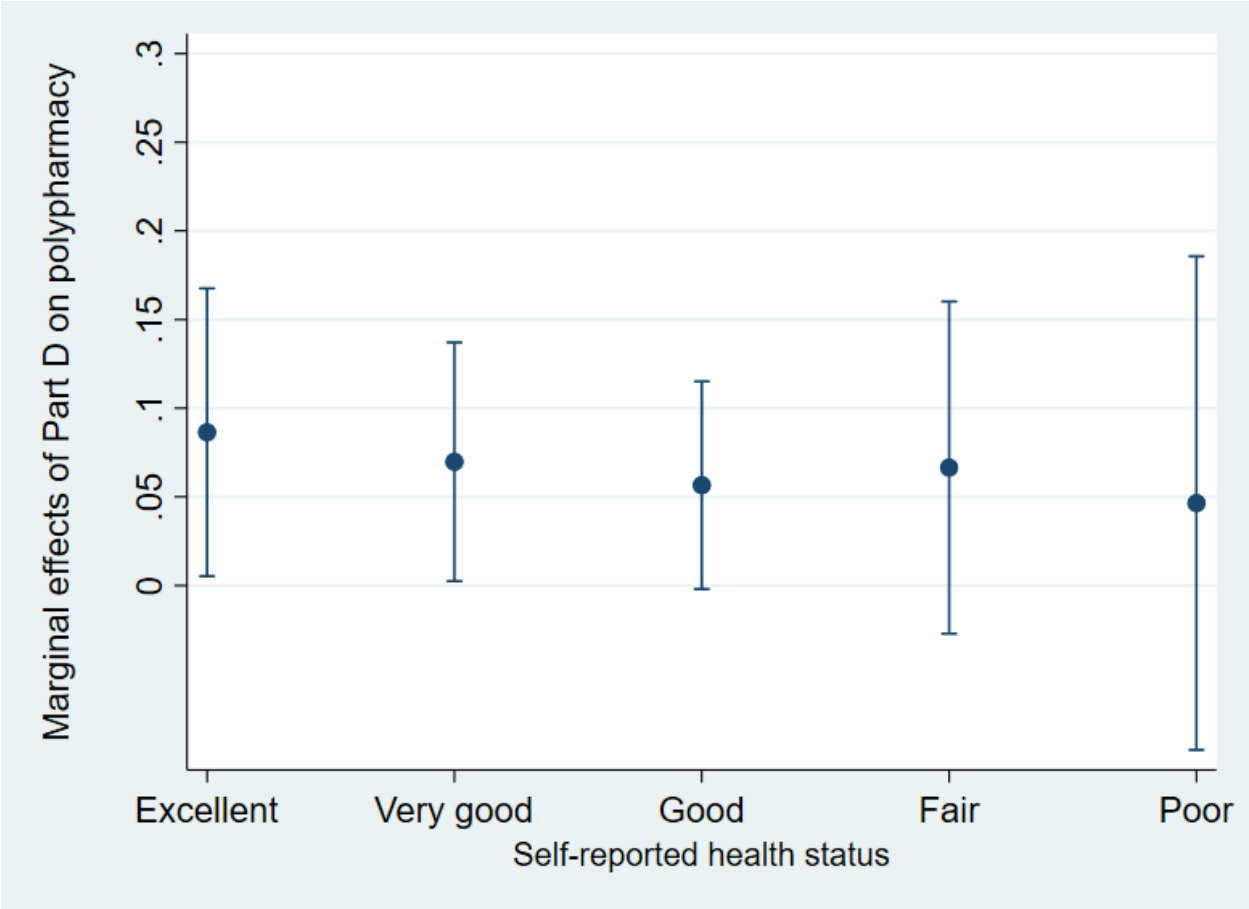
[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Figure 10: Marginal Effects (with 95% Confidence Intervals) of Medicare Part D on Polypharmacy by Obesity Status Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.



[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Figure 11: Marginal Effects (with 95% Confidence Intervals) of Medicare Part D on Polypharmacy by Self-Reported Health Status Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.



[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Table 3: Linear and Logit Regressions of The Impact of Medicare Part D on Dietary Supplement Use and Poly-Supplementation Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.

	Model 1: no covariates		Model 2: Model 1 + demographic covariates		Model 3: Model 2 + health insurance		Model 4: Model 3 + income		Model 5: Model 4 + health conditions	
Outcomes: Use of supplements past month	Count	Used 5+	Count	Used 5+	Count	Used 5+	Count	Used 5+	Count	Used 5+
	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)
Ages 65-74 (vs. 55-64)	0.173 (0.120)	1.148 (0.151)	0.048 (0.206)	0.927 (0.215)	-0.004 (0.206)	0.893 (0.209)	0.058 (0.207)	0.938 (0.221)	0.049 (0.204)	0.936 (0.219)
Post 2006	-0.146 (0.145)	0.768 (0.123)	-0.166 (0.214)	0.705 (0.185)	-0.163 (0.210)	0.703 (0.180)	-0.164 (0.207)	0.707 (0.179)	-0.148 (0.206)	0.718 (0.185)
Ages 65-74 * post 2006	0.149 (0.177)	1.325 (0.261)	0.149 (0.170)	1.364 (0.283)	0.148 (0.170)	1.369 (0.284)	0.136 (0.168)	1.337 (0.276)	0.126 (0.166)	1.338 (0.278)
Mean outcome	1.955	0.131	1.955	0.131	1.955	0.131	1.955	0.131	1.955	0.131
No. respondents	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055

Notes: + p < 0.1, * p < 0.05, ** p < 0.01, *** p<0.001. All analyses excluded survey cycle in 2005-2006 that overlapped with the introduction of Part D.

[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Demographic covariates include age, age squared, race (non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic others, and Hispanic), gender, marital status (married or cohabiting, widowed/divorced/separated, never married), education (less than high school graduate, high school graduate, some college, college graduate or above), and nativity/citizenship status (citizen born in the US, citizen born abroad, not a citizen). Health insurance indicates whether a person has any type of health insurance. Income covariates include household poverty level (less than 100%, 100-199%, 200-299%, 300-399%, 400-499%, 500% or more). Health condition covariates include the number of chronic conditions (none, one or two, and three or more conditions), whether a person is overweight or obese (BMI of at least 25), and self-reported health status (excellent, very good, good, fair, and poor).

Table 4: Linear and Logit Regressions of The Impact of Medicare Part D on Medication Use and Polypharmacy Among U.S. Adults Aged 55-74 With Public Insurance[a]. Data Source: NHANES 1999-2012.

	Model 1: no covariates		Model 2: Model 1 + demographic covariates		Model 3: Model 2 + income		Model 4: Model 3 + health conditions	
Outcomes: Use of prescription medications	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx
	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)
Ages 65-74 (vs. 55-64)	0.669+ (0.386)	1.642+ (0.435)	0.235 (0.550)	1.933 (0.812)	0.274 (0.552)	1.851 (0.788)	-0.134 (0.426)	1.693 (0.828)
Post 2006	0.254 (0.363)	1.204 (0.263)	0.250 (0.469)	1.061 (0.294)	0.243 (0.495)	1.004 (0.323)	0.571 (0.377)	1.371 (0.455)
Ages 65-74 * post 2006	0.145 (0.550)	1.007 (0.338)	0.174 (0.511)	0.974 (0.318)	0.084 (0.496)	0.971 (0.331)	0.177 (0.377)	0.986 (0.378)
Mean outcome	4.087	0.398	4.087	0.398	4.087	0.398	4.087	0.398
Number of respondents	1,190	1,190	1,190	1,190	1,190	1,190	1,190	1,190

Notes: + p < 0.1, * p < 0.05, ** p < 0.01, *** p<0.001. All analyses excluded survey cycle in 2005-2006 that overlapped with the introduction of Part D.

[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Demographic covariates include age, age squared, race (non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic others, and Hispanic), gender, marital status (married or cohabiting, widowed/divorced/separated, never married), education (less than high school graduate, high school graduate, some college, college graduate or above), and nativity/citizenship status (citizen born in the US, citizen born abroad, not a citizen). Health condition covariates include the number of chronic conditions (none, one or two, and three or more conditions), whether a person is overweight or obese (BMI of at least 25), and self-reported health status (excellent, very good, good, fair, and poor).

Table 5: Sensitivity Analyses for Linear and Logit Regressions of The Impact of Medicare Part D on Medication Use and Polypharmacy Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2016.

	Model 1: no covariates		Model 2: Model 1 + demographic covariates		Model 3: Model 2 + health insurance		Model 4: Model 3 + income		Model 5: Model 4 + health conditions	
Outcomes: Use of prescription medications	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx	Rx count	Used 5+ Rx
	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)
Panel A: Difference-in-differences. Sample of individuals without public insurance coverage[a] in all years (1999-2016)										
Ages 65-74 (vs. 55-64)	0.937***	1.823***	0.014	0.995	-0.093	0.931	-0.131	0.894	-0.203	0.776
	(0.123)	(0.188)	(0.208)	(0.171)	(0.211)	(0.160)	(0.211)	(0.154)	(0.171)	(0.143)
Post 2006	0.144	1.081	0.508***	2.027***	0.498***	2.021***	0.507***	2.043***	0.392*	2.056**
	(0.106)	(0.127)	(0.146)	(0.322)	(0.135)	(0.318)	(0.136)	(0.326)	(0.164)	(0.466)
Ages 65-74 * post 2006	0.406*	1.301*	0.447**	1.328*	0.452**	1.334*	0.465**	1.357*	0.401**	1.506**
	(0.164)	(0.171)	(0.162)	(0.174)	(0.162)	(0.176)	(0.158)	(0.177)	(0.137)	(0.224)
Mean outcome	2.908	0.232	2.908	0.232	2.908	0.232	2.908	0.232	2.908	0.232
No. respondents	8,158	8,158	8,158	8,158	8,158	8,158	8,158	8,158	8,158	8,158
Panel B: Difference-in-differences. Sample of individuals without public insurance coverage[a], excluding the Great Recession (1999-2004 and 2011-2016)										
Ages 65-74 (vs. 55-64)	0.937***	1.823***	0.107	1.110	-0.000	1.026	-0.070	0.952	-0.130	0.827
	(0.123)	(0.188)	(0.246)	(0.227)	(0.249)	(0.211)	(0.249)	(0.196)	(0.199)	(0.184)
Post 2006	0.181	1.116	0.548***	2.108***	0.534***	2.099***	0.545***	2.126***	0.404*	2.117**
	(0.115)	(0.139)	(0.152)	(0.347)	(0.139)	(0.343)	(0.142)	(0.356)	(0.168)	(0.505)
Ages 65-74 * post 2006	0.354+	1.271	0.396*	1.293+	0.402*	1.302+	0.427*	1.348*	0.388*	1.547*
	(0.194)	(0.186)	(0.190)	(0.188)	(0.189)	(0.191)	(0.181)	(0.195)	(0.161)	(0.271)
Mean outcome	2.895	0.232	2.895	0.232	2.895	0.232	2.895	0.232	2.895	0.232
No. respondents	5,741	5,741	5,741	5,741	5,741	5,741	5,741	5,741	5,741	5,741
Panel C: Difference-in-differences. Sample of individuals with health insurance, excluding those with public insurance coverage[a] in all years (1999-2016)										
Ages 65-74 (vs. 55-64)	0.802***	1.656***	-0.136	0.904	-0.136	0.904	-0.181	0.869	-0.278	0.742
	(0.143)	(0.196)	(0.230)	(0.170)	(0.230)	(0.170)	(0.230)	(0.164)	(0.191)	(0.153)

Post 2006	0.128	1.037	0.454**	1.898***	0.454**	1.898***	0.460**	1.913***	0.298*	1.830**
	(0.124)	(0.137)	(0.152)	(0.309)	(0.152)	(0.309)	(0.152)	(0.313)	(0.144)	(0.412)
Ages 65-74 * post 2006	0.409*	1.341*	0.466**	1.382*	0.466**	1.382*	0.479**	1.405*	0.455**	1.614**
	(0.182)	(0.196)	(0.175)	(0.199)	(0.175)	(0.199)	(0.171)	(0.200)	(0.153)	(0.267)
Mean outcome	3.039	0.245	3.039	0.245	3.039	0.245	3.039	0.245	3.039	0.245
No. respondents	6,836	6,836	6,836	6,836	6,836	6,836	6,836	6,836	6,836	6,836

Notes: + p < 0.1, * p < 0.05, ** p < 0.01, *** p<0.001. All analyses excluded survey cycle in 2005-2006 that overlapped with the introduction of Part D.
[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Demographic covariates include age, age squared, race (non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic others, and Hispanic), gender, marital status (married or cohabiting, widowed/divorced/separated, never married), education (less than high school graduate, high school graduate, some college, college graduate or above), and nativity/citizenship status (citizen born in the US, citizen born abroad, not a citizen). Health insurance indicates whether a person has any type of health insurance. Income covariates include household poverty level (less than 100%, 100-199%, 200-299%, 300-399%, 400-499%, 500% or more). Health condition covariates include the number of chronic conditions (none, one or two, and three or more conditions), whether a person is overweight or obese (BMI of at least 25), and self-reported health status (excellent, very good, good, fair, and poor).

Table 6: Linear and Logit Regressions of The Impact of Medicare Part D on Daily Use of Prescription Medications and Dietary Supplements Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.

	Model 1: no covariates		Model 2: Model 1 + demographic covariates		Model 3: Model 2 + health insurance		Model 4: Model 3 + income		Model 5: Model 4 + health conditions	
Outcomes: daily use of prescription medications or supplements last month	Count	Used 5+	Count	Used 5+	Count	Used 5+	Count	Used 5+	Count	Used 5+
	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)	Coeff. (SE)	OR (SE)
Panel A: Use of prescription medications										
Ages 65-74 (vs. 55-64)	0.930***	1.826***	0.119	1.100	0.026	1.032	-0.003	0.992	-0.146	0.856
	(0.122)	(0.200)	(0.220)	(0.209)	(0.223)	(0.198)	(0.223)	(0.190)	(0.180)	(0.174)
Post 2006	0.086	0.979	0.392*	1.458*	0.398**	1.464*	0.395*	1.455*	0.322+	1.420
	(0.115)	(0.140)	(0.159)	(0.254)	(0.151)	(0.251)	(0.154)	(0.253)	(0.170)	(0.319)
Ages 65-74 * post 2006	0.490*	1.385*	0.518**	1.409*	0.518**	1.409*	0.523**	1.432*	0.483**	1.614**
	(0.191)	(0.216)	(0.186)	(0.218)	(0.187)	(0.219)	(0.183)	(0.221)	(0.161)	(0.271)
Mean outcome	2.706	0.209	2.706	0.209	2.706	0.209	2.706	0.209	2.706	0.209
No. respondents	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055
Panel B: Use of dietary supplements										
Ages 65-74 (vs. 55-64)	0.203+	1.176	0.077	1.001	0.026	0.961	0.089	1.007	0.080	1.001
	(0.116)	(0.172)	(0.205)	(0.241)	(0.205)	(0.232)	(0.206)	(0.245)	(0.202)	(0.243)
Post 2006	-0.101	0.804	-0.116	0.738	-0.112	0.736	-0.113	0.741	-0.097	0.753
	(0.143)	(0.133)	(0.215)	(0.192)	(0.213)	(0.188)	(0.210)	(0.189)	(0.210)	(0.195)
Ages 65-74 * post 2006	0.112	1.256	0.110	1.281	0.110	1.285	0.097	1.253	0.087	1.254
	(0.175)	(0.260)	(0.167)	(0.277)	(0.168)	(0.279)	(0.166)	(0.270)	(0.164)	(0.269)
Mean outcome	2.040	0.124	2.040	0.124	2.040	0.124	2.040	0.124	2.040	0.124
No. respondents	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055

Notes: + p < 0.1, * p < 0.05, ** p < 0.01, *** p<0.001. All analyses excluded survey cycle in 2005-2006 that overlapped with the introduction of Part D.

[a]: Public insurance includes insurance programs that likely provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Demographic covariates include age, age squared, race (non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic others, and Hispanic), gender, marital status (married or cohabiting, widowed/divorced/separated, never married), education (less than high school graduate, high school graduate, some college, college graduate or above), and nativity/citizenship status (citizen born in the US, citizen born abroad, not a citizen). Health insurance indicates whether a person has any type of health insurance. Income covariates include household poverty level (less than 100%, 100-199%, 200-299%, 300-399%, 400-499%, 500% or more). Health condition covariates include the number of chronic conditions (none, one or two, and three or more conditions), whether a person is overweight or obese (BMI of at least 25), and self-reported health status (excellent, very good, good, fair, and poor).

Table 7: Logit Regressions of The Impact of Medicare Part D on Polypharmacy and Poly-Supplementation Using Different Numerical Thresholds Among U.S. Adults Aged 55-74 Without Public Insurance[a]. Data Source: NHANES 1999-2012.

	Used 1+	Used 2+	Used 3+	Used 4+	Used 5+	Used 6+	Used 7+	Used 8+	Used 9+	Used 10+
	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Panel A: Polypharmacy as outcomes										
Ages 65-74 (vs. 55-64)	0.952 (0.170)	0.905 (0.173)	0.747 (0.133)	0.822 (0.157)	0.834 (0.163)	0.986 (0.259)	0.554+ (0.167)	0.582 (0.194)	1.069 (0.491)	1.222 (0.615)
Post 2006	1.163 (0.278)	1.424+ (0.280)	1.266 (0.230)	1.283 (0.260)	1.399 (0.308)	1.393 (0.349)	1.321 (0.388)	2.156* (0.803)	1.969 (0.965)	2.344 (1.463)
Ages 65-74 * post 2006	1.028 (0.182)	0.928 (0.175)	1.217 (0.193)	1.494* (0.253)	1.572** (0.250)	1.239 (0.265)	1.766* (0.459)	1.924* (0.626)	2.487* (1.054)	2.641+ (1.388)
Mean outcome	0.782	0.612	0.458	0.320	0.218	0.146	0.098	0.067	0.043	0.029
No. respondents	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055
Panel B: Poly-supplementation as outcomes										
Ages 65-74 (vs. 55-64)	0.895 (0.146)	1.141 (0.183)	1.022 (0.197)	1.060 (0.212)	0.936 (0.219)	0.885 (0.293)	0.811 (0.322)	0.757 (0.328)	1.044 (0.605)	1.311 (0.867)
Post 2006	0.844 (0.136)	0.786 (0.139)	0.807 (0.142)	0.736 (0.141)	0.718 (0.185)	0.688 (0.208)	0.773 (0.298)	0.947 (0.425)	1.499 (0.790)	3.075 (2.470)
Ages 65-74 * post 2006	1.066 (0.157)	1.006 (0.137)	1.022 (0.147)	1.229 (0.205)	1.338 (0.278)	1.501 (0.407)	1.686 (0.625)	1.347 (0.588)	1.017 (0.540)	0.930 (0.570)
Mean outcome	0.714	0.485	0.315	0.202	0.131	0.083	0.051	0.036	0.025	0.019
No. respondents	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055	6,055

Notes: + p < 0.1, * p < 0.05, ** p < 0.01, *** p<0.001. All analyses excluded survey cycle in 2005-2006 that overlapped with the introduction of Part D.

[a]: Public insurance includes insurance programs that provided their beneficiaries with prescription drug benefits before Medicare Part D took effect in 2006, including Medicaid, military insurance, Indian health service programs, Children's Health Insurance Program, and any other state-sponsored or government health plans.

Each column is a separate regression model that controls for demographic, health insurance, income, and health covariates. Demographic covariates include age, age squared, race (non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic others, and Hispanic), gender, marital status (married or cohabiting, widowed/divorced/separated, never married), education (less than high school graduate, high school graduate, some college, college graduate or above), and nativity/citizenship status (citizen born in the US, citizen born abroad, not a citizen). Health insurance indicates whether a person has any type of health insurance. Income covariates include household poverty level (less than 100%, 100-199%, 200-299%, 300-399%, 400-499%, 500% or more). Health condition covariates include the number of chronic conditions (none, one or two, and three or more conditions), whether a person is overweight or obese (BMI of at least 25), and self-reported health status (excellent, very good, good, fair, and poor).

CHAPTER 3:

Utilization of Medications with Cognitive Impairment Side Effects and The Implications for Older Adults' Cognitive Function

Objective: Many medications have cognitive impairment, memory loss, amnesia, or dementia as side effects ("cognitive side effects" hereafter), but little is known about trends in the prevalence of these medications or their implications for population-level cognitive impairment.

Data source: I use data from the National Health and Nutrition Examination Survey (1999-2016) to describe trends in the use of medications with cognitive side effects among adults aged 60+ (N=16,937) and their implications for cognitive functioning (measured using word learning and recall, animal fluency, and digit symbol substitution assessments).

Principle findings: Between 1999-2000 and 2015-2016, the prevalence of older adults taking one, two, and at least three medications with cognitive side effects increased by 10.2%, 57.3%, and 298.7%, respectively. Compared to non-users, respondents who simultaneously used three or more medications with cognitive side effects scored 0.22 to 0.27 standard deviations lower in word learning and recall ($p = 0.02$), digit symbol substitution ($p < 0.01$), and the average standardized score of the three assessments ($p < 0.001$).

Conclusion: Concurrent use of medications with cognitive side effects among older adults has increased dramatically over the past two decades. The use of such medications is associated with cognitive impairment and may explain for disparities in cognitive function across subgroups. These findings highlight the need for cognitive screenings

among patients who consume medications with cognitive side effects. They also highlight the synergic effects of polypharmacy and potential drug-drug interactions that result in cognitive deficits.

Introduction

Adults aged 65 and older represent the fastest-growing population in the United States and their numbers are expected to nearly double by 2060, creating urgency around the prevention and treatment of aging-related health conditions (Federal Interagency Forum on Aging-Related Statistics, 2016). Cognitive impairment has emerged as a significant public health concern for older adults as it leads to a loss of independence, worsened quality of life, and increased disability, which in turn have important implications for individuals, families, and government programs (Hurd et al., 2013; Langa et al., 2008; Seeher et al., 2013). In 2002, more than ten million U.S. adults aged 70 and older lived with dementia or milder cognitive impairments without dementia, with an expected doubling by 2050 (Brenda L Plassman et al., 2007; Brenda L Plassman et al., 2008). Although the prevalence of cognitive impairment has declined gradually in the past decades due to better control of some key risk factors (Langa et al., 2017; Sheffield & Peek, 2011), substantial growth in the absolute number of older adults living with cognitive impairment continues to expand the scope of this public health concern.

Risk factors for cognitive impairment have been well-documented in the literature, including age, socio-demographic status, chronic conditions, and health behaviors (Livingston et al., 2017). Despite efforts to document a wide assortment of risk factors, little is known about the consequences of using medications with cognitive side effects on cognitive function among community-dwelling older adults. This is a potentially significant omission. Medications have become increasingly common among older adults. In 2011-2012, 40% of older adults reported using five or more medications in the past month, compared to 22% in 1999-2000. While pharmaceutical innovations are

critical for disease management and prevention, recent research has emphasized the adverse effects of commonly used medications on health, especially under conditions of polypharmacy (Qato et al., 2018). Particularly, older adults taking multiple medications simultaneously are two times more likely to experience adverse drug events and four times more likely to be hospitalized due to adverse drug events, compared to those taking fewer or no medications (Bourgeois et al., 2010; Marcum et al., 2012; Nguyen et al., 2006).

Prior studies on medications with cognitive side effects have produced contradictory results with respect to outcomes and statistical significance, potentially dampening the relevance of cognitive side effects in particular. Studies have found that benzodiazepines, lorazepam, and oxybutynin significantly increase the incidence of amnestic and non-amnestic cognitive impairments, while H(1)-antihistamine agents and tricyclic antidepressants only induce non-amnestic deficits in attention and information processing (Tannenbaum et al., 2012). Other studies have found that benzodiazepines, tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics are associated with an increased risk of Alzheimer's disease, raising concerns that the cognitive side effects of medications are irreversible and long-lasting (de Gage et al., 2014; Gray et al., 2015). Yet, a handful of studies have reported a trivial and potentially non-causal increase in cognitive deficits as a result of using benzodiazepine (Gray et al., 2016; Imfeld et al., 2015).

Further investigation of this topic is warranted, especially in the context of community dwelling adults. It is possible that cognitive side effects of medications are much more

pronounced in naturalistic and population settings. Many prior studies have been clinical in nature, exploring the effects of a single medication or a class of medication, or using relatively small and non-representative samples. For this reason, little is known about how frequently such medications are used in the adult population or about how the use of such medications has changed over time. Moreover, little is known about how many adults simultaneously consume multiple such medications and the consequences of such combinations for cognitive health. Even if much of the evidence suggests that the risks associated with a single medication are small or inconsistent, the total impact of medications with cognitive side effects on population-level cognitive health could be much larger, especially in a context of polypharmacy.

I follow the theoretical framework developed by Inouye & Charpentier (1996) to conceptualize the adverse effects of medications with cognitive side effects on the cognitive health of older adults. This model was originally developed to examine factors that predicted the onset of delirium – an acute disorder of attention and cognition – among hospitalized older adults, though the model can be extended and generalized for the purpose of this study. Risk factors for delirium are multifactorial, but they can be categorized into two interdependent groups factors: predisposing (baseline vulnerability) and precipitating (acute insult) risk factors. Predisposing risk factors documented in prior studies include demographic characteristics and pre-existing conditions (Francis, 1992; Inouye, 1994), while precipitating factors include medication administration, intercurrent illnesses, infections, malnutrition, and environment and psychosocial factors (Inouye & Charpentier, 1996). These factors do not operate individually, but rather interdependently. A patient with vulnerable baseline characteristics may develop delirium

regardless of any precipitating factors. In contrast, patients with low-risk baseline characteristics may require a high level of acute insult to develop delirium. Following this theoretical framework, I hypothesize that precipitating factors such as the use of medications with cognitive side effects is associated with an increased risk of cognitive impairment after controlling for predisposing factors such as socio-demographic characteristics and comorbidity.

This study improves the previous literature by using a nationally representative survey and a comprehensive database of medications that have been previously linked to cognitive impairment. This study has two aims:

1. What are the trends in the utilization of medications with cognitive side effects from 1999 to 2016 among adults aged 60 and older?
2. What is the relationship between cognitive function and concurrent use of medications with cognitive side effects for older adults?

Methods

I used the National Health and Nutrition Examination Survey (NHANES), a nationally representative survey of the civilian noninstitutionalized U.S. population. NHANES was obtained using a multistage probability sampling design to represent the general population but with an oversampling of Black, Hispanic, and adults aged 60 and older. The average non-response rate was 22%. All analyses used survey weight to produce nationally representative estimates and to avoid non-response bias. This study first relied on data from all nine most recent two-year cycles (1999-2000 to 2015-2016) to assess trends in the use of medications with cognitive side effects for adults aged 60 and older

(n=16,937). I then used data in 2011-2012 and 2013-2014 to investigate the association between cognitive function and the use of medications with cognitive side effects (n=2,908), after excluding 697 respondents who were not administered or did not complete all cognitive assessments and 27 respondents who were currently taking anti-dementia or anti-Parkinson's medications. Information on cognitive function was only available in these years.

Cognitive function was measured using a series of objective assessments that remained unchanged in both survey cycles, including word learning and recall, animal fluency, and digit symbol substitution. Respondents who needed a proxy informant or who did not understand any of languages offered by NHANES were not administered these assessments. Non-response among those administered the assessments ranged from 2% to 3%. The word leaning and recall assessment has been successfully implemented in major epidemiological studies in various ethnic and cultural contexts to investigate learning ability for new verbal information (Fillenbaum et al., 2008; Prince et al., 2003). The assessment was comprised of three trials and one delayed recall challenge. In each trial, respondents were asked to read out loud ten unrelated words, one at a time, as they were presented on a computer. Following the presentation, respondents were asked to recall as many words as possible. The delayed word recall challenge took place after the animal fluency and digit symbol substitution tests were completed (approximately 8-10 minutes following the start of the trials). Each correct word was worth one point, and the maximum score was ten.

The animal fluency assessment examined verbal fluency independent of educational attainment (Prince et al., 2003). The test has been proven to differentiate persons with normal cognition from those with mild and more-severe cognitive impairment (Henry et al., 2004). Respondents were instructed to name as many animals as they can in one minute. Each distinct animal was worth one point. The total observed score ranged from 3 to 40.

Finally, the digit symbol substitution assessment was adopted from the Wechsler Adult Intelligence Scale and was used to assess processing speed, sustained attention, and working memory (Dumont & Willis, 2008). The test was conducted on a sheet of paper that contained a key at the top with nine numbers, each paired with a symbol. Respondents had two minutes to copy the corresponding symbols to 133 boxes underneath adjoining numbers. Each correct symbol was worth one point, and the total observed score ranged from 0 to 105.

Using the total scores, I constructed two sets of outcome variables for each assessment. The first set of variables were the standardized scores for each assessment. The second set of variables were indicators for whether a respondent's score was more than one standard deviation below the mean. Finally, I constructed two composite variables to represent global cognitive function, an average standardized score of the three assessments and a binary indicator of whether a person's standardized scores were more than one standard deviation below the mean for at least two assessments. Although these measures cannot substitute for clinical diagnoses of cognitive impairment, they provided

meaningful information to study the association between cognitive impairment and medications with cognitive side effects.

Medications were recorded during the prescription medication interviews. Respondents were asked to show interviewers the containers of all medications they had taken last month. Respondents who could not show a container were asked to verbally report the medication's name. When interviewers entered medication names into a computer, more than 95% of entries resulted in exact or similar matches with an existing drug. The drug database used for the match was obtained from Lexicon Plus, a proprietary database of Cerner Multum that provided, on an annual basis a comprehensive list of all prescription and some non-prescription medications available in the U.S. market.

Medications with cognitive side effects were identified using Micromedex. Prior studies have independently established the accuracy and reliability of the adverse effects listed in Micromedex (Cheng et al., 2010). The database is based on several sources: the U.S. Food and Drug Administration's black box warnings, MedWatch, post-marketing surveillance, and comprehensive literature reviews. I identified 94 medications with cognitive side effects using a keyword search including the following words: cognitive impairment, cognitive decline, memory loss, amnesia, and dementia. This number of medications does not represent all medications with such side effects in the U.S market, but rather the number of medications with cognitive side effects that were consumed by respondents aged 60 and older in this study (see Table 1). I included all 94 medications with cognitive side effects, irrespective of any reported frequency of those side effects as reported in Micromedex. This decision likely underestimated the association between

cognitive function and the use of medications with cognitive side effects, though it is possible that small clinical trials underestimated the prevalence of side-effects among those who took the drug. Using the reported number of medications with cognitive side effects, I constructed a variable that indicated whether in the past 30 days a respondent took no medications with cognitive side effects (the reference category in the analysis model), one medication, two medications, or three or more medications with cognitive side effects. I created a similar variable for the use of medications *without* known cognitive side effects.

-Insert Table 1 About Here-

Length of time a respondent had been taking each medication was recorded during the prescription medication interviews. All responses were converted to days. Respondents who consumed multiple medications with cognitive side effects were assigned to a length of time that corresponded with the length of time for the medication they had been taking the longest. In secondary analyses, the use of medications with and without cognitive side effects was further classified into categories of duration of use (at most one year and more than one year).

Comorbidities that were potentially associated with cognitive health and/or the use of medications such as depression, obesity, and other health conditions were ascertained based on self-reports (Beydoun et al., 2008; Cherbuin et al., 2015; Livingston et al., 2017; Luppino et al., 2010). Depression was measured using a nine-item depression-screening instrument from the Patient Health Questionnaire (PHQ-9), which scored each of the nine *Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition*'s criteria

experienced in the past two weeks from “0” (not at all) to “3” (nearly every day). Respondents were classified as likely having depression if their total score was 10 or higher (Kroenke et al., 2001). Obesity was defined as having a body mass index of at least 30. Other health conditions were measured using a series of self-reported diagnoses of asthma, arthritis, cancer, congestive health failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, hypertension, diabetes, and sleep disorder. Each of these health conditions was introduced in the models as a binary variable.

Other covariates in this paper included socio-demographic characteristics, health behaviors, and access to medical services such as age, gender, marital status (married or living with a partner: reference category, widowed/divorced/separated, never married), educational attainment (less than high school: reference category, high school graduate, some college or two-year degree, college graduate or higher), poverty (less than 100% of federal poverty guideline: reference category, 100-199%, 200-299%, 300-399%, 400-499%, 500% or higher), citizenship, whether a person had any health insurance, whether a person had a routine place for medical care, and smoking (never smoked: reference category, smoked at least 100 cigarettes in the past but not a current smoker (former smoker), smoked at least 100 cigarettes in the past and currently smoke (current smoker)). I included a dummy variable for year to account for any trend in the outcome. To adjust for complex sampling, weighted prevalence estimates of medications with cognitive side effects in each year were calculated using Taylor linearization methods. The statistical significance of trends of medications with cognitive side effects was assessed using logistic regression. Weighted multivariate linear least-squared and logistic regression models were used to investigate the association between cognitive function

and the use of medications with cognitive side effects, controlling for potential confounders. I imputed missing data for all control variables using multiple imputation with chained equations. I generated ten imputed datasets and used them in all analyses. Most control variables had a small number of missing cases (<1%), except for depression and poverty status, which had up to 10% missing cases. Following conventions, I considered a p-value of less than 0.05 as statistically significant and I did not correct for multiple testing due to the exploratory nature of this study.

Results

Figure 1 presents the unadjusted (Panel A) and age/gender adjusted (Panel B) trends in utilization of medications with cognitive side effects from 1999 to 2016 for adults aged 60 and older. In Panel A, about 55.3% (95% CI, 51.3%-59.3%) of older adults did not consume any medications with cognitive side effects in 1999-2000. In 2015-2016, this estimate declined to 37.7% (95% CI, 34.3%-41.2%). The prevalence of older adults taking one medication with such side effects increased modestly by 3.2 percentage points (95% CI, -1.8%-8.3%) over the same period of time. The largest increase was concentrated among those who consumed two or more such medications. Relative to 1999-2000, the prevalence of older adults concurrently taking two or three or more medications with cognitive side effects in 2015-2016 went up by 5.8 percentage points (95% CI, 3.2%-8.4%) and 8.5 percentage points (95% CI, 6.5%-10.5%) respectively. Adjusting for age and gender (Panel B) did not significantly change the interpretation of the results. Table 2 lists 25 medications with the largest change over time in absolute prevalence. A large proportion of the total increase in the prevalence of medications with cognitive side effects was attributed to certain medications or classes of medication that

treated hypercholesterolemia, cardiovascular disease, gastrointestinal disease, and the central nervous system.

-Insert Figure 1 About Here-

-Insert Table 2 About Here-

Table 3 presents descriptive statistics for the use of medications with cognitive side effects, as well as cognitive function measurements and other covariates by the number of medications with cognitive side effects. Overall, 38.6% of respondents did not consume any medications with cognitive side effects, while 9.4% had been taking such medications for at most one year and 52% had been taking those medications for more than one year. Almost 8% of respondents used at least one prescription opioid[5] in the last 30 days, and such use of opioids increased as respondents consumed more medications with cognitive side effects.[6] Consistently across all cognitive measurements, those who took more medications with cognitive side effects scored lower on cognitive assessments. Compared to older adults who did not use any medications with cognitive side effects, those who consumed at least three such medications scored 0.29 standard deviations (SD) (95% CI, -0.43 to -0.14) lower in the average standardized score of the three tests, and

[5] Prescription opioids include all narcotic analgesics and narcotic analgesic combinations, excluding opioids that are often used in treatment for opioid dependence such as buprenorphine and naloxone.

[6] Several studies found that the use of opioids was harmful to cognitive health (Kamboj et al., 2005; Sjøgren et al., 2005). However, Micromedex did not classify any opioids as having cognitive side effects. This may be due to conflicting evidence regarding whether the use of opioid is associated with cognitive impairment (S. L. Chapman et al., 2002; Dublin et al., 2015). For information purposes, I included the prevalence of opioid use in the descriptive statistics table.

were 8.5 percentage points (95% CI, 3.0% to 14.0%) more likely to score more than one standard deviation below the mean for at least two of the tests.

-Insert Table 3 About Here-

Socio-demographic characteristics, health services utilization, health behaviors, and comorbidities also varied by the number of medications with cognitive side effects consumed. Compared to respondents who did not consume medications with cognitive side effects, those who consumed at least three medications with such side effects were more likely to also consume at least three medications *without* cognitive side effects, to be female, older, insured, U.S. citizens, former smokers, to have a routine place for medical care, to be obese, to report other health conditions, and were less likely to have a college degree or higher.

Table 4 presents results from the adjusted multivariate analyses. I found that respondents who consumed at least three medications with cognitive side effects scored 0.22 SD (95% CI, -0.34 to -0.10) lower in the average standardized score of the three assessments, and that this relationship was in part driven by the association between medications with such side effects and the word learning and recall assessment (coefficient, -0.24; 95% CI, -0.43 to -0.04) and the digit symbol substitution assessment (coefficient, -0.27; 95% CI, -0.42 to -0.12). There is no relationship between the use of medications with cognitive side effects and the animal fluency assessment (coefficient, -0.15; 95% CI, -0.33 to 0.03). I also found that taking numerous such medications was critical: the association between medications with cognitive side effects and cognitive function was small and not statistically significant for those taking fewer than three medications. Nonetheless, I

observed a dose-response relationship such that the association between medications with cognitive side effects and cognitive function generally increased over each category of additional medication.

-Insert Table 4 About Here-

In Table 5, I found similar patterns between medications with cognitive side effects and whether a respondent scored more than one standard deviation below the mean for each assessment. Particularly, compared to the reference group, individuals consuming at least three medications with cognitive side effects were about two times (OR, 2.10; 95% CI, 1.25 to 3.53) more likely to score more than one standard deviation below the mean for at least two tests, and this result was also driven by the relationship between medications with cognitive side effects and respondents' performance on the word learning and recall and the digit symbol substitution assessments.

-Insert Table 5 About Here-

In both Tables 4 and 5, I followed a previous study and introduced a categorical variable for the number of medications *without* cognitive side effects into the models (Qato et al., 2018). If the relationship between medications with cognitive side effects and cognitive function was driven by unobserved heterogeneity in health, the relationship between medications *without* cognitive side effects and cognitive function should be equally significant as that between medications with cognitive side effects and cognitive function. I found no significant relationship between medications *without* cognitive side effects and cognitive function, except for the digit symbol substitution and the composite outcomes

in Table 4, and in this case the coefficients were smaller than the coefficients for three or more medications with side effects.

In Table 6, I further classified the use of medications with and without cognitive side effects into categories of duration of use (at most one year and more than one year). Consistent with previous results in Tables 4 and 5, only the use of at least three medications with cognitive side effects was associated with cognitive deficits, and this association was unlikely to have been driven by the duration of use. I also found that more recent use (at most one year) of three or more medications with such side effects was more deleterious to cognitive health compared to having used three of more such medications for more than a year. Although the estimates were not significantly different from one another, these results potentially suggest that the negative consequences of medications with cognitive side effects might be short-term or reversible.

-Insert Table 6 About Here-

Finally, in Figures 2 to 6, I assessed the heterogeneous association between medications with cognitive side effects and the global cognitive score (average standardized score of the three assessments) by socio-demographic subgroups according to age, gender, educational attainment, race/ethnicity, and marital status. Overall, I observed the negative consequences of medications with cognitive side effects among all subgroups: among younger respondents (under 75 years of age), both men and women, all education subgroups (high school graduate or lower and college or higher), non-Hispanic whites, non-Hispanic others, and all marital status categories (married or cohabiting and not

married or cohabiting). The heterogeneity that exists across subgroups may be explained by the more frequent use of medications among certain subgroups.

-Insert Figures 2 to 6 About Here-

Discussion

To my knowledge, this study was the first to assess trends in the utilization of medications with cognitive side effects among U.S. community-dwelling older adults. I found that between 1999-2000 and 2015-2016, the prevalence of older adults taking one, two, or at least three medications with cognitive side effects increased by 10.2%, 57.3%, and 298.7%, respectively. Much of the increase in utilization of medications with cognitive side effects was attributed to an increase in consumption of medications that treated hypercholesterolemia, the central nervous system, or cardiovascular disease. Concurrent use of three or more such medications was associated with reductions in the global cognitive score, performance on the word learning and recall assessment, and performance on the digit symbol substitution assessments. These relationships persisted even after excluding individuals who were currently taking medications for dementia or Parkinson's disease, and after controlling for socio-demographic characteristics, access to health services, health behaviors, and health conditions. Medications without known cognitive side effects were not associated with declines in the cognitive tests scores.

The summary measures of the use of medications with cognitive side effects produced coefficients that were either similar to or smaller than those produced in studies of specific medications or types of medication. Using a longitudinal survey that was representative of the population aged 65 and older in England and Wales, Fox et al.

(2011) reported that exposure to at least one anticholinergic medication[7] at the baseline was associated with a reduction of 1.27% in the Mini-Mental State Examination score, compared to respondents who did not take any anticholinergics. Using a longitudinal survey in France, Ancelin et al. (2006) found that consistent users of anticholinergics scored 0.6 to 0.8 standard deviations lower in various cognitive tests. My estimates for the use of a single medication with cognitive side effects were much smaller than those in Ancelin et al. (2006), in part because I included in this study many medications other than anticholinergics that had smaller incidence rates of cognitive impairment. Nonetheless, this study contributed to the existing literature by demonstrating the increasing trend in prevalence of concurrent use of medications with cognitive side effects among community-dwelling older adults, and the association between the use of such medications and cognitive health under conditions of polypharmacy. I find that the use of three or more medications with side effects is much more consequential than the sum of three individual medications with side effects.

The role of medications in the cognitive performance of older adults has likely been underappreciated, especially when a decline in performance might reasonably be attributed to a normal aging process. Although there are numerous guidelines for the diagnosis and treatment of chronic physical diseases (Bingley et al., 2001; Chobanian et al., 2003; Criner et al., 2015; Wender et al., 2013), there are currently no guidelines for

[7] Examples include antiemetics, antispasmodics, bronchodilators, antiarrhythmic drugs, antihistamines, analgesics, antihypertensives, antiparkinsonian agents, corticosteroids, skeletal muscle relaxants, ulcer drugs, and psychotropic drugs

the screening of cognitive impairment. Part of this may reflect the limited clinical benefits of such screenings. Following a review of the literature, the U.S. Preventive Services Task Force (2015) concluded that there was insufficient evidence on the benefits of screening for cognitive impairment. Yet a large number of older adults report worrisome cognitive impairments (Aigbogun et al., 2017), and, given the trends documented here, medication use may play an increasingly important role in their experience. In tandem with a lack of clinical guidelines for screening cognitive impairment, the growing intensity of diagnosis and treatment for chronic and physical diseases may contribute significantly to cognitive impairment among older adults. Physicians could limit the risk of cognitive impairment from side effects by collecting information on their patients' cognitive function prior to and during drug administration and adjust prescriptions and doses accordingly.

The results also highlight the impact of polypharmacy. The most significant side effects documented in this study were limited to those taking three of more medications. Although most people who take medications with such side effects take only one or two, polypharmacy is increasingly common. In this study, about 9% of older adults took three or more medications with cognitive side effects in the past 30 days. Although the prevalence of older adults taking at least five medications increased by 81.8% from 1999-2000 to 2011-2012 (Kantor et al., 2015), the present study found that the prevalence of older adults taking at least three medications with cognitive side effects has increased considerably more over this baseline increase in polypharmacy, by almost 300% between 1999-2000 and 2015-2016. Polypharmacy may present unique risks for side effects, amplifying the effects of each of the medications in a set. Further, polypharmacy also

increases the risk of drug-drug interactions that may lead to negative cognitive outcomes. Prior research has shown that taking multiple medications is a risk factor for dementia and delirium, as well as other adverse events (Jyrkkä et al., 2011; Martin et al., 2000). Research on the reasons for an increase in polypharmacy is limited, though prior studies points to the growing presence of comorbidity (Slabaugh et al., 2010), the failure to consider comorbidity in clinical practice guidelines (Tinetti et al., 2004), visiting multiple providers (Col et al., 1990), and marked variation in patterns of medical practice of individual providers (Hovstadius & Petersson, 2012). Since exposure to adverse side effects is positively correlated with the number of medications taken (Marcum et al., 2012), efforts to reduce polypharmacy might also lessen exposure to multiple drugs with similar side effects. As the pharmaceutical treatment of chronic disease is increasingly common, future research should further investigate its spillover effects to other illnesses and symptoms.

To help guide clinical decisions, Table 7 provides the most common combinations of medications with cognitive side effects among respondents who consumed at least three such medications. Such combinations of medications in part reflect the common chronic conditions triad for U.S. older adults (Ward & Schiller, 2013). All combinations, for instance, include either antihyperlipidemic agents or proton pump inhibitors. While prior studies found no association between cognitive function and the use of antihyperlipidemic agents (Bitzur, 2016) or conflicting evidence in the case of proton pump inhibitors (Gomm et al., 2016; Kuller, 2016), most studies have only examined these medications individually. It is possible that the association between these medications and cognitive impairment is larger under conditions of polypharmacy,

especially when antihyperlipidemic agents or proton pump inhibitors are combined with other medications that have cognitive side effects. Although the clinical benefits of antihyperlipidemic agents and proton pump inhibitors might outweigh the risks of cognitive side effects, clinicians might want to be cautious when prescribing these medications in combination with others that also have cognitive side effects.

-Insert Table 7 About Here-

Some medications in Appendix Table 1 are available over the counter (OTC). An increase in the consumption of medications with cognitive side effect may be in part due to the rapidly growing availability of OTC medications (S.-A. Francis et al., 2005). Many Americans are either unaware of the side effects of OTC medications or incorrectly believe that such medications do not have significant side effects (Wilcox et al., 2005). Almost 60% of patients used OTC medications in the past month, but only 58% of those who used such medications informed their physician about it and, for their part, physicians only asked about OTC medications during 37% of visits (Sleath et al., 2001). The lack of communication between physicians and patients and the growing availability of OTC medications may result in duplicate prescribing of medications with cognitive side effects. Carefully monitoring patients' use of OTC medications can prevent the risk of combining OTC and prescription medications that both have cognitive side effects.

Finally, I found that medications with cognitive side effects were more debilitating to cognitive health among younger adults than among older adults (Figure 2). This finding suggests that the association between medications with cognitive side effect and cognitive function was not mainly driven by poor health in old ages. The finding also

implies that the selection into consuming these medications at young ages due to the early onset of chronic conditions and comorbidity can be more debilitating to cognitive health than those that occur at older ages (Huang et al., 2010). In addition, young adults generally have more cognitive abilities than older adults, as many cognitive abilities – such as conceptual reasoning, memory, and processing speed – gradually diminish over time (Harada et al., 2013). The low stock of cognitive abilities among older adults may in part explain why medications with cognitive side effects play a less important role in their cognitive health compared to that of younger adults.

While this study improved the previous literature by using nationally representative data and including a comprehensive list of all medications with cognitive side effects, it faced several limitations. First, I was not able to establish a causal relationship between cognitive function and medications with cognitive side effects. Due to the cross-sectional nature of the NHANES, it was challenging to determine whether medications with cognitive side effects caused cognitive impairment or if cognitive impairment led to the onset of other health conditions that required pharmaceutical treatment involving additional cognitive side effects. Second, the medications in this study not only involved cognitive side effects but also other side effects that might indirectly influence cognitive function. I addressed both issues by controlling for a comprehensive list of health conditions, including conditions that might influence a respondent's cognitive function, but there were likely other unobserved conditions that are influential. Third, although Micromedex is a reliable source of information on adverse side effects, it is possible that there were medications with cognitive side effects that were not included in the database. Fourth, since NHANES only collected data on outpatient and over-the-counter

medications, I lacked information on medications administered to inpatients at hospitals. To address some forms of unobserved heterogeneity, I followed another similar study and included in all analysis models the number of medications *without* any known cognitive side effects (Qato et al., 2018). I found that there was almost no association between medications without such side effects and cognitive function. This suggests both that unobserved heterogeneity with respect to health is unlikely to explain the results and that there were few medications with cognitive side effects that have not been correctly identified by Micromedex. Finally, the data lacked information on dosage of medications associated with cognitive side effects. This is an important omission because the association between medications with cognitive side effects and cognitive health may depend on the treatment intensity. I did, however, attempt to test the effects of treatment intensity in other ways. In a secondary analysis presented in Table 4, I further classified the use of medications with and without cognitive side effects into categories of duration of use (at most one year and more than one year). I found that the association between medications with cognitive side effects and cognitive function was unlikely to have been driven by differences in the duration of use. I also found that more recent use (at most one year) of three or more medications with such side effects was more deleterious to cognitive health compared to having used three or more medications for more than a year, a result consistent with the fact that side-effects occur as a consequence of the recent use of medication. While the duration of medications cannot perfectly substitute for information on dosage, duration of use does reflect the long-run amount of medication that a person has been consuming prior to the interview.

Conclusion

This study demonstrated a strong relationship between taking multiple medications with cognitive side effects and cognitive functioning. Almost 9% of older adults take three or more such medications, and this percentage is likely to increase more in the future. The investigation of cognitive side effects is an important frontier for future research and could help to explain important trends and disparities. Research on the population-level implications of medication use could help to explain, among other things, the decline in intelligence test scores beginning in the 21st century (Flynn & Shayer, 2018), as well as some of the apparent sociodemographic variation in cognitive function among older adults (Zaninotto et al., 2018).

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Table 1. Medications with Cognitive Side Effects Consumed by U.S. Adults Aged 60+ in NHANES from 1999-2000 to 2015-2016

Acamprosate	Fluorouracil	Pantoprazole
Alprazolam	Fluoxetine	Phenobarbital
Amitriptyline	Fluvastatin	Phenytoin
Amitriptyline Hydrochloride/Perphenazine	Heparin	Pitavastatin
Atorvastatin	Hydrochlorothiazide/Propranolol	Pravastatin
Baclofen	Ibuprofen	Prednisolone
Bendroflumethiazide/Nadolol	Interferon Alfa-2A	Pregabalin
Benztropine	Isoniazid	Progesterone
Ciprofloxacin	Ketoprofen	Promethazine
Clomipramine	Lamotrigine	Propafenone
Clonazepam	Leuprolide	Propranolol
Conjugated Estrogens	Levetiracetam	Pyridoxine
Cyclopentolate	Levofloxacin	Quinidine
Cyclophosphamide	Lorazepam	Rabeprazole
Cyclosporine	Lovastatin	Ramelteon
Cyproheptadine	Meclizine	Ribavirin
Dexlansoprazole	Mefloquine	Rosuvastatin
Diazepam	Methocarbamol	Scopolamine
Diltiazem	Methotrexate	Simvastatin
Dorzolamide	Methyldopa	Tamsulosin
Dronabinol	Montelukast	Temazepam
Enzalutamide	Moxifloxacin	Testosterone
Esomeprazole	Naproxen	Tolterodine
Estazolam	Niacin/Simvastatin	Topiramate
Esterified Estrogens	Nifedipine	Trazodone

Estradiol	Nortriptyline	Tretinoin
Estradiol/Norethindrone	Ofloxacin	Triazolam
Estradiol/Norgestimate	Omeprazole	Valproic Acid
Conjugated Estrogens/Medroxyprogesterone Acetate	Omeprazole/Sodium Bicarbonate	Zaleplon
Estrogens/Methyltestosterone	Oxcarbazepine	Zolmitriptan
Estropipate	Oxybutynin	Zolpidem
Etidronate		

Figure 1. Unadjusted and Adjusted Weighted Prevalence of U.S. Adults Aged 60+ Taking Medications with Cognitive Side Effects, with 95% Confidence Intervals. Data Source: NHANES 1999-2000 to 2015-2016.

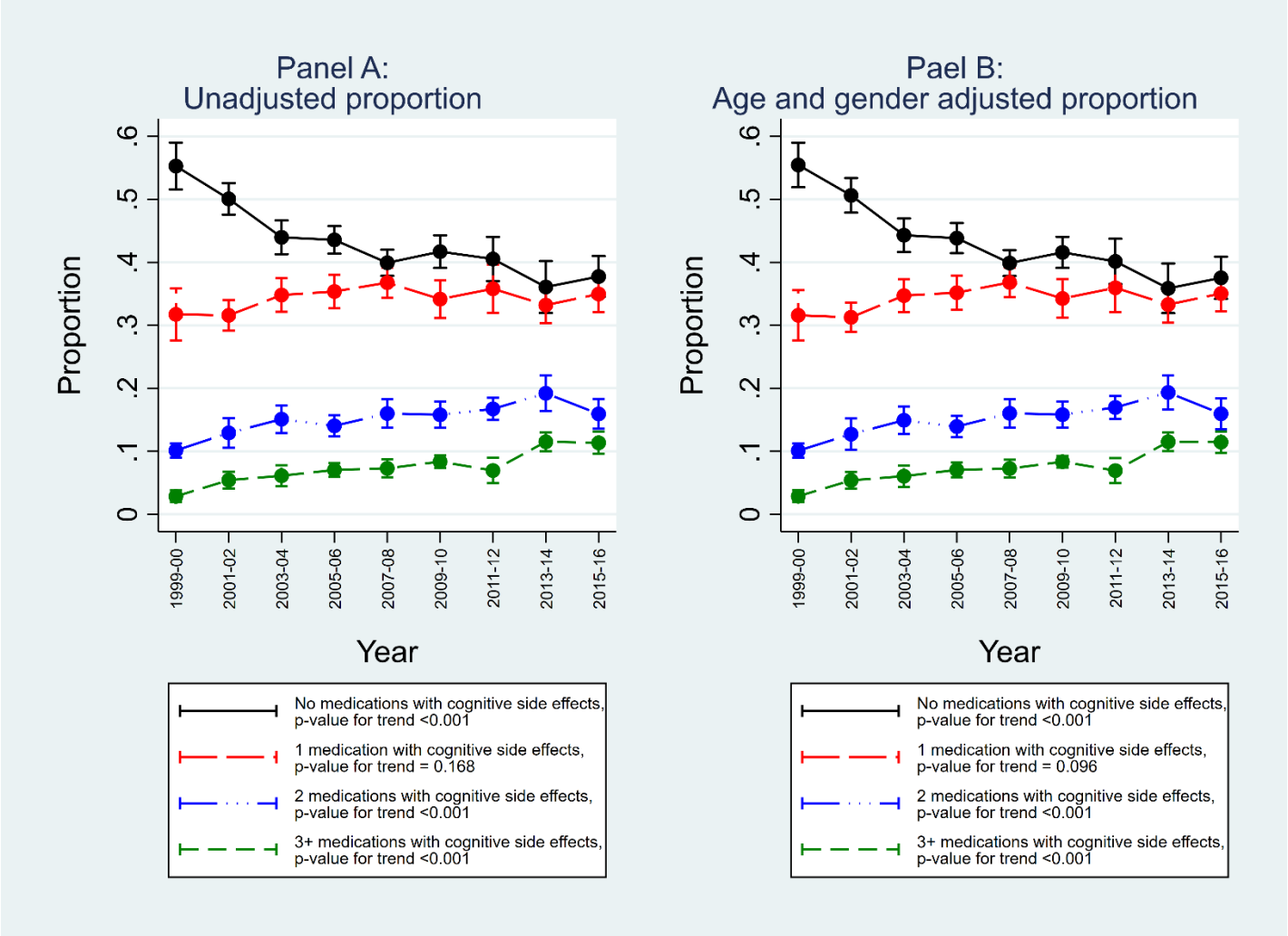


Table 2. Top 25 Medications with the Largest Change in Utilization Among U.S. Adults Aged 60+ from 1999-2000 to 2015-2016. Data Source: NHANES 1999-2000 to 2015-2016.

Medications	Weighted Prevalence of Utilization Among U.S. Adults Aged 60+ (%)									Difference Between 2015-2016 and 1999-2000 (%)	P-value for Trend [a]
Survey cycles:	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016		
Simvastatin	5.81	7.20	8.09	10.74	13.45	18.94	18.68	14.97	14.35	8.54	<0.001
Atorvastatin	7.36	10.67	13.38	16.06	14.44	9.40	9.63	15.05	14.99	7.63	<0.001
Conjugated estrogens	7.08	10.35	3.18	1.60	2.12	1.33	1.07	0.83	0.60	-6.48	<0.001
Omeprazole	4.48	4.48	2.44	4.34	7.23	9.29	9.95	12.44	10.43	5.94	<0.001
Pravastatin	2.45	2.56	3.46	1.60	2.46	2.74	4.82	5.60	7.12	4.67	<0.001
Rosuvastatin	0.00	0.00	0.51	0.87	2.47	3.24	3.37	6.77	4.54	4.54	<0.001
Gabapentin	0.55	1.98	2.18	1.84	2.79	3.12	3.60	4.67	4.34	3.79	<0.001
Tamsulosin	0.76	1.24	2.54	2.61	2.56	3.03	3.53	4.34	4.43	3.67	<0.001
Esomeprazole	0.00	0.00	3.56	4.53	4.75	3.96	2.81	2.94	3.28	3.28	0.11
Nifedipine	3.38	2.52	2.22	1.90	1.27	1.86	1.18	0.85	0.83	-2.55	<0.001
Pantoprazole	0.05	1.32	2.96	2.25	2.04	2.02	1.60	3.69	2.58	2.53	<0.001
Montelukast	0.44	0.94	1.57	1.50	1.90	2.43	1.27	1.91	2.97	2.53	0.001
Lovastatin	0.98	1.60	1.73	3.60	3.16	4.04	3.25	3.15	2.90	1.92	<0.001
Propranolol	2.30	1.17	1.57	2.19	1.45	0.62	1.03	0.78	0.43	-1.86	0.001
Diltiazem	3.89	4.78	4.23	3.92	2.86	2.13	1.77	1.95	2.07	-1.82	<0.001
Pregabalin	0.00	0.00	0.00	0.16	0.27	1.11	0.34	0.99	1.70	1.70	<0.001
Zolpidem	1.01	0.75	1.65	1.84	1.65	1.88	1.39	3.02	2.47	1.47	0.003
Fluoxetine	0.86	1.31	1.20	1.34	2.01	1.69	0.81	2.70	2.29	1.44	0.01
Meclizine	1.87	1.34	1.28	0.53	1.11	0.76	0.88	0.63	0.44	-1.43	0.05
Fluvastatin	1.33	1.04	1.04	0.96	0.41	0.02	0.00	0.00	0.00	-1.33	0.01
Alprazolam	1.63	1.34	2.36	2.08	2.63	1.02	1.88	3.30	2.89	1.26	0.02
Cyclosporine	0.00	0.25	0.05	0.36	0.21	0.44	0.28	0.72	1.23	1.23	0.02
Clonazepam	0.30	0.57	0.63	0.42	0.81	1.06	1.78	0.77	1.44	1.14	0.001
Naproxen	1.96	1.47	1.54	1.55	1.70	1.15	1.68	1.41	0.92	-1.04	0.83
Baclofen	0.02	0.00	0.10	0.12	0.10	0.48	0.24	0.35	0.90	0.87	0.003
No. observations	1834	1872	1901	1570	2154	2073	1791	1841	1901		

[a]: P-value is obtained from logistic regression.

Table 3. Descriptive Statistics of Cognitive Function Measurements and Covariates Among U.S. Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.

	All respondents		Number of medications with cognitive side effects taken by respondents								P-value [a]
			None		1 medication		2 medications		3+ medications		
	N=2,908		N=1,180		N=941		N=526		N=261		
Cognitive assessment score, mean[c] (SD)[c]											
Word learning and recall	6.3	(2.3)	6.4	(2.3)	6.2	(2.2)	6.1	(2.4)	6.0	(2.3)	0.04
Animal fluency	18.2	(5.7)	18.7	(6.0)	18.0	(5.1)	17.9	(5.8)	17.3	(6.0)	0.03
Digit symbol substitution	52.3	(16.8)	54.3	(17.0)	52.2	(16.0)	50.3	(17.0)	47.5	(16.7)	< 0.001
Whether score was more than 1 standard deviation (SD) below the mean, N[b] (%)[c]											
Word learning and recall	432	(11.4)	148	(9.3)	142	(12.1)	97	(14.0)	45	(12.9)	0.08
Animal fluency	691	(15.9)	266	(14.8)	210	(14.1)	138	(17.3)	77	(24.8)	0.02
Digit symbol substitution	846	(16.9)	323	(14.0)	250	(16.0)	179	(20.0)	94	(26.9)	< 0.001
Composite global cognitive function											
Average standardized score of 3 tests, mean[c] (SD)[c]	-0.0	(1.00)	0.1	(1.03)	-0.0	(0.93)	-0.1	(1.02)	-0.2	(1.00)	< 0.001
Whether 2+ test scores were more than one SD below the mean, N[b] (%)[c]	543	(11.4)	200	(9.7)	155	(9.6)	128	(15.3)	60	(18.2)	< 0.001
Whether used medications WITH cognitive side effects last 30 days, N[b] (%)[c]											
None	1180	(38.6)									
1 medication	941	(34.7)									
2 medications	526	(17.7)									
3+ medications	261	(9.0)									
Whether used medications WITHOUT cognitive side effects last 30 days, N[b] (%)[c]											
None	557	(18.5)	430	(34.2)	95	(11.8)	23	(5.2)	9	(3.1)	< 0.001
1 medication	490	(17.8)	275	(25.8)	136	(15.4)	65	(11.5)	14	(5.3)	< 0.001
2 medications	470	(17.6)	179	(16.5)	175	(19.9)	96	(21.0)	20	(6.4)	< 0.001
3+ medications	1391	(46.1)	296	(23.5)	535	(52.9)	342	(62.4)	218	(85.2)	< 0.001
Whether used medications WITH cognitive side effects last 30 days and duration of use, N[b] (%)[c]											
None	1180	(38.6)	N/A		N/A		N/A		N/A		
Used 1+ medication, at most 1 year	298	(9.4)	N/A		218	(21.4)	63	(8.8)	17	(4.5)	< 0.001
Used 1+ medication, > 1 year	1430	(52.0)	N/A		723	(78.6)	463	(91.2)	244	(95.5)	< 0.001

Whether used medications WITHOUT cognitive side effects last 30 days and duration of use, N[b] (%)[c]											
None	557	(18.5)	430	(34.2)	95	(11.8)	23	(5.2)	9	(3.1)	< 0.001
Used 1+ medication, at most 1 year	261	(8.2)	128	(11.6)	79	(7.3)	35	(4.1)	19	(5.2)	< 0.001
Used 1+ medication, > 1 year	2090	(73.3)	622	(54.2)	767	(80.9)	468	(90.7)	233	(91.8)	< 0.001
Whether used any prescription opioid last 30 days, N[b] (%)[c]											
	254	(7.9)	39	(3.3)	78	(6.2)	63	(11.3)	74	(27.9)	< 0.001
Race & ethnicity, N[b] (%)[c]											
Non-Hispanic White	1380	(79.5)	494	(77.0)	468	(80.7)	271	(80.3)	147	(83.7)	0.09
Hispanic	550	(7.0)	266	(8.7)	150	(5.6)	91	(6.7)	43	(5.8)	0.03
Non-Hispanic Black	697	(8.4)	288	(8.7)	230	(8.6)	123	(8.2)	56	(7.3)	0.76
Non-Hispanic others	281	(5.0)	132	(5.6)	93	(5.1)	41	(4.8)	15	(3.1)	0.22
Gender, N[b] (%)[c]											0.03
Women	1493	(54.1)	597	(53.7)	471	(50.6)	275	(56.8)	150	(64.1)	
Men	1415	(45.9)	583	(46.3)	470	(49.4)	251	(43.2)	111	(35.9)	
Age groups, N[b] (%)[c]											
60-69	1581	(56.8)	736	(62.0)	463	(53.4)	243	(50.6)	139	(59.7)	0.004
70-79	855	(29.3)	293	(26.6)	317	(32.1)	175	(32.2)	70	(24.7)	0.03
80+	472	(13.9)	151	(11.4)	161	(14.5)	108	(17.2)	52	(15.6)	0.04
Marital status, N[b] (%)[c]											
Married or partnered	1676	(65.1)	669	(62.7)	553	(67.3)	306	(65.7)	148	(66.2)	0.22
Widowed/divorced/separated	1063	(30.5)	426	(31.6)	337	(28.8)	198	(31.6)	102	(30.5)	0.71
Never married	165	(4.3)	83	(5.7)	49	(3.9)	22	(2.7)	11	(3.4)	0.12
Education, N[b] (%)[c]											
Less than high school	741	(15.7)	290	(13.0)	223	(15.5)	156	(20.1)	72	(19.4)	0.05
High school graduate	680	(22.1)	268	(20.5)	228	(23.9)	124	(22.5)	60	(20.9)	0.41
Some college	816	(31.6)	323	(31.9)	275	(31.5)	133	(29.5)	85	(34.6)	0.71
College graduate or above	668	(30.6)	297	(34.6)	215	(29.1)	112	(28.0)	44	(25.1)	0.03
Poverty, N[b] (%)[c]											
<100% poverty threshold	455	(9.4)	182	(9.4)	136	(8.7)	81	(9.3)	56	(12.0)	0.18
100-199%	794	(23.6)	319	(24.0)	247	(22.7)	159	(25.6)	69	(21.7)	0.55
200-299%	376	(15.3)	155	(14.2)	121	(14.5)	63	(17.2)	37	(19.7)	0.41
300-399%	323	(13.4)	115	(12.2)	121	(14.1)	58	(14.1)	29	(14.7)	0.63
400-499%	207	(10.5)	80	(10.1)	72	(10.9)	40	(10.3)	15	(10.5)	0.98
500%+	505	(27.8)	217	(30.1)	173	(29.0)	83	(23.5)	32	(21.4)	0.13
U.S. citizenship, N[b] (%)[c]											< 0.001
Not U.S. citizen	198	(2.6)	134	(4.7)	41	(1.6)	15	(1.0)	8	(1.0)	
U.S. citizen	2707	(97.4)	1044	(95.3)	899	(98.4)	511	(99.0)	253	(99.0)	

Had any health insurance, N[b] (%)[c]											< 0.001
Yes	2666	(94.5)	1005	(90.5)	903	(97.0)	505	(97.7)	253	(96.0)	
No	238	(5.5)	173	(9.5)	37	(3.0)	20	(2.3)	8	(4.0)	
Had routine place for medical care, N[b] (%)[c]											< 0.001
Yes	2739	(95.7)	1032	(91.0)	925	(98.3)	523	(99.6)	259	(98.7)	
No	169	(4.3)	148	(9.0)	16	(1.7)	3	(0.4)	2	(1.3)	
Smoking status, N[b] (%)[c]											
Never smoked	1432	(49.6)	633	(53.9)	454	(49.3)	242	(47.1)	103	(37.8)	0.004
Former smoker	1106	(39.3)	376	(34.4)	385	(40.9)	221	(40.8)	124	(51.8)	0.002
Current smoker	368	(11.0)	170	(11.8)	101	(9.9)	63	(12.1)	34	(10.4)	0.79
Health conditions, N[b] (%)[c]											
Asthma	401	(13.9)	124	(11.7)	122	(11.0)	80	(15.4)	75	(31.7)	< 0.001
Arthritis	1417	(49.9)	428	(37.9)	468	(48.1)	326	(65.2)	195	(78.1)	< 0.001
Cancer	589	(24.0)	203	(22.5)	209	(25.2)	116	(23.5)	61	(27.4)	0.51
Congestive heart failure	202	(6.7)	41	(3.5)	67	(6.5)	60	(12.4)	34	(10.0)	< 0.001
Coronary heart disease	261	(9.4)	35	(2.6)	100	(11.4)	84	(17.4)	42	(15.4)	< 0.001
Heart attack	244	(8.5)	45	(3.1)	88	(9.7)	83	(16.3)	28	(11.5)	< 0.001
Angina	157	(5.8)	26	(1.6)	57	(5.9)	45	(11.2)	29	(13.0)	< 0.001
Emphysema	106	(4.6)	23	(2.7)	34	(3.8)	26	(7.3)	23	(10.8)	< 0.001
Bronchitis	207	(7.7)	71	(6.7)	61	(6.6)	44	(11.0)	31	(9.4)	0.15
Stroke	200	(6.3)	53	(4.6)	69	(6.4)	50	(8.2)	28	(9.7)	0.07
Hypertension	1257	(39.4)	507	(39.6)	398	(39.7)	237	(37.7)	115	(40.5)	0.90
Diabetes	678	(20.4)	155	(10.2)	272	(25.5)	159	(28.1)	92	(28.7)	< 0.001
Sleep disorder	946	(34.5)	261	(23.1)	301	(33.3)	226	(44.8)	158	(67.9)	< 0.001
Depression (PHQ-9), N[b] (%)[c]											< 0.001
Yes (score >= 10)	258	(7.2)	73	(4.5)	68	(5.9)	67	(10.4)	50	(17.7)	
No (score < 10)	2602	(92.8)	1085	(95.5)	857	(94.1)	452	(89.6)	208	(82.3)	
Obese, N[b] (%)[c]											0.003
Yes (BMI >= 30)	1081	(37.7)	380	(32.9)	371	(37.1)	207	(42.4)	123	(51.8)	
No (BMI < 30)	1778	(62.3)	779	(67.1)	560	(62.9)	307	(57.6)	132	(48.2)	

[a]: P-value indicates if means are significantly different across respondents who took none, one, two, or at least three medications with cognitive side effects, based on logistics regression, survey weights, and 10 imputed datasets.

[b]: Unweighted and non-imputed raw frequency. The numbers may not add up to the total due to missing data.

[c]: Weighted estimates.

Table 4. Adjusted Linear Least-Squared Regressions of Standardized Cognitive Test Scores on Utilization of Medications with Cognitive Side Effects for Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.

Outcome:	Standardized scores			Composite measure
	Word learning and recalls	Animal Fluency	Digit Symbol Substitution	Average standardized score of three tests
	Coef. (SE)	Coef. (SE)	Coef. (SE)	Coef. (SE)
Whether taking medications WITH cognitive side effects				
None (reference)				
1 medication	-0.02 (0.06)	-0.04 (0.06)	0.00 (0.06)	-0.02 (0.05)
2 medications	-0.10 (0.06)	0.01 (0.08)	-0.03 (0.07)	-0.04 (0.05)
3+ medications	-0.24* (0.09)	-0.15 (0.09)	-0.27** (0.07)	-0.22*** (0.06)
Whether taking medications WITHOUT cognitive side effects				
None (reference)				
1 medication	0.00 (0.07)	-0.10 (0.08)	-0.11 (0.08)	-0.07 (0.05)
2 medications	-0.10 (0.06)	-0.05 (0.08)	-0.07 (0.07)	-0.07 (0.05)
3+ medications	-0.07 (0.05)	-0.07 (0.08)	-0.17* (0.06)	-0.10* (0.05)
Race & ethnicity				
Non-Hispanic White (reference)				
Hispanic	-0.20** (0.06)	-0.23*** (0.06)	-0.58*** (0.05)	-0.34*** (0.05)
Non-Hispanic Black	-0.15* (0.06)	-0.49*** (0.05)	-0.65*** (0.05)	-0.43*** (0.04)
Non-Hispanic others	0.11 (0.08)	-0.46*** (0.10)	-0.09 (0.07)	-0.15* (0.05)
Female	0.36*** (0.04)	0.00 (0.05)	0.34*** (0.03)	0.23*** (0.03)
Age (in years)	-0.05*** (0.00)	-0.04*** (0.00)	-0.05*** (0.00)	-0.05*** (0.00)
Marital status				
Married or living with partner (reference)				
Widowed, divorced, separated	-0.05 (0.04)	0.02 (0.05)	-0.02 (0.04)	-0.02 (0.03)
Never married	-0.02 (0.11)	-0.04 (0.13)	-0.02 (0.10)	-0.03 (0.09)
Educational attainment				
Less than high school (reference)				
High school graduate	0.05 (0.07)	0.13* (0.05)	0.39*** (0.04)	0.19*** (0.04)
Some college or AA degree	0.23*** (0.06)	0.42*** (0.05)	0.61*** (0.04)	0.42*** (0.03)
College graduate or above	0.26* (0.10)	0.72*** (0.08)	0.77*** (0.05)	0.59*** (0.06)
Poverty				

<100% federal guideline (reference)				
100-199%	-0.01 (0.06)	0.05 (0.06)	0.10 (0.06)	0.05 (0.05)
200-299%	0.14 (0.08)	0.05 (0.09)	0.24** (0.06)	0.14* (0.05)
300-399%	0.18* (0.08)	0.08 (0.09)	0.41*** (0.07)	0.22*** (0.05)
400-499%	0.05 (0.09)	0.13 (0.08)	0.44*** (0.08)	0.21** (0.06)
500%+	0.17 (0.09)	0.13 (0.08)	0.38*** (0.08)	0.23** (0.07)
Not U.S. citizen	-0.21** (0.07)	-0.26* (0.11)	-0.46*** (0.07)	-0.31*** (0.07)
Has any health insurance	0.09 (0.07)	0.10 (0.12)	0.14 (0.08)	0.11 (0.06)
Has routine place for medical care	0.17* (0.07)	-0.01 (0.12)	0.07 (0.08)	0.08 (0.07)
Smoking				
Never smoked (reference)				
Smoked 100+ cigarettes, not current smoker	0.05 (0.06)	0.02 (0.05)	0.02 (0.05)	0.03 (0.04)
Smoked 100+ cigarettes, current smoker	-0.00 (0.07)	0.01 (0.09)	-0.15* (0.06)	-0.04 (0.05)
Depression (PHQ-9 >= 10)	-0.10 (0.07)	-0.25** (0.07)	-0.17 (0.09)	-0.17** (0.05)
Obese (BMI >= 30)	0.09 (0.05)	0.07 (0.05)	0.06 (0.04)	0.07 (0.04)
Year fixed effect (2013-2014 vs. 2011-2012)	0.33*** (0.06)	-0.03 (0.05)	-0.04 (0.04)	0.09* (0.03)
Health conditions [a]	Yes	Yes	Yes	Yes
No. observations	2,908	2,908	2,908	2,908

Notes: [a] Health conditions include a set of binary indicators for whether a person has ever been told by a health professional that they have asthma, arthritis, cancer, congestive health failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, diabetes, hypertension, and sleep disorder.

* p<0.05, ** p<0.01, *** p<0.001. Standard errors are in parentheses. All analyses were weighted using survey weights.

Table 5. Adjusted Logistic Regressions of Whether Cognitive Assessment Scores Are More Than One Standard Deviation Below the Mean on Utilization of Medications with Cognitive Side Effects for Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.

	Whether scores are one standard deviation below the mean			**Composite measure**
Outcome:	Word learning and recalls	Animal Fluency	Digit Symbol Substitution	Whether 2+ test scores are more than one standard deviation below the mean
	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Whether taking medications WITH cognitive side effects				
None (reference)				
1 medication	1.38* (0.22)	0.77 (0.12)	1.20 (0.18)	0.88 (0.15)
2 medications	1.55* (0.28)	0.85 (0.13)	1.34 (0.29)	1.38 (0.23)
3+ medications	2.04* (0.64)	1.59 (0.39)	2.82*** (0.67)	2.10** (0.54)
Whether taking medications WITHOUT cognitive side effects				
None (reference)				
1 medication	0.68 (0.15)	1.10 (0.27)	0.98 (0.24)	0.92 (0.23)
2 medications	1.08 (0.25)	0.98 (0.25)	0.61* (0.14)	0.82 (0.21)
3+ medications	0.83 (0.18)	1.41 (0.33)	1.22 (0.28)	1.28 (0.27)
Race & ethnicity				
Non-Hispanic White (reference)				
Hispanic	1.60* (0.35)	1.62* (0.34)	4.54*** (0.77)	2.28** (0.56)
Non-Hispanic Black	1.39 (0.30)	3.23*** (0.55)	5.18*** (0.83)	3.25*** (0.82)
Non-Hispanic others	0.69 (0.18)	2.46*** (0.53)	0.99 (0.19)	1.18 (0.32)
Female	0.60* (0.11)	0.88 (0.15)	0.51*** (0.09)	0.70* (0.12)
Age (in years)	1.13*** (0.02)	1.09*** (0.01)	1.15*** (0.01)	1.14*** (0.02)
Marital status				
Married or living with partner (reference)				
Widowed, divorced, separated	0.93 (0.17)	1.12 (0.18)	1.21 (0.22)	1.14 (0.14)
Never married	1.20 (0.45)	1.18 (0.34)	1.61 (0.51)	1.66 (0.60)
Educational attainment				
Less than high school (reference)				

High school graduate	1.06 (0.21)	0.75 (0.12)	0.37*** (0.05)	0.61* (0.12)
Some college or AA degree	0.74 (0.13)	0.41*** (0.07)	0.20*** (0.03)	0.29*** (0.06)
College graduate or above	0.51** (0.12)	0.34*** (0.07)	0.15*** (0.03)	0.21*** (0.04)
Poverty				
<100% federal guideline (reference)				
100-199%	0.88 (0.17)	0.93 (0.17)	0.91 (0.17)	1.01 (0.21)
200-299%	0.73 (0.21)	0.91 (0.23)	0.58** (0.11)	0.64 (0.18)
300-399%	0.51* (0.14)	0.67 (0.14)	0.25*** (0.06)	0.44* (0.13)
400-499%	0.58 (0.19)	0.65 (0.23)	0.30*** (0.09)	0.47* (0.17)
500%+	0.65 (0.23)	0.60 (0.18)	0.39** (0.12)	0.51 (0.23)
Not U.S. citizen	1.37 (0.37)	1.82 (0.76)	3.75*** (0.89)	2.07* (0.55)
Has any health insurance	0.90 (0.25)	1.07 (0.27)	0.76 (0.19)	0.79 (0.20)
Has routine place for medical care	0.55 (0.23)	0.70 (0.22)	0.43* (0.13)	0.42* (0.14)
Smoking				
Never smoked (reference)				
Smoked 100+ cigarettes, not current smoker	0.61* (0.11)	1.00 (0.14)	0.85 (0.12)	0.72* (0.11)
Smoked 100+ cigarettes, current smoker	0.85 (0.22)	1.11 (0.22)	1.42 (0.38)	1.19 (0.25)
Depression (PHQ-9 >= 10)	1.48 (0.34)	1.87*** (0.29)	1.69* (0.42)	2.18*** (0.40)
Obese (BMI >= 30)	0.79 (0.13)	0.80 (0.12)	0.74 (0.14)	0.72 (0.12)
Year fixed effect (2013-2014 vs. 2011-2012)	0.55*** (0.09)	0.89 (0.09)	1.00 (0.14)	0.81 (0.13)
Health conditions [a]	Yes	Yes	Yes	Yes
Number of observations	2,908	2,908	2,908	2,908

Notes: [a] Health conditions include a set of binary indicators for whether a person has ever been told by a health professional that they have asthma, arthritis, cancer, congestive health failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, diabetes, hypertension, and sleep disorder.

* p<0.05, ** p<0.01, *** p<0.001. Standard errors are in parentheses. All analyses were weighted using survey weights.

Table 6. Adjusted Linear and Logistic Regressions of Composite Cognitive Measures on Utilization of Medications with Cognitive Side Effects and Duration of Using These Medications for Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.

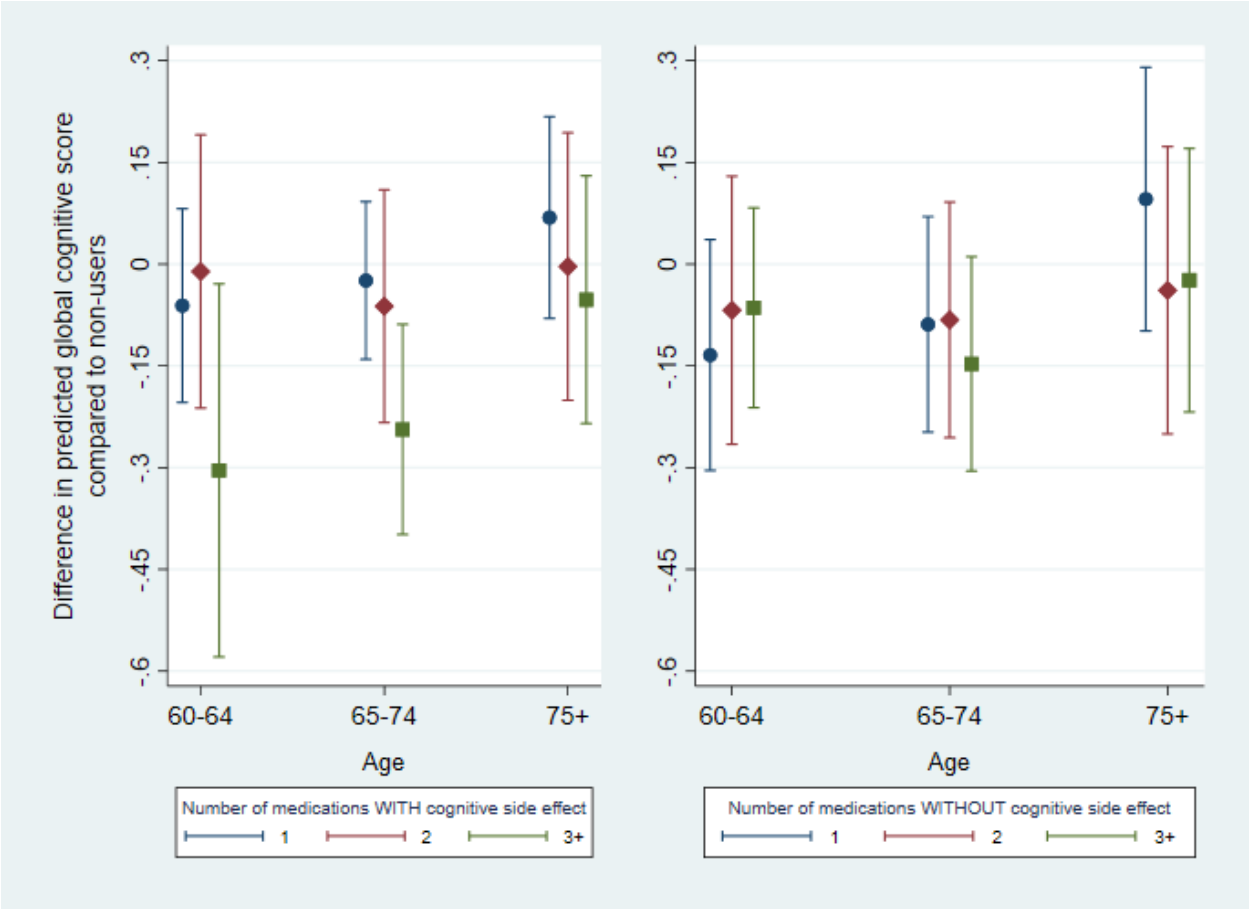
	Global cognitive measures	
Outcome:	Average standardized score of the 3 tests	Whether 2+ test scores are more than one standard deviation below the mean
	Coef. (SE)	OR (SE)
Whether taking medications WITH cognitive side effects and duration of using such medications		
None (reference)		
1 medication		
At most one year	-0.00 (0.07)	0.81 (0.21)
More than one year	-0.01 (0.05)	0.87 (0.14)
2 medications		
At most one year	-0.08 (0.09)	1.02 (0.38)
More than one year	-0.02 (0.05)	1.35 (0.22)
3+ medications		
At most one year	-0.69** (0.25)	14.80** (11.38)
More than one year	-0.19** (0.06)	1.79* (0.48)
Whether taking medications WITHOUT cognitive side effects and duration of using such medications		
None (reference)		
1 medication		
At most one year	-0.07 (0.06)	0.98 (0.42)
More than one year	-0.04 (0.06)	0.76 (0.20)
2 medications		

At most one year	0.01 (0.08)	0.48 (0.25)
More than one year	-0.06 (0.06)	0.79 (0.22)
3+ medications		
At most one year	0.04 (0.15)	1.37 (0.59)
More than one year	-0.09 (0.04)	1.12 (0.24)
Number of observations	2,908	2,908

Notes: All analyses controlled for race, age, gender, marital status, educational attainment, poverty, citizenship, health insurance coverage, whether the person has a routine place for medical care, smoking status, binary indicator for each self-reported health condition (asthma, arthritis, cancer, congestive health failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, diabetes, hypertension, and sleep disorder), depression (PHQ-9 scale), obesity (BMI of at least 30), and time trends.

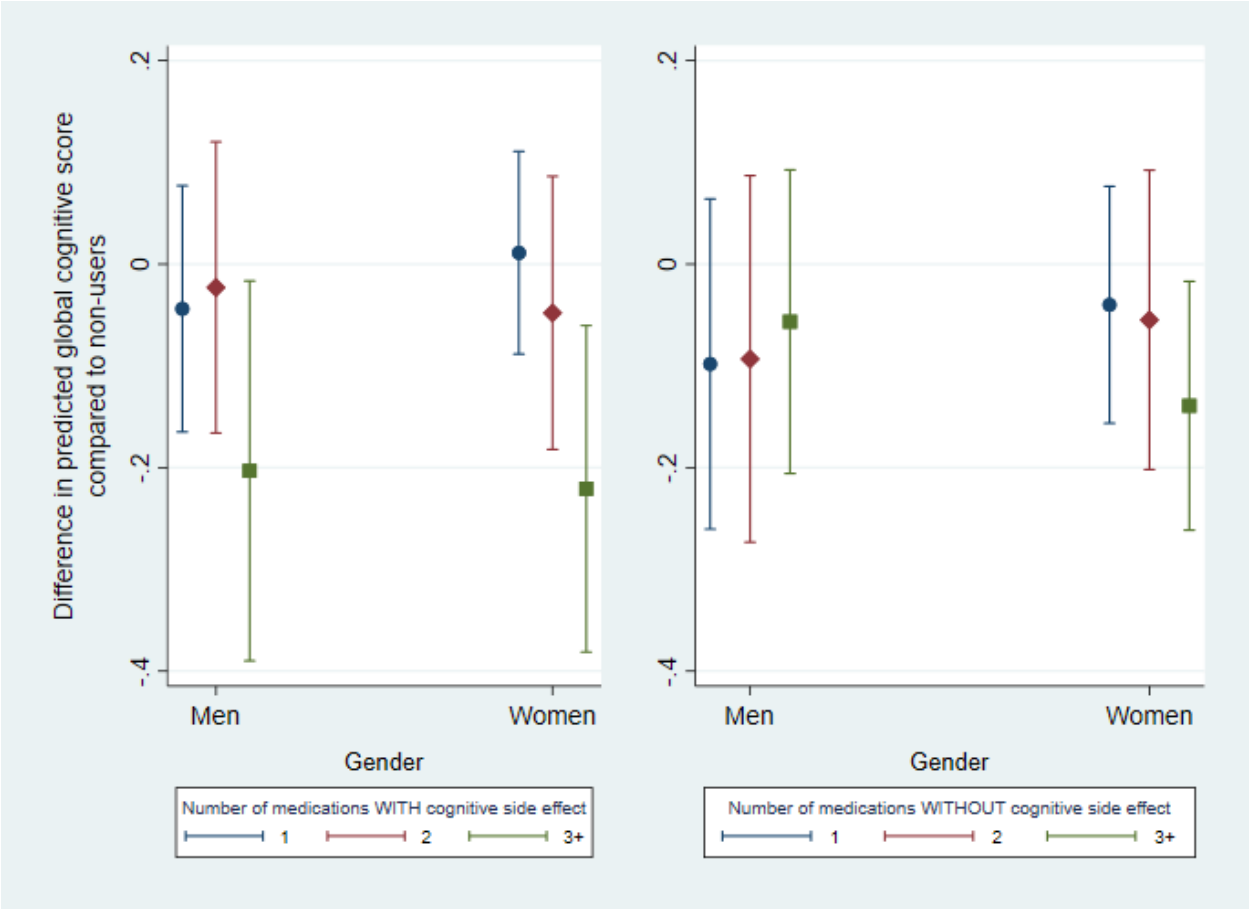
* $p<0.05$, ** $p<0.01$, *** $p<0.001$. Standard errors are in parentheses. All analyses were weighted using survey weights.

Figure 2: Marginal Effects (with 95% Confidence Intervals) of Medications With/Without Cognitive Side Effects on Global Cognitive Score by Age Among Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.



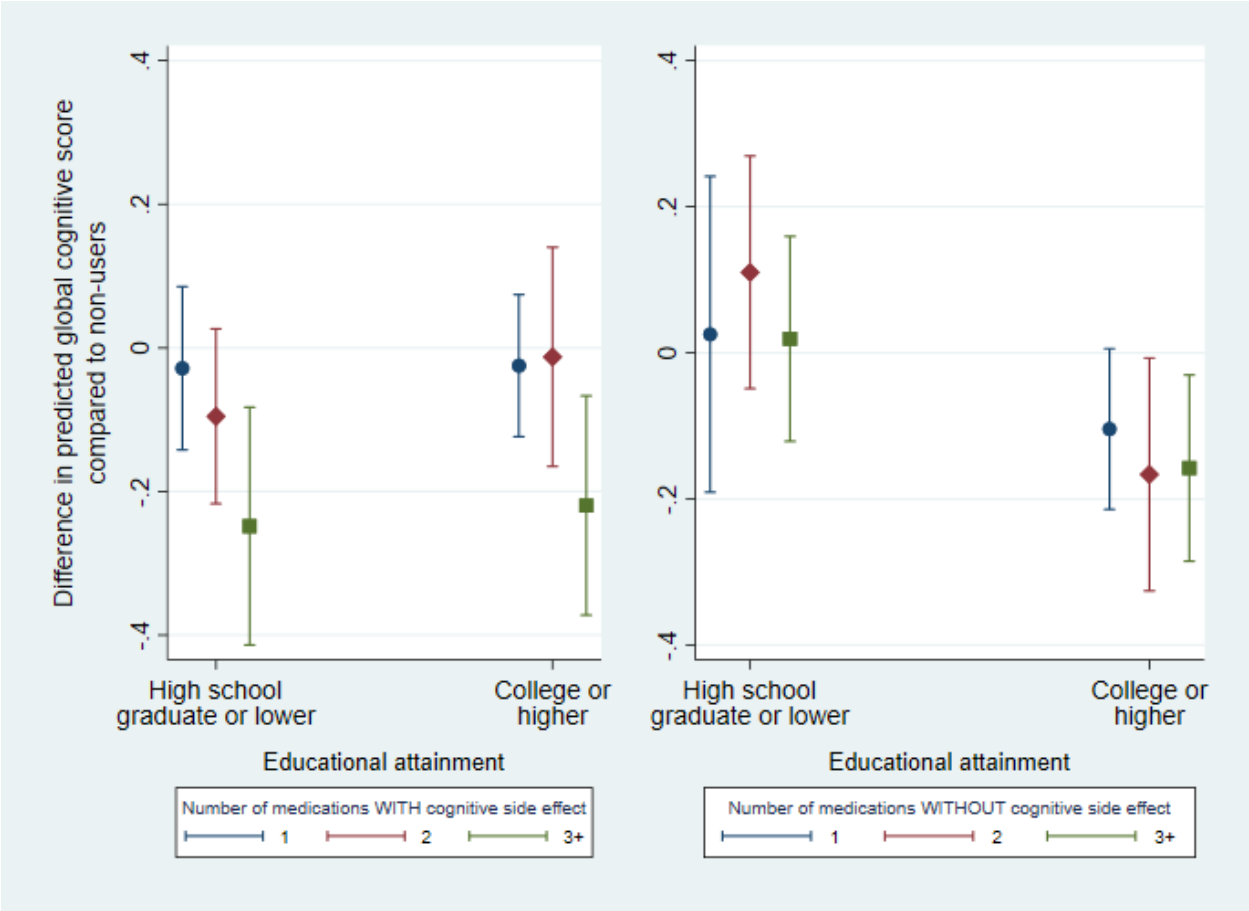
Notes: The marginal effects were calculated from the linear regression of the global cognitive score (average of the three standardized cognitive assessment scores) on the interactions between medications with/without cognitive side effects and age groups (60-64, 65-74, and 75+), while controlling for other covariates such as race, gender, marital status, educational attainment, poverty, citizenship, health insurance coverage, whether the person has a routine place for medical care, smoking status, binary indicator for each self-reported health condition (asthma, arthritis, cancer, congestive health failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, diabetes, hypertension, and sleep disorder), depression (PHQ-9 scale), obesity (BMI of at least 30), and time trends.

Figure 3: Marginal Effects (with 95% Confidence Intervals) of Medications With/Without Cognitive Side Effects on Global Cognitive Score by Gender Among Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.



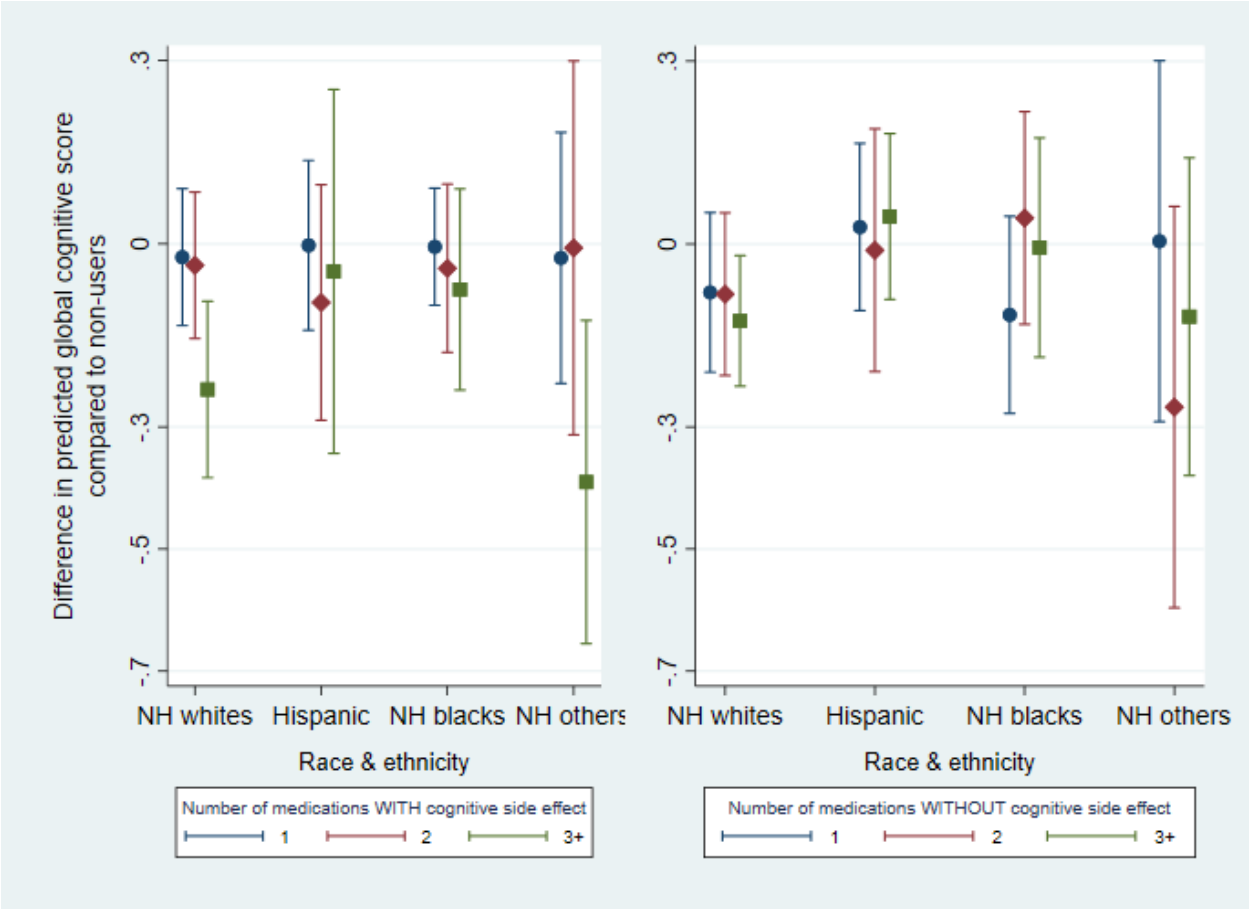
Notes: The marginal effects were calculated from the linear regression of the global cognitive score (average of the three standardized cognitive assessment scores) on the interactions between medications with/without cognitive side effects and gender, while controlling for other covariates such as race, age, marital status, educational attainment, poverty, citizenship, health insurance coverage, whether the person has a routine place for medical care, smoking status, binary indicator for each self-reported health condition (asthma, arthritis, cancer, congestive health failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, diabetes, hypertension, and sleep disorder), depression (PHQ-9 scale), obesity (BMI of at least 30), and time trends.

Figure 4: Marginal Effects (with 95% Confidence Intervals) of Medications With/Without Cognitive Side Effects on Global Cognitive Score by Educational Attainment Among Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.



Notes: The marginal effects were calculated from the linear regression of the global cognitive score (average of the three standardized cognitive assessment scores) on the interactions between medications with/without cognitive side effects and educational attainment (high school graduate or lower and college or higher), while controlling for other covariates such as race, gender, age, marital status, poverty, citizenship, health insurance coverage, whether the person has a routine place for medical care, smoking status, binary indicator for each self-reported health condition (asthma, arthritis, cancer, congestive health failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, diabetes, hypertension, and sleep disorder), depression (PHQ-9 scale), obesity (BMI of at least 30), and time trends.

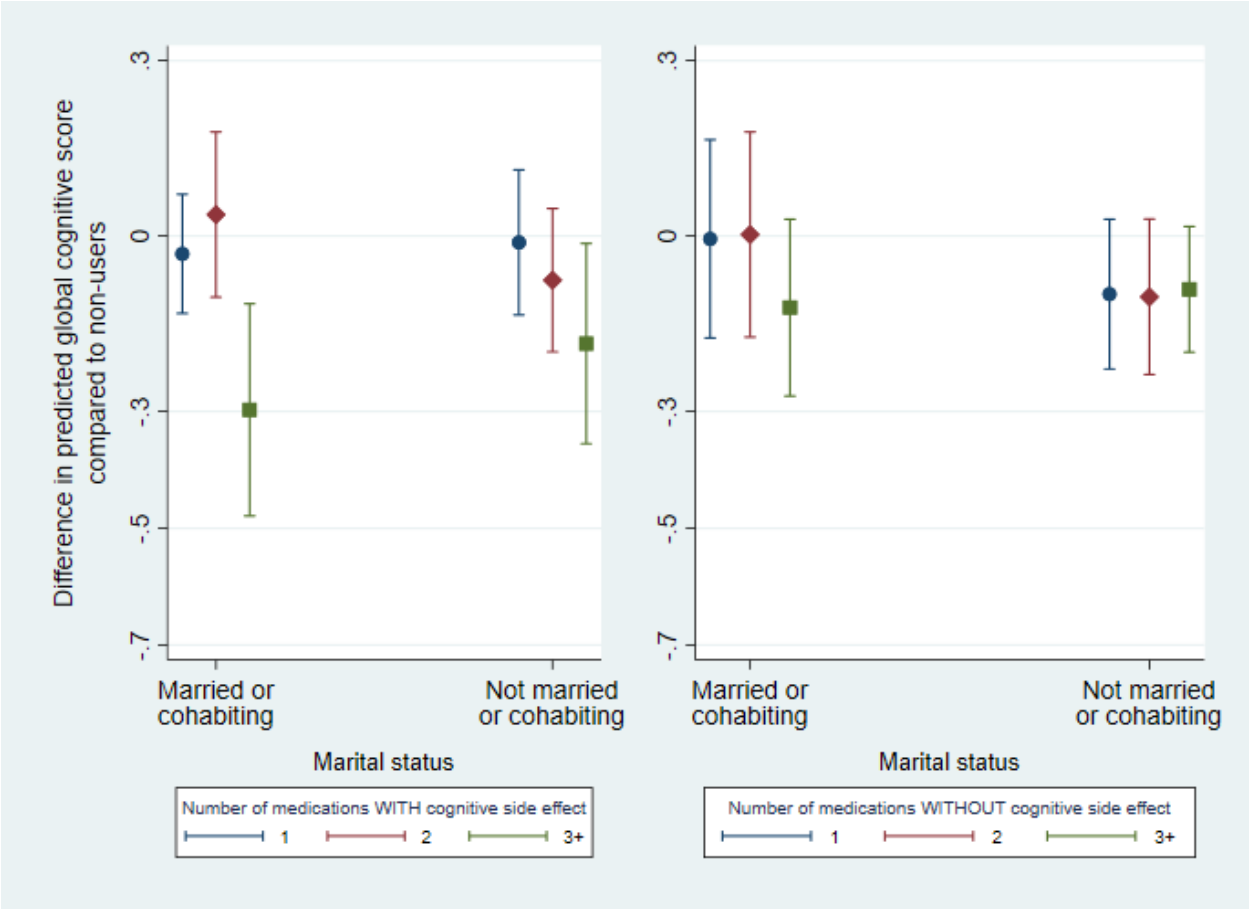
Figure 5: Marginal Effects (with 95% Confidence Intervals) of Medications With/Without Cognitive Side Effects on Global Cognitive Score by Race/Ethnicity Among Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.



Notes: The marginal effects were calculated from the linear regression of the global cognitive score (average of the three standardized cognitive assessment scores) on the interactions between medications with/without cognitive side effects and race/ethnicity (non-Hispanic whites, Hispanic, non-Hispanic blacks, and non-Hispanic others), while controlling for other covariates such as age, gender, marital status, educational attainment, poverty, citizenship, health insurance coverage, whether the person has a routine place for medical care, smoking status, binary indicator for each self-reported health condition (asthma, arthritis, cancer, congestive health failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, diabetes, hypertension, and sleep disorder), depression (PHQ-9 scale), obesity (BMI of at least 30), and time trends.

NH: non-Hispanic.

Figure 6: Marginal Effects (with 95% Confidence Intervals) of Medications With/Without Cognitive Side Effects on Global Cognitive Score by Marital Status Among Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.



Notes: The marginal effects were calculated from the linear regression of the global cognitive score (average of the three standardized cognitive assessment scores) on the interactions between medications with/without cognitive side effects and marital status (married or cohabiting and not married or cohabiting), while controlling for other covariates such as race, age, gender, educational attainment, poverty, citizenship, health insurance coverage, whether the person has a routine place for medical care, smoking status, binary indicator for each self-reported health condition (asthma, arthritis, cancer, congestive health failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, diabetes, hypertension, and sleep disorder), depression (PHQ-9 scale), obesity (BMI of at least 30), and time trends.

Table 7. Most Common Combinations of Medications with Cognitive Side Effects Among Adults Aged 60+ Who Consumed At Least Three Medications with Cognitive Side Effects. Data Source: NHANES 1999-2000 to 2015-2016.

Combinations of medications with cognitive side effects	N	%
Anticonvulsants - antihyperlipidemic agents - proton pump inhibitors	66	5.31
Omeprazole-gabapentin-simvastatin		
Omeprazole-atorvastatin-gabapentin		
Omeprazole-gabapentin-pravastatin		
Pantoprazole-gabapentin-simvastatin		
Pantoprazole-atorvastatin-gabapentin		
Omeprazole-pregabalin-atorvastatin		
Esomeprazole-gabapentin-simvastatin		
Rabeprazole-atorvastatin-gabapentin		
Antiadrenergic agents - antihyperlipidemic agents - proton pump inhibitors	37	3.2
Omeprazole-tamsulosin-simvastatin		
Omeprazole-tamsulosin-atorvastatin		
Pantoprazole-tamsulosin-simvastatin		
Pantoprazole-tamsulosin-atorvastatin		
Omeprazole-tamsulosin-pravastatin		
Esomeprazole-tamsulosin-simvastatin		
Esomeprazole-tamsulosin-rosuvastatin		
Sex hormones - antihyperlipidemic agents - proton pump inhibitors	23	3.02
Conjugated estrogens-omeprazole-atorvastatin		
Omeprazole-simvastatin-testosterone		
Esomeprazole-estrogens methyltestosterone-atorvastatin		
Conjugated estrogens-omeprazole-simvastatin		
Conjugated estrogens-esomeprazole-atorvastatin		
Anxiolytics, sedatives, and hypnotics - antihyperlipidemic agents - proton pump inhibitors	33	2.91
Alprazolam-omeprazole-simvastatin		
Alprazolam-esomeprazole-atorvastatin		
Esomeprazole-atorvastatin-zolpidem		
Alprazolam-omeprazole-lovastatin		
Alprazolam-omeprazole-atorvastatin		
Antidepressants - antihyperlipidemic agents - proton pump inhibitors	26	2.86
Omeprazole-trazodone-simvastatin		
Omeprazole-fluoxetine-simvastatin		
Pantoprazole-fluoxetine-simvastatin		

Pantoprazole-amitriptyline-simvastatin		
Pantoprazole-amitriptyline-fluoxetine-lovastatin		
Anticonvulsants - antidepressants - antihyperlipidemic agents	26	2.02
Amitriptyline-diazepam-simvastatin		
Amitriptyline-atorvastatin-gabapentin		
Trazodone-gabapentin-simvastatin		
Trazodone-diazepam-simvastatin		
Clonazepam-fluoxetine-simvastatin		
Antiarrhythmic agents - antihyperlipidemic agents - proton pump inhibitors	27	1.87
Diltiazem-omeprazole-simvastatin		
Diltiazem-omeprazole-atorvastatin		
Diltiazem-esomeprazole-simvastatin		
Omeprazole-propranolol-simvastatin		
Omeprazole-phenytoin-simvastatin		
Leukotriene modifiers - antihyperlipidemic agents - proton pump inhibitors	16	1.59
Montelukast-omeprazole-atorvastatin		
Montelukast-pantoprazole-simvastatin		
Montelukast-omeprazole-simvastatin		
Montelukast-omeprazole-rosuvastatin		
Montelukast-rabeprazole-simvastatin		
Antidepressants - antihyperlipidemic agents - anxiolytics, sedatives, and hypnotics	12	1.5
Alprazolam-amitriptyline-atorvastatin		
Fluoxetine-rosuvastatin-zolpidem		
Atorvastatin-fluoxetine-zolpidem		
Amitriptyline-simvastatin-zaleplon		
Amitriptyline-rosuvastatin-zolpidem		
Analgesics - antihyperlipidemic agents - proton pump inhibitors	19	1.27
Omeprazole-ibuprofen-simvastatin		
Esomeprazole-naproxen-atorvastatin		
Pantoprazole-ibuprofen-simvastatin		
Omeprazole-ibuprofen-pravastatin		
Naproxen-omeprazole-rosuvastatin		

Notes: Estimates were based on 1,153 adults aged 60+ who consumed at least three medications with cognitive side effects in the past 30 days using the pooled NHANES data from 1999-2000 to 2015-2016. Frequency was unweighted while percentage was weighted using survey weights.

CHAPTER 4:

The Consequences of Medications with Insomnia, Depression, Anxiety, and Suicidal Side Effects on U.S. Adults' Mental Health and Use/Cost of Mental Health Services.

Objective: To document the trends in using medications with insomnia, depression, anxiety, and suicidal side effects ("mental health side effect" hereafter) among U.S. adults from 1996 to 2016, and to investigate the association between the use of these medications and psychiatric distress and the use of mental health services.

Data source: Nationally representative sample of adults aged 25-84 from the Medical Expenditure Panel Survey (MEPS) in 1996-2016 (N = 211,551). Psychological distress is measured using the Kessler-6 scale.

Principal findings: In 2016, 50% U.S. adults used medications with mental health side effects, an increase from 45% in 1996. Much of the growth was driven by increasing use of medications with insomnia (relative increase of 66.8% between 1996 and 2016), anxiety (relative increase of 80.7%), and suicidal (relative increase of 77.3%) side effects. Compared to respondents who did not consume medications with mental health side effects at the baseline, individuals who used three or more of these medications simultaneously had higher odds of reporting psychological distress (OR = 1.859, $p < 0.001$), new mental disorders at follow-up (OR = 1.986, $p < 0.001$), having more visits for mental disorders at follow-up (coefficient = 0.153, $p < 0.001$), having higher total charges for mental disorders at follow-up (coefficient = 103.2, $p < 0.001$), and using more psychotropic medications for treatments of mental disorders at follow-up (OR = 2.273, $p < 0.001$). In contrast, the use of medications without known mental health side

effects was not associated with psychological distress or the use of mental health services.

Conclusion: Concurrent use of medications with mental health side effects has increased significantly since 1996. The use of these medications was associated with an increase in psychological distress and the use/costs of mental health services. Since many medications with mental health side effects are intended for treatments of physical disease, these findings suggest that physicians may have neglected the role of mental health when proving care to patients, and that any mental health side effects may be subsequently treated by prescribing psychotropic medications. These findings also suggest an important role of polypharmacy in amplifying the side effects of medications.

Introduction

Mental disorders refers to a wide range of conditions that influence one's mood, thinking, and behaviors (Mental Health: A Report of the Surgeon General, 1999). It has been estimated that more than one-fourth of American adults currently have at least one mental disorder, and half will develop a mental disorder in their lifetime (Kessler, Berglund, et al., 2005; Kessler, Chiu, et al., 2005). The most common mental disorders are anxiety disorders (lifetime prevalence of 31.5%), mood disorders (28%), and impulse-control disorders (25.4%) (Kessler, Berglund, et al., 2005). Although many U.S. adults have at least one mental disorder, only 15.5% of them receive treatment (Thorpe et al., 2017). While mental illness is a significant public health concern itself, its association with other chronic and physical conditions has important implications for morbidity and mortality (Chapman et al., 2005; Evans et al., 2005). In 2010, mental and substance disorders accounted for 183.9 million disability-adjusted life years worldwide, 8.6 million years of life lost, and 175.3 million years lost due to disability, and these burdens have increase by 37.6% since 1990 (Whiteford et al., 2013). Having a mental disorder is also associated with increased health care utilization and costs. In 2013, mental disorders collectively represented the costliest conditions in the United States, which totaled $201 billion in health care expenditures (Roehrig, 2016). The total cost would be even higher when adding lost earnings wages and disability benefits, which were estimated to be $193 billion and $24 billion in 2002, respectively (Insel, 2008).

Not only is the prevalence of mental disorders high and their consequences on morbidity and mortality are alarming, the age of onset and cohort-differences in mental disorders

are also of important concerns to policy makers. While the age of onset varies significantly, many disorders first occur in young ages, from 11 years old for anxiety and impulse-control disorders to 30 years old for mood disorders (Kessler, Berglund, et al., 2005). In addition, adolescents and young adults are much more likely to experience mood and anxiety disorders than older adults (Kessler et al., 2012). Since the early onset of mental disorders is a significant predictor for late-life mental and cognitive illnesses (Kraaij et al., 2002; Schoevers et al., 2005), a large number of young adults reporting worrisome mental illness today implies that the future aging population may be mentally sicker and require more health care resources than the current one.

Given the adverse health consequences and financial burdens of mental disorders on individuals, families, and society, prior studies have investigated risk factors of mental disorders to provide recommendations for public health interventions. Well-documented risk factors include dietary factors, drugs and substance abuse, family background, socioeconomic status, lifestyle, medical history and comorbidity, and trauma (Köhler et al., 2018). However, little is known about the role of medications in mental health, despite the growing popularity of medication use. In 2011-2012, almost 60% of American adults used at least one prescription medication and 15% used at least five, an increase from 51% and 8.2% in 1999-2000 respectively (Kantor et al., 2015). While medication use is important and critical for disease management, a growing literature suggests that many commonly used medications have adverse effects on mental disorders (Gorton et al., 2016; Lavigne, 2016; Qato et al., 2018). For example, Qato et al. (2018) used a nationally representative sample of U.S. adult from the National Health and

Nutrition Examination Survey (NHANES) and found that the prevalence of using at least one medication with depression as a potential side effect increased from 35% in 2005-2006 to 38.4% in 2013-2014. The prevalence of using at least three of such medications increased even more: from 6.9% to 9.5% during the same period, or a relative increase of almost 38%. The authors also found that respondents who consumed at least three medications with depression side effects were 10.7 percentage points more likely to report depressive symptoms, compared to nonusers.

Despite previous evidence on the adverse consequences of medications on mental health, more research on this topic is warranted. Many prior studies only focused on a single medication or a class of medication, and/or used a non-representative sample (Gorton et al., 2016). As such, little is known about the adverse consequences of medications on mental health at the population level and how the use of these medications has changed over time. Qato et al. (2018) was the first to investigate trends in the prevalence of medications with depression as a potential side effect at the population level and how the use of these medications influenced depression among community-dwelling adults. While the authors improved the existing literature by using a nationally representative sample of U.S. adults and examining more than 200 medications that had depression as a potential side effect, their study faced several limitations. First, their definition of medications with depression side effect only included medications with depression, depressive disorder, suicide, suicidal thoughts, suicidal ideation, or suicidal behavior listed as common or serious adverse effects. There are medications with other potential side effects that may also influence mental health, such as anxiety or insomnia (Baglioni et al., 2011). Second,

the authors only investigated depression as an outcome without considering other interrelated mental disorders such as anxiety or impulse-control disorders. Third, their study used a cross-sectional survey, which might limit their ability to address reverse causation and unobservable heterogeneity. Fourth, little is known about how the use of these medications influenced respondents' subsequent use of mental health services and the costs associated with those services. Finally, although Qato et al. (2018) significantly improved the previous literature by including in their study both younger adults and older adults, they did not investigate whether the association between medications with depression side effect and concurrent depression differed by age. There are conflicting theories and evidence on whether such association is larger among older adults or among young adults. On the one hand, older adults are expected to experience more adverse drug reactions due to decreasing hepatic metabolism and renal clearance (Leon, 2011; Shi & Klotz, 2011), having more chronic conditions (Ward & Schiller, 2013), and consuming multiple medications simultaneously (Kantor et al., 2015). On the other hand, the selection of young and healthy adults into taking multiple medications with depression as a potential side effect may signal an early onset of chronic conditions that can be more debilitating to health than those that occur at older ages (Huang et al., 2010). The extent to which theory dominates the other explains for the age-differences in adverse drug reactions.

The present study seeks to improve the existing literature by using a longitudinal national representative survey from 1996 to 2016 and examining a comprehensive list of

medications on the U.S. market that have mental health side effects. The study has four aims:

1. What is the trend in the prevalence of using medications with insomnia, depression, anxiety, or suicidal side effects ("mental health side effects") among community-dwelling adults aged 25-84 from 1996 to 2016?
2. What is the association between the use of medications with mental health side effects and subsequent nonspecific psychological distress and mental disorders?
3. What is the association between medications with mental health side effects and subsequent use of mental health services and total costs associated with these services?
4. How does the relationship differ by age?

Methods

Data comes from the 2004-2015 Medical Expenditure Panel Survey (MEPS). Although the MEPS has been fielded every single year from 1996 to 2016, I selected the 2004-2015 surveys because nonspecific psychological distress was not collected until 2004. Moreover, data on utilization and cost of mental health services in 2016 are not yet available due to the replacement of the International Classification of Diseases (ICD)-9 with the ICD-10. However, when assessing trends in the use of medications with mental health side effects, I used the full sample from 1996 to 2016.

The MEPS is a nationally representative and longitudinal survey of the civilian non-institutionalized U.S. population, drawn from a subsample of households that participated in the prior year's National Health Interview Survey (NHIS). Both MEPS and NHIS oversample Black, Hispanic, Asian, and low-income respondents to improve the precision of estimates for these subgroups. The overall MEPS response rate, after accounting for nonresponse rate from the NHIS, ranges from 46% to 71%.

MEPS respondents enter the survey annually as members of a unique survey panel. For a graphical illustration of the MEPS study design, please refer to the IPUMS-MEPS's user guideline: https://meps.ipums.org/meps/userNotes_MEPS_panel_design.shtml. MEPS then interviews participants of each panel five times over two calendar years. During each interview, one informant who is most knowledgeable about health and health care use in the household will typically report for all household members. The average recall period for each interview round is five months. For each calendar year, data from interview rounds 1, 2, and 3 are included for individuals in the first year of their panel, and data from interview rounds 3, 4, and 5 are included for individuals in the second year of their panel. Collectively, respondents from two overlapping panels in each calendar year provide nationally representative estimates of their health status, socio-demographic characteristics, chronic conditions, and medication use. Note that MEPS data in most years are not independent of one another because most respondents are in the survey for two consecutive years. However, it is still valid to pool data from multiple calendar years despite this lack of independence because MEPS was designed to be nationally representative in each calendar year, provided that the survey weight and the variance

structure are properly specified in all analyses (Agency for Healthcare Research and Quality, 2019).

Following the completion of the household interview, MEPS interviewers asked respondents for permission to contact their medical providers (i.e. physicians, hospitals, home health agencies, and pharmacies) to confirm information that the respondents reported[8]. Collected information included the date of visits, diagnoses and procedures, charges, payments, detailed information on medications, dates when prescriptions were filled, sources and amounts of payments. Collected information was only used to impute missing data and improve the precision of estimates. Response rates vary by the types of medical providers, but typically range from 75% to 85%. For this reason, MEPS is one of the most comprehensive data sources on national-level medical utilization and expenditures, as well as individual characteristics such as socio-demographic characteristics, health behaviors, and health conditions.

This study used a merged sample of respondents from 2004 to 2015, which combined the full year consolidated files with the medical condition files, the event files, and the prescribed medicine files. Information on end-of-the-year socio-demographic

[8] Note that MEPS only contacted medical providers to confirm information reported by respondents, and in many cases, asked for more information about an event reported by a respondent (i.e. cost or diagnosis for a reported doctor visit). Additional events reported by medical providers but not by the respondents were not included in the data to avoid the discrepancy in the number of events between respondents who gave permission to contact their medical providers and those who did not.

characteristics was obtained from the full year consolidated files, while round-specific information on the use of medications, self-reported chronic conditions, and the use and costs of health services came from the remaining files. I first selected respondents aged 25 to 84 (N = 248,741). Respondents aged 85 and older were dropped because MEPS censored age at 85, and unobservable characteristics of the oldest population might be systematically different from those of the general population. I excluded respondents who were under 25 years of age because all analysis models controlled for educational attainment. Restricting the sample to those aged 25 and older allowed respondents to complete their educational attainment. After excluding 33,886 respondents without mental health assessment[9], 3,304 respondents with missing information on any of the covariates described shortly below, the final sample included 211,551 respondents. In a sensitivity analysis not reported here, I used multiple imputation with chained equations to handle missing data, but the interpretation of the results did not change because only 1.5% of the sample had missing data on covariates. The results in this paper come from the analytic sample without missing data.

Nonspecific psychological distress. MEPS measures nonspecific psychological distress over a 30-day recall period using a five point Likert-type scale developed by Ronald C. Kessler and is widely known as the Kessler 6 Scale (K6) (Kessler et al., 2002, 2003). The K6 scale has been successfully implemented in major epidemiological studies in various

[9] Respondents were not eligible for the mental health assessment if there was no record of the person in the interview round, if they were deceased or institutionalized, if they had moved out of the U.S. or to a military facility, if their disposition status was inapplicable.

ethnic and cultural contexts to investigate six manifestations of nonspecific psychological distress (Furukawa et al., 2003; Kessler et al., 2003, 2010). Interviewers asked respondents for the frequency with which, in the past four weeks, they felt so sad that nothing could cheer them up, felt nervous, felt restless or fidgety, felt hopeless, felt that everything was an effort, and felt worthless. Acceptable responses for all six questions fell into five categories, ranging from "none of the time," "a little of the time," "some of the time," "most of the time," to "all of the time," and were assigned a corresponding value from 0 to 4. The summed responses of the K6 scale therefore ranges from 0 to 24, where 0 represents the lowest level of nonspecific psychological distress, and 24 indicates the highest level of nonspecific psychological distress.

I classified respondents as likely having major nonspecific psychological distress if their score was 13 or higher. This cutoff point has been proven to have a classification accuracy of 0.92 for serious mental illness, as defined by the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (Kessler et al., 2003). I also used each individual K6 question as an outcome variable to investigate which aspect of nonspecific psychological distress was driving the result observed in the composite K6 score. For each question, I created a binary variable that took a value of 1 if a person reported the frequency of "most of the time" or "all of the time." (scores 3 and 4).

Self-reported mental disorders. To supplement the analysis using the K6 scale, I used self-reported information on whether a respondent had any mental disorders as a secondary outcome. These self-reported measures have been previously used to study the prevalence of mental disorders and health seeking behaviors (Olfson et al., 2016; Thorpe

et al., 2017). Medical condition data were collected from household respondents during each round. However, only conditions indicated as being "current" were included in the medical condition files. MEPS defines a condition as being "current" if the person was currently experiencing the condition or if the condition was associated with a specific event that occurred during the reference period of the interview round (i.e. outpatient visit, inpatient visit, emergency department visit, office-based visit, prescription medication). Each medical condition was recorded as verbatim text, which was then coded to fully specified ICD-9 by professional coders. All ICD-9 codes were verified, and the error rates did not exceed 2.5% for any coders. ICD-9 condition codes were further aggregated into mutually-exclusive clinical classification codes (Elixhauser et al., 1998). Most ICD-9 conditions within each clinical classification code are clinically homogenous. Mental disorders in MEPS are coded from 650 to 670[10]. Using these clinical classification codes, I created an indicator for whether a person experienced any new mental disorders, either treated or untreated, in each interview round relative to the previous round.

Use and costs of mental health services were measured by linking the medical condition files to the event files. Most conditions recorded in the medical condition files corresponded to at least one event (i.e. outpatient visit, inpatient visit, emergency department visit, office-based visit, prescription medications used) in the event files. Each event included the following information: date of the visit, whether the respondent

[10] See a list of all clinical classification codes here:

https://meps.ahrq.gov/data_stats/download_data/pufs/h154/h154app3.html

saw a doctor, type of care received, type of services received, whether medications were prescribed during the visit, flat fee charges, imputed sources of payments, total payments and total charges. Using detailed information at the visit-level, I calculated the total number of visits in each round regardless of the place of service (outpatient, inpatient, emergency department, office-based), and the total charges (including charges for visits and prescription medications) for all mental disorders that a respondent reported in the medical condition files. I adjusted all charges to reflect 2016 dollars.

Previous studies have assessed the validity of events reported in MEPS. While inpatient stays and the number of inpatient hospital nights were accurately reported in MEPS compared to the linked Medicare data (Zuvekas & Olin, 2009b), office visits, emergency department visits, and Medicare expenditure are underreported by 12% to 34% (Zuvekas & Olin, 2009a). Regardless, underreporting of utilization and costs for certain events was unlikely to affect behavioral analyses because the magnitude of the misreport was not different across subgroups (Zuvekas & Olin, 2009a).

Medications. MEPS documents the use of prescription medications, nonprescription medications, and dietary supplements for each interview round. The prescription medication files contain information[11] on the name and national drug code of each medication; quantity, form, strength, and the number of days supplied; Multum therapeutic drug classes; the condition(s) that each medication was intended for, the date when respondents started using each medication; and the total cost of each medication.

[11] Information was either self-reported or imputed after MEPS contacted the respondents' pharmacy.

Interviewers asked respondents to report all medications, including all refills, that they consumed since the last interview round. Interviewers then entered the complete medication names into a computer, which were automatically matched with an existing drug in the database. The drug database used for the match was obtained from Lexicon Plus, a proprietary database of Cerner Multum that provided, on an annual basis, a comprehensive list of all prescription and some non-prescription medications available in the U.S. market.

The quality of prescription medication data has been independently assessed in prior studies. Hill, Zuvekas, & Zodet (2011) linked MEPS prescription drug database to Medicare Part D claim data and found that while the number of medications and total expenditures were generally in accordance with those in claim data, respondents had the tendency of underreporting different types of medication consumed and overreporting the number of refills for each medication. Despite such discrepancy, these authors suggested that behavioral analyses were unlikely to be affected because misreport did not vary across socio-demographic subgroups. In this study, I removed all medication refills due to overreporting, and treat each distinct reported medication in each interview round as a course of treatment. I also created a series of binary variables that indicated whether respondents used any antidepressants; anxiolytics, sedatives, hypnotics; anticonvulsants; and antipsychotics for treatment of any mental disorders (clinical classification codes 650-670).

Medications with potential mental health side effects. Medications with depression or suicide as potential side effects were obtained from Qato et al. (2018). Similar to Qato et

al. (2018), I used the Micromedex database to identify medications with insomnia and anxiety side effects. Prior studies have independently established the accuracy and reliability of adverse effects listed in Micromedex (Cheng et al., 2010). The database is based on several sources: the U.S. Food and Drug Administration's black box warnings, MedWatch, post-marketing surveillance, clinical trials, and comprehensive literature reviews. In this study, medications with insomnia side effects were identified using a keyword search including the following words: insomnia and sleep disorder; medications with anxiety side effects were detected using the following search words: anxiety, anxious, and nervous. Consistent with the study by Qato et al. (2018), I classified medications as having insomnia and anxiety as potential side effects if their adverse effects are listed as common or serious in Micromedex. Note that the lists of medications with different mental health side effects are not mutually exclusive. A medication with insomnia as a side effect may also have depression as a potential side effect.

I identified 98 medications with insomnia side effect, 124 medications with depression side effect, 41 medications with anxiety side effect, and 107 medications with suicidal side effect (Tables 1-4). It is important to note that these numbers do not represent the full set of medications with mental health side effects in the U.S market, but rather the number of medications with mental health side effects consumed by respondents aged 25-84 in the analytic sample from 1996 to 2016. Using the reported number of medications with mental health side effects, I constructed a variable that indicated whether during the recall period of an interview round (usually five months on average), a respondent took no medications with *any* mental health side effects (the reference category in the

regression models), one medication, two medications, or at least three medications with *any* mental health side effects.

-Insert Tables 1 to 4 About Here-

Chronic conditions. Many medications with mental health side effects are intended for treatment of chronic conditions that have been found to be correlated with the onset of depression (Köhler et al., 2018). I controlled in all analysis models the number of self-reported chronic conditions that the person was currently experiencing during interview round, either treated or untreated. Using the definition of chronic conditions from Goodman et al. (2013), I classified the following conditions as being chronic: hypertension, congestive heart failure, coronary artery disease, cardiac arrhythmias, hyperlipidemia, stroke, arthritis, asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease, dementia (Alzheimer's, and other senile dementias), diabetes, hepatitis, human immunodeficiency virus (HIV), and osteoporosis. Using the number of self-reported chronic conditions, I created a variable that represented whether a respondent had no chronic conditions (the reference category), one conditions, two conditions, or at least three conditions during a round of interview. Controlling for each individual chronic condition as a binary variable did not alter the interpretation of the results.

*Pain***.** A growing number of studies has found that pain and depressive symptoms usually coexist and share similar biological pathways and neurotransmitters (Bair et al., 2003). 65% of depressive patients experience some type of pain, and up to 85% of patients with

pain also report depressive symptoms (Bair et al., 2003). In addition, pain is one of the leading reasons for seeking medical care (Komaroff, 1990; Kroenke, 2001), which may increase patients' exposure to medication use. MEPS respondents reported the frequency that pain interfered with their work in the last four weeks, including both work outside of the home and housework. Possible responses included "none of the time," "a little of the time," "some of the time," "most of the time," and "all of the time." I created a binary variable that indicated whether the person experienced any pain, regardless of the reported frequency.

Other covariates. In all models, I controlled for socio-demographic variables that were potentially associated with one's depression and the use of medications such as race (non-Hispanic white: reference category, non-Hispanic black, Hispanic, or others); age and age squared; gender; marital status (married or living with a partner: reference category, widowed/divorced/separated, or never married); educational attainment (less than high school: reference category, high school graduate, college or higher); whether the person's household income was under the federal poverty threshold; whether the person has private insurance, public insurance (i.e. Medicaid or State Children's Health Insurance Program), Medicare, and/or any other insurance; and whether the person is obese (BMI is at least 30). I also included a dummy variable for each year and each region (Northeast, Midwest, South, West) to account for any secular trends in the outcomes.

To adjust for complex and multistage sampling, I calculated weighted prevalence estimate of medications with mental health side effects in each year using Taylor linearization methods. I used logistic regression to assess the statistical significance of trends of medications with mental health side effects. In each calendar year, I used information on the reported use of medications with mental health side effects in round 1 (or 3) to predict subsequent mental health and use/costs of mental health services in round 2 (or 4) for respondents in the first (or second) year of their panel. *Rounds 1 and 3 will be referred to as the baseline, while rounds 2 and 4 will be referred to as the follow-up hereafter*. Weighted multivariate linear least-squared and logistic regression models were used to investigate the association between the use of medications with mental health side effects at baseline and mental distress (K6) at follow-up, whether a respondent reported any new mental disorders at follow-up, whether a respondent had more visits for mental health disorders at follow-up compared to baseline, and whether a respondents used more psychotropic medications for treatment of mental disorders at follow-up compared to baseline. Weighted two-part model was used to estimate the relationship between the use of medications with mental health side effects at the baseline and changes in the number of visits and total charges for mental disorders between the baseline and follow-up due to their zero-heavy count data. The first part of the model estimated the probability of having a non-zero and non-negative[12] value using a logit regression. The second part estimated changes in the number of visits/charges associated

[12] Some respondents had a negative value because they had fewer visits or charges at the follow-up compared to at the baseline.

with mental disorders conditional on having any using a Gamma generalized linear model with log link.

For analysis of the K6 and each element in the K6 scale, I controlled for whether a person had any mental disorders at the baseline to avoid reverse causation and reduce the threat of spuriousness, using an indicator for whether a person reported having any mental disorders (treated or untreated) or used any psychotropic medications for treatment of mental disorders such as antidepressants, anxiolytics, sedatives, hypnotics, anticonvulsants, and antipsychotics. This is because the K6 was only collected in rounds 2 and 4 for each respondent; therefore, no information was available at the baseline (rounds 1 and 3). Regardless, self-reported mental disorders and the use of medications for treatment of mental disorders are relatively reasonable indicators for psychological distress at the baseline. I also controlled for changes in the number of medications with mental health side effects between the baseline and follow-up (decline in the number of medications with such side effects or no changes: reference category, an increase of one, two, or three of such medications). As a test for sensitivity, I included in all models the use of medications *without* any of known mental health side effects and changes in the reported number of these medications between the baseline and follow-up. If the association between medications with mental health side effects and the outcome was driven by any unobservable heterogeneity in health, the relationship between medications without mental health side effects and the outcome should be equally significant as that between medications with mental health side effects and the outcome. Lastly, all models controlled for socio-economic characteristics, chronic conditions, pain, and health

insurance status as described above, as well as a series of dummy variables for year and region fixed effects.

To assess whether the association between medications with mental health side effects and mental health outcomes varied by age, I included in the analytic models an interaction term between the categories of medications with/without mental health side effects and a categorical variable for age (25-44, 45-64, and 65-84). I then computed the marginal effects of medications with and without mental health side effects on the outcomes for each age group, while holding all other covariates constant.

In several sensitivity analyses, I repeated the main analyses for three sub-samples: respondents with at most one self-reported chronic condition at the baseline, respondents without any self-reported mental disorders (either treated or untreated) at baseline, and respondents with at least one self-reported mental disorder at baseline. The first sub-sample included relatively healthy respondents without comorbidity, while the second sub-sample consisted of respondents without any existing mental disorders at baseline. If the association between medications with mental health side effects and mental health was not mainly driven by comorbidity and existing mental disorders, I expect to observe similar results in the first and second sub-samples compared to those in the main analysis. I repeated the same analyses for the third sub-sample of respondents with pre-existing mental disorders in order to investigate whether the use of medications with mental health side effects worsened mental health for these respondents (i.e. developing new mental disorders or having more office visits at the follow-up).

Results

Figure 1 presents unadjusted (Panel A) and age/sex adjusted (Panel B) trends in the use of medications with any mental health side effects from 1996 to 2016 for U.S. adults aged 25-84. In Panel A, 55% of U.S. adults aged 25-84 in 1996 did not use medications with any mental health side effects. In 2016, this prevalence dropped to 49.5% ($p < 0.001$). Further investigation suggests that while the prevalence of using one or two of these medications has been relatively stable or even slightly declining over the same period, the reported use of three or more medications with mental health side effects has increased from 21.9% to 29.8% ($p < 0.001$, or a relative increase of 36.2%). The increase in concurrent use of at least three of these medications could be in part due to factors such as the introduction of new medications on the market, the increase in chronic conditions and comorbidity in the population (Ward & Schiller, 2013), or the growing availability of over-the-counter medications with mental health side effects (Qato et al., 2018).

-Insert Figure 1 About Here-

Figure 2 examines the unadjusted and age/sex adjusted prevalence of U.S. adults aged 25-84 who used at least one medication with insomnia, depression, anxiety, and suicidal side effects, respectively. Although more adults who used medications with depression as a potential side effect than medications with any other side effects in every single year, the prevalence of using medications with depression side effect was relatively stagnant between 1996 and 2016 (37.3% in 2016 vs. 36.5% in 1996, $p = 0.40$). In contrast, the use of at least one medication with insomnia, anxiety, and suicidal side effects has been

increasing between 1996 and 2016 by 11.3 percentage points ($p < 0.001$, relative increase of 66.8%), 6.3 percentage points ($p < 0.01$, relative increase of 80.7%), and 11.2 percentage points ($p < 0.001$, relative increase of 77.3%), respectively.

-Insert Figure 2 About Here-

Table 5 presents descriptive statistics of the outcomes and the control variables for the full analytic sample, and by the number of medications with potential mental health side effects. Overall, 68.6% of respondents reported not using medications with mental health side effects, while 17.7%, 7.5%, and 6.3% reported using one, two, and at least three of those medications. Between the baseline and follow-up, 77.3% of respondents consumed at most the same number of medications with mental health side effects, while 14.4%, 5.1%, and 3.2% increased their consumption by one, two, or three of such medications, respectively.

-Insert Table 5 About Here-

Respondents who used at least three medications with mental health side effects were much more likely to report psychological distress (K6), mental disorders, having at least one visit associated with such mental disorder(s), and more visits and higher costs associated with mental disorders between the baseline and follow-up. For example, among respondents who reported using at least three medications with mental health side effects at the baseline, 19.6% likely had mental distress at follow-up, 9.8% had at least one new mental disorder at follow-up, 18.7% had more visits for mental disorders at follow-up compared to at the baseline, and 12.5% used more psychotropic medications at

follow-up compared to at the baseline, compared to 3.3%, 4.0%, 2.2%, and 3.6% among respondents who did not use such medications, respectively (p-value < 0.001 for all comparisons). Additionally, individuals who reported using at least three medications with mental health side effects on average had an increase of 0.63 visits and $242 in total charges for mental disorders between the baseline and follow-up (p-value < 0.001 for both comparisons) compared to individuals who did not use these medications. Note that there is a dose-response relationship, such that the prevalence of psychological distress and the use/costs of mental health services increased for every additional medication consumed that have mental health side effects.

I also found that respondents who used more medications with mental health side effects tended to be white; aged 65 to 84; married or cohabiting with a partner; divorced, widowed, or separated; high school graduated; low-income; publicly insured; obese; had any pain that interfered with work or housework; and were more chronically ill (p < 0.001 for all variables). Respondents who used more medications with mental health side effects were systematically sicker than non-users. Some of the most common chronic conditions among individuals who consumed at least three medications with mental health side effects were hypertension (56.4%), hyperlipidemia (46.5%), arthritis (25.2%), chronic obstructive pulmonary disease (17.9%), and diabetes (23.8%).

Table 6 presents evidence for the association between the use of medications with mental health side effects and psychological distress (K6), each individual question in the K6 scale, and whether a respondent reported any new mental disorder at follow-up relative to

the baseline. In column (1), compared to non-users, those who used one, two, or at least three of those medications with mental health side effects at the baseline reported a higher K6 score by 0.113 ($p < 0.001$), 0.224 ($p < 0.001$), and 1.318 ($p < 0.001$) points, respectively. A similar pattern was observed when investigating psychological distress (K6 score of at least 13) in column (2). Consuming at least three medications with mental health side effects was associated with an increase in the odds of psychological distress by 1.859 times ($p < 0.001$). Further investigation into each individual question in the K6 scale in columns (3) to (8) revealed that using these medications was associated with all aspects of psychological distress. Finally, medications with mental health side effect are also significantly associated with the likelihood of reporting a new mental disorder during follow-up (column 9). The odds of reporting a new mental disorder increased by almost two times when using three or more of these medications when compared to not using any ($p < 0.001$). In all analyses, I observed a dose-response such that the incidence of psychological distress or self-reported mental disorder increased with every additional medication with mental health side effects.

-Insert Table 6 About Here-

If the association between medications with mental health side effects and mental health was driven by unobserved heterogeneity in health, then one should expect to observe similar results for medications *without* these side effects. I found that the use of medications without known mental health side effects was generally not associated with worsened mental health, and in a few cases, such use was even beneficial to mental health. There was an exception for the outcome of whether the respondent felt that

everything was an effort (column 3 of Table 6). Using at least three medications *without* known mental health side effects was associated with an increase in the odds of feeling that everything was an effort by 1.132 times ($p < 0.05$). However, the magnitude of the coefficient for medications without known mental health side effects was significantly smaller than that for medications with these side effects. These findings suggest that the use of medications with mental health side effects at the baseline was associated with worsened mental health at follow-up. These associations, however, were unlikely to have been driven by unobservable heterogeneity in health.

In Table 7, I demonstrate the association between the use of medications with mental health side effects at the baseline and changes in use and costs of mental health services between the baseline and follow-up. In columns (1) to (3), compared to nonusers, those who used at least three medications with mental health side effects reported higher odds (OR = 2.346, $p < 0.001$) of having at least one additional visit for mental disorders at follow-up relative to baseline, 0.152 more visits between the baseline and follow-up for mental disorders ($p < 0.001$), and an increase of more than $100 in total charges between baseline and follow-up for visits with mental health diagnoses ($p < 0.001$). I also found that respondents used more psychotropic medications for treatment of mental disorders at follow-up compared to at the baseline as a result of consuming medications with mental health side effects. For example, the odds of using at least one additional antidepressant; anxiolytics, sedatives, or hypnotics; anticonvulsants; and antipsychotics at follow-up relative to baseline increased by more than two times for individuals consuming at least three medications with mental health side effects compared to nonusers (columns 4 to 8 of Table 7). The dose-response was observed for all outcomes. Similar to results in Table

6, I found that the associations between medications *without* known mental health side effects and the use/costs of mental health services were generally trivial and, in many cases, they were associated with a decline in utilization and costs.

-Insert Table 7 About Here-

To ensure that the associations between medications with mental health side effects and mental health outcomes were not driven by comorbidity or individuals who already had mental disorders at the baseline, I repeated all analyses for three sub-samples: respondents with at most one chronic condition at baseline, respondents without any preexisting mental disorders at baseline, and respondents with at least one pre-existing mental disorder at baseline.

I observed similar results among respondents with at most one chronic condition at the baseline in Tables 8 and 9. In some cases, the associations between medications with mental health side effects and mental health outcomes were even slightly larger than those of the full analytic sample in Tables 6 and 7. This implies that the results were applicable to relatively more-healthy respondents and were not driven by comorbidity. I also found similar patterns among respondents with and without any preexisting mental disorders at the baseline (Tables 10 to 13). However, the associations between medications with mental health side effects and mental health outcomes were much larger among respondents with preexisting mental disorders at the baseline compared to those without these preexisting conditions. As such, the results observed in the full analytic sample were likely driven by those with preexisting mental disorders. Regardless, mental

health side effects were likely associated with an onset of mental disorders among those without these disorders at the baseline and worsened mental health among those who already had these disorders.

-Insert Tables 8 to 13 About Here-

In Figures 3 to 9, I present the marginal effect of medications with mental health side effects on mental health and use/costs of mental health services by age groups (25-44, 45-64, and 65-84). Figures 3 and 4 demonstrate the age-profile of the association between medications with mental health side effects and nonspecific psychological distress (K6 score and whether the K6 score is at least 13). Among respondents aged 25-44, medications with mental health side effects had significantly negative consequences on mental health, regardless of the number of doses taken. For middle-aged and older adults, the association between medications with mental health side effects and nonspecific psychological distress did not become statistically significant until the respondent consumed at least three of those medications. A similar finding has been documented in Huang et al. (2010). The declining association between medications with mental health side effects and mental health across age groups is worth noting. Among respondents who consumed two or at least three medications with mental health side effects, young adults aged 25-44 were more likely to experience psychological distress than middle-aged and older adults.

-Insert Figures 3 and 4 About Here-

In Figures 5 to 7, I present the association between medications with mental health side effects and whether a respondent developed at least one new mental disorder at follow-up, whether a respondent had more visits for mental disorders at follow-up, and whether a respondent used more psychotropic medications[13] for treatments of mental disorders at follow-up compared to at the baseline. Across all age groups, respondents were much more likely to develop a new mental disorder, had more visits, and used more psychotropic medications for mental disorders when taking at least one medication with side effect, relative to nonusers. The association increased with every additional medication taken. The age differences in such associations were less significant than those in Figures 3 and 4. Medications with mental health side effects seemed to have relatively equal impacts on respondents regardless of their age.

-Insert Figures 5 to 7 About Here-

Finally, Figures 8 and 9 illustrate the marginal effects of medications with mental health side effects on changes in the number of visits and total costs for visits with mental disorder diagnoses between follow-up and baseline. Using medications with mental health side effects at the baseline was associated with an increase in the number of visits or total costs for mental disorders across all age groups. However, the association did not become statistically significant until a person consumed at least three of these medications. Moreover, the increase in visits and totals costs was larger for adults aged

[13] Medications used for treatment of mental disorders include antidepressant; anxiolytics, sedatives, or hypnotics; anticonvulsants; and antipsychotics.

25-44 compared to adults aged 65-84, although the estimates were not significantly different from one another.

-Insert Figures 8 and 9 About Here-

Discussion

This chapter investigated the trends in using medications with mental health side effects among community-dwelling adults from 1996 to 2016. It then examined the extent to which the use of these medications was associated with worsened mental health, as well as increased utilization and costs of mental health services.

The findings are six-fold. First, I found that the use of medications with mental health side effects has increased significantly since 1996, and much of the increase was attributed to the use of medications with insomnia, anxiety, and suicidal side effects, rather than medications with depression as a potential side effect. Second, I found that the use of medications with any mental health side effects was detrimental to mental health and was associated with an increase in the onset of new mental disorders, especially under conditions of polypharmacy. Third, concurrent use of medications with mental health side effects was associated with an increase in the number of visits and costs for mental disorders, as well as the subsequent use of psychotropic medications for treatments of mental disorders. Fourth, while medications with mental health side effects had negative consequences on health and health care use/costs, I found that medications without any known mental health side effects were not associated with worsened mental

health or increased use/cost of mental health services. In some cases, taking medications without mental health side effects was even beneficial to mental health and reduced the use and costs for mental health services. Fifth, medications with mental health side effects were more detrimental to mental health among respondents who already had mental disorders at the baseline compared to those without these preexisting disorders. Finally, I found that young adults were equally impacted, or in some cases, they were more likely to be impacted by medications with mental health side effects compared to middle-aged and older adults. While the association between medications with mental health side effects and nonspecific psychological distress (K6) declined over age (Figures 3 and 4), such age discrepancy was less significant for other outcomes (Figures 5 to 9). This may be due to underreporting or recall bias of psychological symptoms in the K6 scale among older adults (Lyness et al., 1995). Underreporting or recall bias were alleviated for other outcomes (i.e. self-reported mental disorders, visits and costs associated with mental disorders, and the use of psychotropic medications for treatments of mental disorders) because MEPS contacted respondents' medical providers to correct and impute missing information. Moreover, the large and significant association between the use of medications with mental health side effects and several outcomes for young adults may also be attributed to the selection to using multiple of these medications as a result of an early onset of chronic conditions that can be more detrimental to health than those that occur at older ages (Huang et al., 2010)

These findings imply that physicians are likely to have neglected the important role of mental health when proving care to patients. Many of medications that have mental

health side effects in this study are intended for the treatments of chronic and physical diseases such as antihypertensives, proton pump inhibitors, respiratory agents, and hormonal modifiers. While these medications may be beneficial for controlling and treating disease for which they are intended, many of them may induce psychological distress and the use/costs of mental health services. The decision to prescribe these medications may in part reflect physicians' belief that physical health should be prioritized over mental health, and that any mental health side effects can be treated later by prescribing more psychotropic medications after physical conditions are under control (Tamblyn, 1996). In this study, I found that the use of medications with mental health side effects indeed induced the use of additional psychotropic medications for treatments of mental disorders at the follow-up. To avoid adverse consequences of medications on mental health, physicians may want to conduct mental health screenings before and during administration of medications with potential mental health side effects, especially when patients consume multiple of these medications simultaneously, in order to adjust medication doses.

While many medications with mental health side effects are harmful to mental health, I found that medications without these known side effects did not have any adverse consequences, even when used in a set. This finding aligns with prior studies by Qato et al. (2018) and Do and Schnittker (2020). In many cases, the use of medications without known mental health side effects was even beneficial to mental health and reduced subsequent use and costs of mental health services. The results hold even after controlling for socio-demographic and preexisting medical conditions, as well as excluding

respondents with any existing mental disorders or respondents with multiple chronic conditions. It is possible that the use of medications without known mental health side effects helps manage chronic and physical conditions that have been found to have a detrimental effects on mental health (Köhler et al., 2018). These findings bridge the gap between the literature on polypharmacy and the literature on medication side effects. Much of the adverse consequences of polypharmacy on health may be mainly due to consuming multiple medications with certain side effects. As such, any policies that aim to address polypharmacy should focus on reducing the inappropriate use of medications with adverse side effects instead of medications without known side effects.

Finally, the literature on polypharmacy typically focuses on older adults because they are at higher risks of experiencing adverse drug reactions due to biological and medical reasons. As such, little is known about the role of polypharmacy or medications with side effects in mental health of younger adults. In this study, I found that medications with mental health side effects were as harmful to the mental health of younger adults as they were to older adults. For self-reported nonspecific psychological distress (K6 scale), I found that the bar was even lower for young adults. Using one, two, or at least three medications with mental health side effects had adverse effects on psychological distress for young adults, while the association was not observed among older adults until they consumed at least three medications with these side effects. This finding has been previously observed in a study by Huang et al. (2010) that investigated the association between polypharmacy and the risk of falls among diabetic patients. The authors found that using four to five medications simultaneously increased the risk of falls among

young adults compared to those using one or no medications. For older diabetic adults, the authors did not observe a significant relationship between polypharmacy and falls until patients consumed six to seven medications. In addition, I found that using at least three medications with mental health side effects was much more harmful to young adults' psychological distress than it was for older adults (Figure 4). It is possible that for young and healthy adults, the selection into concurrently using at least three medications with mental health side effects may be attributed to the early onset of chronic conditions that can be more debilitating to health than those that occur in older ages. For other outcomes such as the development of new mental disorders, the use of psychotropic medications, and use/costs of mental health services, I found that the associations between these outcomes and the use of medications with mental health side effects did not significantly vary by age groups. Future studies should investigate the consequences of polypharmacy and medications with side effects among the young adult population.

Conclusion

This study presents a significant increase in the use of medications with insomnia, depression, anxiety, or suicidal side effects among community-dwelling U.S. adults in the past two decades. Exposure to these medications was associated with psychological distress, the development of new mental disorders, and the use/costs of mental health services across all age groups, especially under the condition of polypharmacy. These results highlight the needs for mental health screenings among patients who consume medications with mental health side effects. They also highlight the synergic effects of polypharmacy and potential drug-drug interactions that result in mental disorders.

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Figure 1: Unadjusted and Adjusted Weighted Prevalence of U.S. Adults Aged 25-84 Taking Medications with Any Insomnia, Depression, Anxiety, or Suicidal Side Effects. Data Source: MEPS 1996-2016.

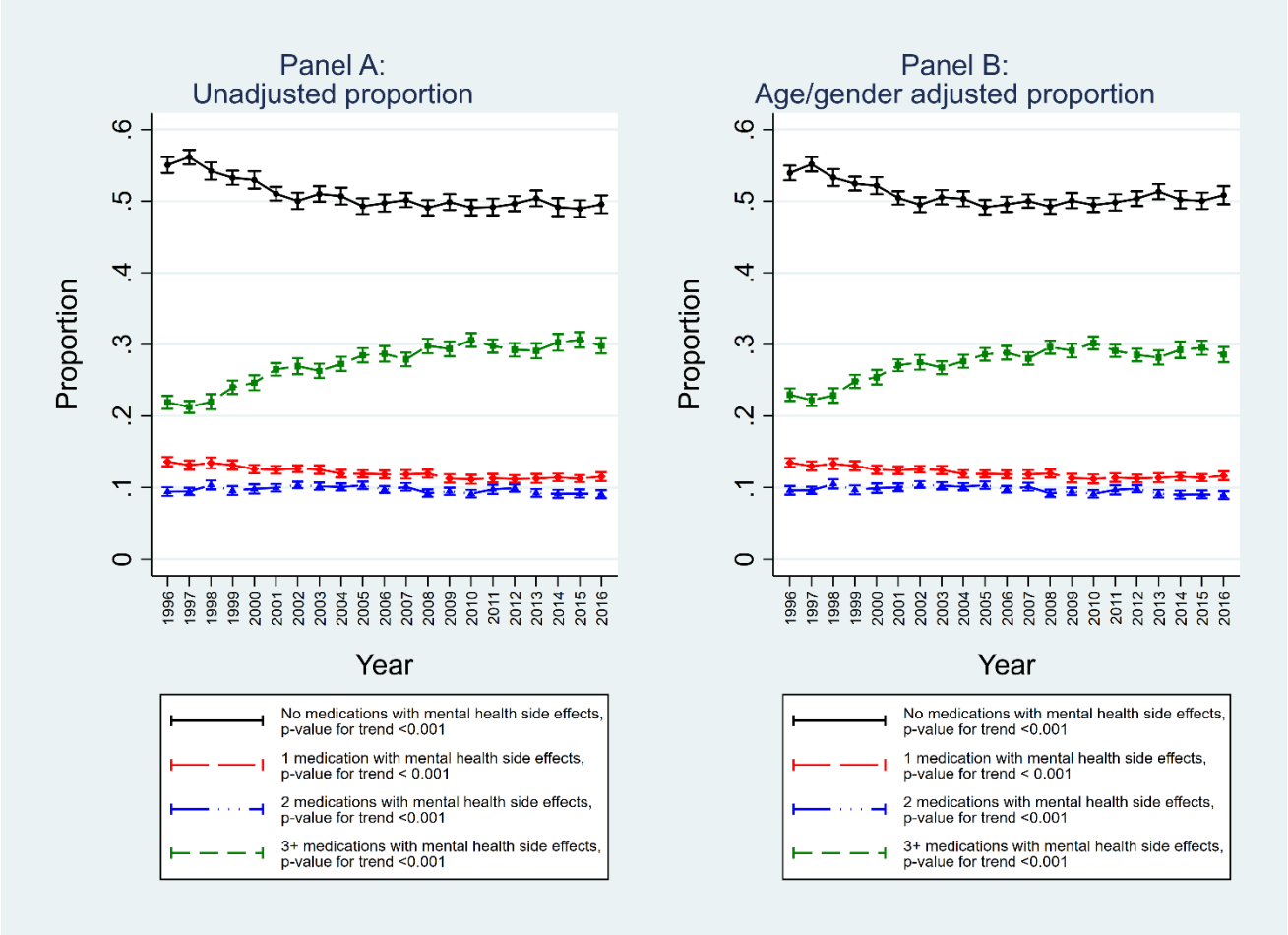


Figure 2: Unadjusted and Adjusted Weighted Prevalence of U.S. Adults Aged 25-84 Taking Medications with Individual Side Effect of Insomnia, Depression, Anxiety, or Suicide. Data Source: MEPS 1996-2016.

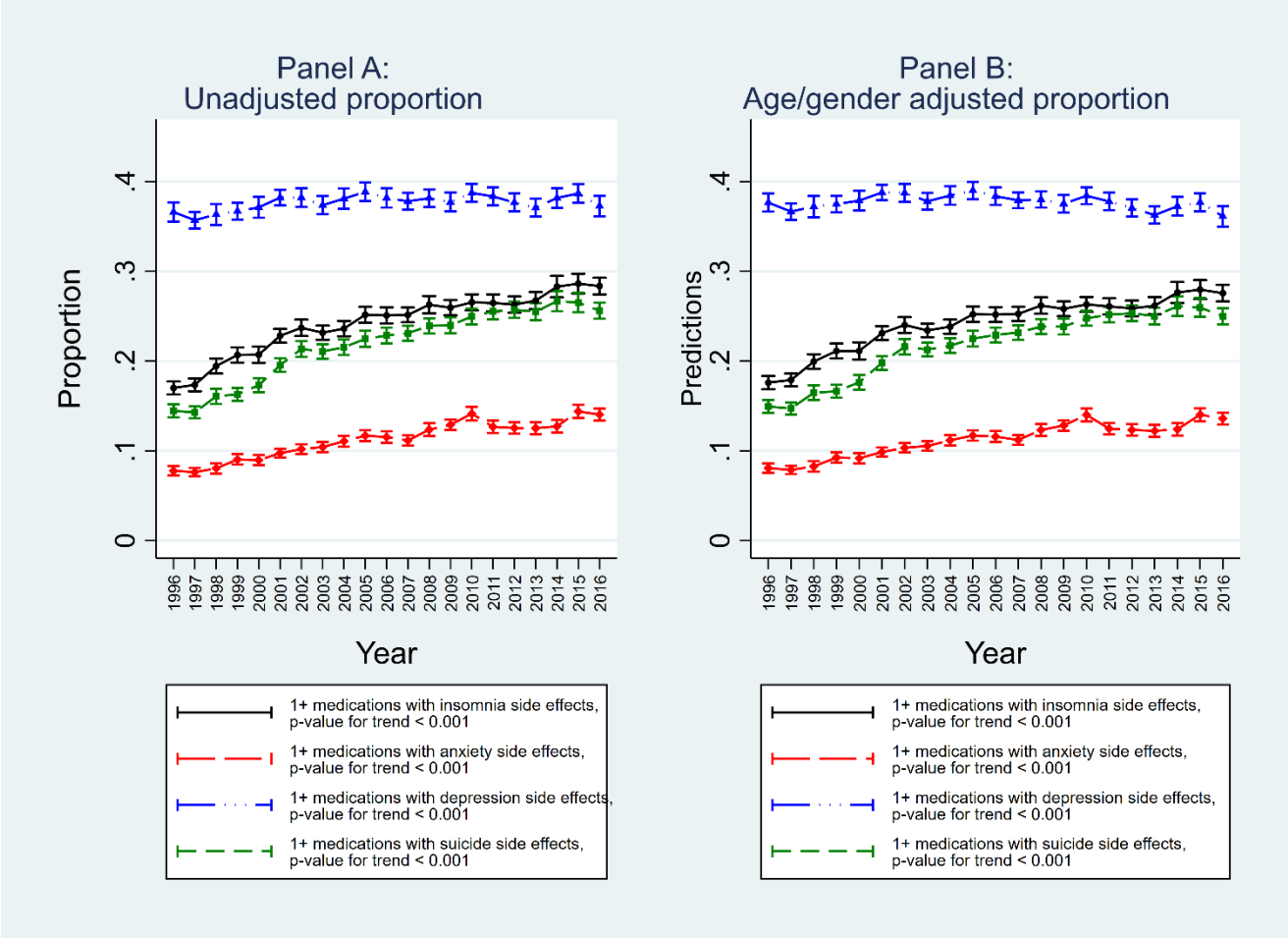


Table 1: Medications with Insomnia Side Effect Consumed by U.S. Adults Aged 25-84 in MEPS 1996-2016.

Abacavir	Emtricitabine	Phentermine
Abacavir-Lamivudine	Emtricitabine-Rilpivirine-Tenofovir	Pindolol
Acamprosate	Emtricitabine-Tenofovir	Piperacillin-Tazobactam
Acetaminophen	Escitalopram	Pramipexole
Acetaminophen-Tramadol	Exemestane	Progesterone
Amantadine	Felbamate	Propranolol
Amphetamine-Dextroamphetamine	Fentanyl	Pseudoephedrine
Amphotericin B	Fexofenadine-Pseudoephedrine	Quetiapine
Anastrozole	Fluoxetine	Raltegravir
Aripiprazole	Fluvoxamine	Ramelteon
Armodafinil	Formoterol	Ribavirin
Asenapine	Guanfacine	Rimantadine
Atomoxetine	Interferon Beta-1B	Roflumilast
Benzphetamine	Lamivudine-Zidovudine	Selegiline
Boceprevir	Lamotrigine	Sertraline
Buprenorphine-Naloxone	Letrozole	Sibutramine
Bupropion	Leuprolide	Sildenafil
Butorphanol	Levofloxacin	Tacrolimus
Carteolol	Levothyroxine	Tamsulosin
Cetirizine-Pseudoephedrine	Lindane	Tenofovir
Ciprofloxacin	Lisdexamfetamine	Theophylline
Citalopram	Loratadine-Pseudoephedrine	Thyroid
Clomipramine	Mefloquine	Tiagabine
Dalfampridine	Megestrol	Tramadol
Daptomycin	Methylphenidate	Tranylcypromine
Desloratadine-Pseudoephedrine	Milnacipran	Trazodone
Desvenlafaxine	Modafinil	Valproic Acid
Dexmethylphenidate	Mycophenolate Mofetil	Varenicline

Diflunisal	Mycophenolic Acid	Venlafaxine
Divalproex	Nabumetone	Vilazodone
Donepezil	Ofloxacin	Zileuton
Duloxetine	Paroxetine	Zoledronic Acid
Efavirenz	Peginterferon Alfa-2A	

Table 2: Medications with Depression Side Effect Consumed by U.S. Adults Aged 25-84 in MEPS 1996-2016.

Abacavir-Lamivudine	Drospirenone-Estradiol	Magnesium Gluconate
Acebutolol	Drospirenone-Estradiol-Levomefolate	Medroxyprogesterone
Acetaminophen-Hydrocodone	Emtricitabine	Megestrol
Acetaminophen-Oxycodone	Enalapril	Metaproterenol
Acitretin	Enalapril-Hydrochlorothiazide	Metaxalone
Acyclovir	Esomeprazole	Methocarbamol
Albuterol	Esterified Estrogens	Methotrexate
Amiodarone	Esterified Estrogens-Methyltestosterone	Methyldopa
Amphetamine-Dextroamphetamine	Estradiol	Methylprednisolone
Anastrozole	Estradiol-Levonorgestrel	Metolazone
Aspirin	Estradiol-Norethindrone	Metoprolol
Atenolol	Estradiol-Norgestimate	Metronidazole
Atenolol-Chlorthalidone	Estropipate	Montelukast
Atropine-Diphenoxylate	Estradiol	Morphine
Azathioprine	Estradiol-Ethynodiol	Nabumetone
Baclofen	Estradiol-Etonogestrel	Nisoldipine
Bendroflumethiazide-Nadolol	Estradiol-Levonorgestrel	Norethindrone
Benzphetamine	Estradiol-Norethindrone	Omeprazole
Betamethasone	Estradiol-Norgestimate	Oxybutynin
Betaxolol	Estradiol-Norgestrel	Oxycodone
Bicalutamide	Etonogestrel	Pantoprazole
Brimonidine	Exemestane	Phentermine
Brimonidine-Timolol	Famotidine	Pimozide
Cabergoline	Fentanyl	Prazosin
Cetirizine	Flecainide	Prednisolone
Cimetidine	Fluphenazine	Prednisone
Clonidine	Galantamine	Propafenone
Conjugated Estrogens	Goserelin	Propranolol

Conjugated Estrogens-Medroxyprogesterone	Guaifenesin-Hydrocodone	Quinapril
Cortisone	Haloperidol	Rabeprazole
Cyclobenzaprine	Homatropine-Hydrocodone	Ranitidine
Cyclosporine	Hydrochlorothiazide-Metoprolol	Rasagiline
Dantrolene	Hydrocodone	Risedronate
Desogestrel-Estradiol	Hydrocodone-Ibuprofen	Tamoxifen
Dexamethasone	Hydrocortisone	Telmisartan
Dexlansoprazole	Hydroxyprogesterone	Testosterone
Dexmethylphenidate	Hydroxyzine	Theophylline
Dienogest-Estradiol	Ibuprofen	Timolol
Donepezil	Indomethacin	Tizanidine
Dorzolamide-Timolol	Lansoprazole	Trandolapril
Dronabinol	Losartan	Triamcinolone
Drospirenone-Estradiol		

Table 3: Medications with Suicidal Side Effect Consumed by U.S. Adults Aged 25-84 in MEPS 1996-2016.

Acamprosate	Escitalopram	Olanzapine
Acetaminophen	Esomeprazole	Oxandrolone
Acetaminophen-Hydrocodone	Eszopiclone	Oxcarbazepine
Acetaminophen-Tramadol	Ferrous Sulfate	Paroxetine
Alprazolam	Finasteride	Peginterferon Alfa-2A
Amantadine	Fluoxetine	Phenelzine
Amitriptyline	Fluoxetine-Olanzapine	Phenytoin
Amitriptyline-Chlordiazepoxide	Flurazepam	Prednisone
Amitriptyline-Perphenazine	Fluticasone	Pregabalin
Amoxicillin-Clavulanate	Fluvoxamine	Progesterone
Aripiprazole	Gabapentin	Protriptyline
Armodafinil	Haloperidol	Quetiapine
Asenapine	Hydrocortisone	Raltegravir
Aspirin	Iloperidone	Ramelteon
Atomoxetine	Imipramine	Ranitidine
Bupropion	Interferon Beta-1A	Ribavirin
Butabarbital	Interferon Beta-1B	Risperidone
Carbamazepine	Isotretinoin	Rivastigmine
Carbidopa-Entacapone-Levodopa	Lamotrigine	Roflumilast
Carbidopa-Levodopa	Leuprolide	Selegiline
Chlordiazepoxide	Levetiracetam	Sertraline
Chlorzoxazone	Levonorgestrel	Sibutramine
Ciprofloxacin	Lorazepam	Tapentadol
Citalopram	Lurasidone	Topiramate
Clomipramine	Mefloquine	Tramadol
Clonazepam	Memantine	Trazodone
Clorazepate	Methylphenidate	Triazolam
Dapsone	Metoclopramide	Valproic Acid
Desipramine	Milnacipran	Varenicline
Desvenlafaxine	Mirtazapine	Venlafaxine
Diazepam	Modafinil	Vilazodone

Didanosine	Montelukast	Zafirlukast
Doxepin	Moxifloxacin	Zaleplon
Duloxetine	Nefazodone	Zolpidem
Efavirenz	Nortriptyline	Zonisamide
Efavirenz-Emtricitabine-Tenofovir	Ofloxacin	

Table 4: Medications with Anxiety Side Effect Consumed by U.S. Adults Aged 25-84 in MEPS 1996-2016.

Acamprosate	Estazolam	Modafinil
Amantadine	Exemestane	Mycophenolate Mofetil
Aripiprazole	Fentanyl	Paliperidone
Armodafinil	Fluoxetine	Peginterferon Alfa-2A
Carbidopa-Levodopa	Fluvoxamine	Propafenone
Cetirizine-Pseudoephedrine	Glatiramer	Pseudoephedrine
Chlorpheniramine-Hydrocodone	Guaifenesin-Hydrocodone-Pseudoephedrine	Risperidone
Codeine-Phenylephrine-Promethazine	Hydrocodone	Topiramate
Dalfampridine	Hydrocodone-Pseudoephedrine	Tretinoin
Desvenlafaxine	Levothyroxine	Triazolam
Dexmethylphenidate	Lindane	Valproic Acid
Dronabinol	Lisdexamfetamine	Venlafaxine
Efavirenz-Emtricitabine-Tenofovir	Mefloquine	Ziprasidone
Epinephrine	Methylphenidate	

Table 5. Descriptive Statistics for Mental Health, Medication Use, and Control Variables for U.S. Adults Aged 25-84. Data Source: MEPS 2004-2015.

	All respondents		Number of medications with any insomnia, depression, suicide, or anxiety side effects[a]								P-value[b]
			None		1 medication		2 medications		3+ medications		
	N = 211,551		N = 151,337		N = 33,883		N = 14,225		N = 12,106		
Binary outcomes at follow-up[c], N[d] (%)[e]											
Mental distress (K6 >= 13)	12390	(5.0)	5924	(3.3)	2187	(5.2)	1527	(8.7)	2752	(19.6)	p < 0.001
Felt everything an effort most/all of the time	17896	(7.5)	9469	(5.4)	3095	(7.6)	1967	(11.7)	3365	(25.5)	p < 0.001
Felt hopeless most/all of the time	9076	(3.6)	4627	(2.5)	1567	(3.5)	1034	(5.7)	1848	(13.0)	p < 0.001
Felt nervous most/all of the time	11801	(4.9)	5821	(3.3)	2112	(5.1)	1409	(8.2)	2459	(17.6)	p < 0.001
Felt restless most/all of the time	13902	(5.8)	7238	(4.2)	2480	(6.1)	1624	(9.3)	2560	(18.1)	p < 0.001
Felt sad most/all of the time	7393	(2.8)	3712	(2.0)	1274	(2.7)	865	(4.6)	1542	(10.5)	p < 0.001
Felt worthless most/all of the time	8055	(3.3)	3962	(2.2)	1394	(3.3)	960	(5.4)	1739	(12.5)	p < 0.001
Any new mental disorders at follow-up	9775	(5.0)	5621	(4.0)	1921	(5.8)	1057	(7.4)	1176	(9.8)	p < 0.001
Whether had more outpatient, inpatient, office-based, emergency visits for mental disorders at follow-up	8712	(4.5)	3137	(2.2)	1851	(5.6)	1423	(10.2)	2301	(18.7)	p < 0.001
Used more of any four medications below for treatment of mental disorders at follow-up	9434	(5.0)	4748	(3.6)	1978	(6.1)	1195	(8.4)	1513	(12.5)	p < 0.001
Used more antidepressants	7371	(4.0)	3788	(3.0)	1475	(4.6)	887	(6.3)	1221	(10.1)	p < 0.001
Used more anxiolytics, sedatives, or hypnotics	4157	(2.2)	1617	(1.2)	862	(2.6)	656	(4.7)	1022	(8.6)	p < 0.001
Used more anticonvulsants	3173	(1.7)	1095	(0.8)	623	(1.9)	537	(3.8)	918	(7.7)	p < 0.001
Used more antipsychotics	2417	(1.2)	822	(0.6)	427	(1.3)	402	(2.9)	766	(6.4)	p < 0.001
Continuous outcomes at follow-up[c], mean[d] (standard error)											
K6 total score	3.34	(0.02)	2.81	(0.02)	3.57	(0.03)	4.59	(0.06)	6.97	(0.08)	p < 0.001
Changes in number of outpatient, inpatient, office-based, emergency visits for mental disorders between baseline and follow-up	0.16	(0.01)	0.09	(0.01)	0.19	(0.02)	0.33	(0.03)	0.63	(0.05)	p < 0.001
Changes in total costs for mental disorders between baseline and follow-up[f]	76.46	(7.02)	46.01	(4.14)	97.60	(10.99)	166.97	(29.80)	241.50	(87.75)	p < 0.001

Independent variables[a], N[d] (%)[e]											
Number of medications WITH insomnia, depression, suicidal, and anxiety side effects											
None	151337	(68.6)									
1 medication	33883	(17.7)									
2 medications	14225	(7.5)									
3+ medications	12106	(6.3)									
Number of medications WITHOUT insomnia, depression, suicidal, and anxiety side effects											
None	134356	(61.1)									
1 medication	31552	(16.2)									
2 medications	17849	(9.1)									
3+ medications	27794	(13.6)									
Changes in number of medications WITH insomnia, depression, suicidal, and anxiety side effects between baseline and subsequent round											
Decline or no changes	166584	(77.3)	120437	(77.7)	26061	(76.6)	10891	(76.4)	9195	(76.0)	$p < 0.001$
Increase of 1 medication	28681	(14.4)	19915	(14.2)	4932	(14.9)	2071	(14.7)	1763	(14.8)	$p = 0.065$
Increase of 2 medications	9971	(5.1)	6753	(5.0)	1737	(5.1)	759	(5.4)	722	(5.9)	$p = 0.001$
Increase of 3+ medications	6315	(3.2)	4232	(3.1)	1153	(3.4)	504	(3.4)	426	(3.3)	$p = 0.048$
Changes in number of medications WITHOUT insomnia, depression, suicidal, and anxiety side effects between baseline and subsequent round											
Decline or no changes	151197	(70.1)	111886	(72.2)	22636	(67.0)	9143	(64.6)	7532	(62.4)	$p < 0.001$
Increase of 1 medication	30248	(15.1)	19689	(14.0)	5754	(16.8)	2523	(17.8)	2282	(19.1)	$p < 0.001$
Increase of 2 medications	13902	(6.9)	9035	(6.3)	2613	(7.8)	1214	(8.4)	1040	(8.6)	$p < 0.001$
Increase of 3+ medications	16204	(7.9)	10727	(7.5)	2880	(8.4)	1345	(9.3)	1252	(9.9)	$p < 0.001$
Race											
Non-Hispanic White	104477	(69.1)	67230	(64.9)	20005	(76.4)	9050	(79.6)	8192	(82.0)	$p < 0.001$
Non-Hispanic Black	37145	(10.8)	27582	(11.9)	5547	(8.9)	2304	(8.7)	1712	(7.4)	$p < 0.001$
Hispanic	51583	(13.1)	42009	(15.4)	5863	(9.1)	2095	(7.6)	1616	(6.9)	$p < 0.001$
Others	18346	(6.9)	14516	(7.9)	2468	(5.6)	776	(4.1)	586	(3.7)	$p < 0.001$
Female	115305	(52.2)	76418	(47.2)	21345	(61.2)	9256	(63.4)	8286	(67.1)	$p < 0.001$
Age groups											
25-44	93171	(41.9)	75536	(47.5)	11498	(34.3)	3710	(26.3)	2427	(19.6)	$p < 0.001$
45-64	83370	(40.1)	56939	(38.7)	14221	(41.6)	6260	(43.3)	5950	(48.5)	$p < 0.001$
65-84	35010	(18.0)	18862	(13.8)	8164	(24.1)	4255	(30.3)	3729	(31.9)	$p < 0.001$
Marital status											
Married or cohabiting	123510	(60.8)	89678	(61.3)	20088	(62.5)	7770	(58.4)	5974	(53.9)	$p < 0.001$

Divorced, widowed, or separated	47033	(21.4)	29467	(19.0)	8640	(23.2)	4433	(28.4)	4493	(34.0)	p < 0.001
Never married	41008	(17.8)	32192	(19.7)	5155	(14.3)	2022	(13.1)	1639	(12.1)	p < 0.001
Educational attainment											
Less than high school	43595	(12.9)	32157	(13.1)	5950	(10.9)	2841	(13.1)	2647	(15.2)	p < 0.001
High school graduate	64726	(29.7)	45998	(29.5)	10241	(29.0)	4457	(30.7)	4030	(33.0)	p < 0.001
College or above	103230	(57.4)	73182	(57.4)	17692	(60.1)	6927	(56.3)	5429	(51.7)	p < 0.001
Household income <100% federal poverty guideline	32849	(9.9)	22817	(9.5)	4800	(9.0)	2485	(11.1)	2747	(15.7)	p < 0.001
Has private insurance	126526	(69.3)	90449	(69.5)	21970	(73.6)	8257	(67.0)	5850	(57.6)	p < 0.001
Has public insurance, Medicaid, or SCHIP	30997	(9.6)	18804	(8.0)	5426	(9.8)	3054	(13.9)	3713	(21.6)	p < 0.001
Has Medicare insurance	41688	(20.7)	21121	(15.0)	9467	(27.0)	5312	(36.0)	5788	(46.9)	p < 0.001
Has any other health insurance	2487	(1.2)	1486	(5.9)	507	(1.4)	246	(1.7)	248	(2.1)	p < 0.001
Whether obese (BMI >= 30)	68727	(30.8)	45705	(28.3)	11907	(32.7)	5698	(38.4)	5417	(43.1)	p < 0.001
Any pain that interfered with work/housework	100490	(47.2)	61739	(40.5)	18973	(53.3)	9861	(66.4)	9917	(80.1)	p < 0.001
Number of reported/treated chronic conditions											
None	125484	(57.5)	105590	(68.2)	13645	(41.8)	4001	(29.3)	2248	(19.2)	p < 0.001
1 condition	39398	(19.5)	24686	(17.3)	8577	(25.1)	3574	(25.1)	2561	(21.4)	p < 0.001
2 conditions	22825	(11.2)	11912	(8.2)	5661	(16.2)	2832	(20.0)	2420	(20.0)	p < 0.001
3+ conditions	23844	(11.7)	9149	(6.3)	6000	(16.9)	3818	(25.6)	4877	(39.4)	p < 0.001
Specific types of reported/treated chronic conditions											
Hypertension	58607	(27.7)	30198	(20.0)	14065	(38.6)	7260	(48.6)	7084	(56.4)	p < 0.001
Congestive heart failure	1629	(0.8)	612	(0.4)	378	(1.0)	273	(1.7)	366	(2.9)	p < 0.001
Coronary artery disease	9746	(5.0)	3679	(2.7)	2531	(7.5)	1565	(10.8)	1971	(16.0)	p < 0.001
Cardiac arrhythmias	5681	(3.2)	2296	(1.8)	1468	(4.8)	927	(7.0)	990	(8.8)	p < 0.001
Hyperlipidemia	43545	(22.2)	22124	(16.0)	10385	(30.6)	5436	(38.4)	5600	(46.5)	p < 0.001
Stroke	3381	(1.6)	1389	(0.9)	753	(2.0)	538	(3.4)	701	(5.8)	p < 0.001
Arthritis	14210	(7.4)	5725	(4.3)	3295	(9.8)	2162	(15.5)	3028	(25.2)	p < 0.001
Asthma	12041	(5.8)	5638	(3.8)	2587	(7.4)	1614	(10.6)	2202	(17.3)	p < 0.001
Cancer	10795	(6.3)	5179	(4.4)	2696	(9.2)	1458	(11.2)	1462	(13.1)	p < 0.001
Chronic kidney disease	169	(0.07)	57	(0.03)	41	(0.10)	21	(0.1)	50	(0.4)	p < 0.001
Chronic obstructive pulmonary disease	11438	(6.1)	5319	(4.0)	2468	(7.6)	1505	(10.8)	2146	(17.9)	p < 0.001
Dementia, Alzheimer's, and other senile dementias)	1185	(0.5)	419	(0.2)	261	(0.6)	211	(1.4)	294	(2.2)	p < 0.001
Diabetes	24671	(10.6)	13065	(7.9)	5456	(13.7)	2963	(18.1)	3187	(23.8)	p < 0.001
Hepatitis	738	(0.3)	346	(0.2)	155	(0.4)	98	(0.6)	139	(1.0)	p < 0.001

Human immunodeficiency virus (HIV)	493	(0.2)	202	(0.1)	102	(0.2)	67	(0.4)	122	(0.8)	p < 0.001
Osteoporosis	3443	(1.8)	1586	(1.2)	864	(2.6)	468	(3.3)	525	(4.2)	p < 0.001
Region of residence											
Northeast	32740	(18.0)	23027	(18.0)	5596	(19.1)	2309	(18.2)	1808	(15.4)	p = 0.006
Midwest	41728	(22.1)	28170	(21.3)	7463	(23.6)	3236	(23.9)	2859	(25.2)	p < 0.001
South	81078	(37.1)	57684	(36.8)	12835	(36.6)	5609	(38.2)	4950	(39.8)	p = 0.001
West	56005	(22.8)	42456	(24.0)	7989	(20.8)	3071	(19.7)	2489	(19.5)	p < 0.001

[a]: Measured in rounds 1/3 (baseline)

[b]: p-value for differences in the variable across categories of medications with side effects.

[c]: Measured in rounds 2/4.

[d]: unweighted frequency.

[e]: weighted prevalence or mean.

[f]: adjusted to 2016 dollars

Table 6. Adjusted Linear Least-Squared and Logit Regressions of Mental Health on Medication Use for Adults Aged 25-84. Data Source: MEPS 2004-2015.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	Overall K6 scale [a]		**Individual questions of the K6 scale (score >=3) [a]**						**Mental disorders [a]**
Outcome:	Raw score	Whether score >=13	Felt everything an effort	Felt hopeless	Felt nervous	Felt restless	Felt sad	Felt worthless	Any new mental disorders at follow-up
	OLS	Logit	Logit	Logit	Logit	Logit	Logit	Logit	Logit
	Coeff. (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Number of medications WITH any insomnia, depression, suicidal, or anxiety side effects at baseline [b]									
None (reference)									
1 medication	0.113***	1.085	1.057	1.021	1.076	1.151***	0.990	1.007	1.334***
	(0.030)	(0.046)	(0.033)	(0.049)	(0.043)	(0.047)	(0.053)	(0.053)	(0.052)
2 medications	0.224***	1.214***	1.155**	1.107	1.169**	1.266***	1.112	1.086	1.598***
	(0.048)	(0.060)	(0.051)	(0.064)	(0.064)	(0.068)	(0.075)	(0.069)	(0.083)
3+ medications	1.318***	1.859***	1.936***	1.634***	1.696***	1.736***	1.623***	1.597***	1.987***
	(0.077)	(0.113)	(0.098)	(0.102)	(0.098)	(0.110)	(0.123)	(0.108)	(0.121)
Number of medications WITHOUT any insomnia, depression, suicidal, or anxiety side effects at baseline [b]									
None (reference)									
1 medication	0.043	0.959	1.039	0.996	1.037	1.014	0.908*	1.000	1.043
	(0.031)	(0.038)	(0.035)	(0.043)	(0.044)	(0.038)	(0.043)	(0.048)	(0.042)
2 medications	0.026	0.955	1.022	0.946	0.989	0.983	0.996	0.948	1.058
	(0.043)	(0.045)	(0.042)	(0.053)	(0.050)	(0.049)	(0.056)	(0.054)	(0.051)
3+ medications	0.059	0.939	1.132**	0.908	0.923	0.988	0.867*	1.001	0.935
	(0.050)	(0.048)	(0.049)	(0.052)	(0.047)	(0.049)	(0.051)	(0.063)	(0.049)

Mean outcome	3.301	0.049	0.074	0.035	0.048	0.057	0.028	0.032	0.050
No. of persons	211,551	211,551	211,551	211,551	211,551	211,551	211,551	211,551	211,551

Note: * p<0.05, ** p<0.01, *** p<0.001
All analyses control for changes in the number of medications with and without side effects consumed between round 1 and round 2 (for those in the first year of their panel) and between round 3 and round 4 (for those in the second year of their panel), race/ethnicity, gender, age and age squared, marital status, education, poverty, health insurance coverage, obesity, number of chronic conditions, whether had any pain that interfered with normal work outside the house or housework in the past 4 weeks, year and region fixed-effects.
[a]: Measured in round 2 for those in the 1st year of their panel, and round 4 for those in the 2nd year.
[b]: Measured in round 1 for those in the 1st year of their panel, and round 3 for those in the 2nd year.

Table 7. Adjusted Logit and Two-Part Model Regressions of Utilization/Cost of Mental Health Services on Medication Use for Adults Aged 25-84. Data Source: MEPS 2004-2015.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Health services utilization [a]							
Outcome:	Whether had more visits for mental disorders at follow-up	Changes in number of visits for mental disorders between baseline and follow-up	Changes in cost for mental disorders between baseline and follow-up	Whether used more psychotropic medications for mental disorders at follow-up	Whether used more antidepres-sants for mental disorders at follow-up	Whether used more anxiolytics, sedatives, or hypnotics for mental disorders at follow-up	Whether used more anticonvul-sants for mental disorders at follow-up	Whether used more antipsych-otics for mental disorders at follow-up
	Logit	Two-part model	Two-part model	Logit	Logit	Logit	Logit	Logit
	OR (SE)	Marginal effect (SE)	Marginal effect (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Number of medications WITH any insomnia, depression, suicidal, or anxiety side effects at baseline [b]								
None (reference)								
1 medication	1.359***	0.030*	11.103	1.415***	1.274***	1.410***	1.276**	0.955
	(0.071)	(0.013)	(9.684)	(0.067)	(0.068)	(0.096)	(0.102)	(0.100)
2 medications	1.715***	0.047*	31.411*	1.737***	1.538***	1.856***	1.735***	1.309*
	(0.114)	(0.018)	(15.642)	(0.104)	(0.106)	(0.141)	(0.156)	(0.159)
3+ medications	2.346***	0.152***	103.274***	2.272***	2.224***	2.519***	2.543***	1.909***
	(0.167)	(0.026)	(23.050)	(0.190)	(0.179)	(0.250)	(0.277)	(0.241)
Number of medications WITHOUT any insomnia, depression, suicidal, or anxiety side effects at baseline [b]								
None (reference)								
1 medication	1.000	0.005	-1.817	0.967	0.971	0.954	0.940	1.033
	(0.047)	(0.015)	(9.432)	(0.041)	(0.043)	(0.062)	(0.066)	(0.082)
2 medications	0.965	-0.012	4.367	0.976	0.878*	1.059	1.055	1.039
	(0.057)	(0.017)	(11.136)	(0.056)	(0.057)	(0.084)	(0.103)	(0.106)

3+ medications	0.818***	-0.027	-1.608	0.785***	0.790***	0.969	0.896	0.936
	(0.046)	(0.015)	(10.842)	(0.045)	(0.052)	(0.068)	(0.078)	(0.095)
Mean outcome	0.045	0.158	76.465	0.050	0.040	0.022	0.017	0.012
No. of persons	211,551	211,551	211,551	211,551	211,551	211,551	211,551	211,551

Note: * p<0.05, ** p<0.01, *** p<0.001
All analyses control for changes in the number of medications with and without side effects consumed between round 1 and round 2 (for those in the first year of their panel) and between round 3 and round 4 (for those in the second year of their panel), race/ethnicity, gender, age and age squared, marital status, education, poverty, health insurance coverage, obesity, number of chronic conditions, whether had any pain that interfered with normal work outside the house or housework in the past 4 weeks, year and region fixed-effects.
[a]: Measured in round 2 for those in the 1st year of their panel, and round 4 for those in the 2nd year.
[b]: Measured in round 1 for those in the 1st year of their panel, and round 3 for those in the 2nd year.

Table 8. Adjusted Linear Least-Squared and Logit Regressions of Mental Health on Medication Use for Adults Aged 25-84 With at Most One Chronic Condition. Data Source: MEPS 2004-2015.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	Overall K6 scale [a]		**Individual questions of the K6 scale (score >=3) [a]**						**Mental disorders [a]**
Outcome:	Raw score	Whether score >=13	Felt everything an effort	Felt hopeless	Felt nervous	Felt restless	Felt sad	Felt worthless	Any new mental disorders at follow-up
	OLS	Logit	Logit	Logit	Logit	Logit	Logit	Logit	Logit
	Coeff. (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Number of medications WITH any insomnia, depression, suicidal, or anxiety side effects at baseline [b]									
None (reference)									
1 medication	0.118***	1.117*	1.032	1.005	1.062	1.214***	0.982	1.008	1.392***
	(0.033)	(0.057)	(0.044)	(0.059)	(0.053)	(0.061)	(0.068)	(0.065)	(0.069)
2 medications	0.244***	1.225**	1.142*	1.021	1.112	1.277***	1.136	1.095	1.745***
	(0.060)	(0.084)	(0.067)	(0.082)	(0.079)	(0.085)	(0.105)	(0.095)	(0.118)
3+ medications	1.268***	1.975***	1.842***	1.719***	1.696***	1.826***	1.589***	1.559***	2.249***
	(0.099)	(0.162)	(0.145)	(0.143)	(0.129)	(0.151)	(0.159)	(0.145)	(0.184)
Number of medications WITHOUT any insomnia, depression, suicidal, or anxiety side effects at baseline [b]									
None (reference)									
1 medication	0.065	0.960	1.061	1.013	1.092	1.018	0.941	1.004	1.072
	(0.034)	(0.044)	(0.044)	(0.053)	(0.057)	(0.044)	(0.055)	(0.056)	(0.051)
2 medications	0.095	1.011	1.105	1.064	1.073	1.035	1.117	1.045	1.055
	(0.050)	(0.059)	(0.057)	(0.071)	(0.064)	(0.057)	(0.077)	(0.078)	(0.061)
3+ medications	0.170*	0.987	1.270***	0.969	0.966	1.073	0.890	1.123	0.968
	(0.069)	(0.070)	(0.083)	(0.084)	(0.065)	(0.068)	(0.082)	(0.102)	(0.072)
Mean outcome	3.003	0.038	0.059	0.028	0.039	0.048	0.022	0.026	0.044

No. of persons	164,882	164,882	164,882	164,882	164,882	164,882	164,882	164,882	164,882

Note: * p<0.05, ** p<0.01, *** p<0.001

All analyses control for changes in the number of medications with and without side effects consumed between round 1 and round 2 (for those in the first year of their panel) and between round 3 and round 4 (for those in the second year of their panel), race/ethnicity, gender, age and age squared, marital status, education, poverty, health insurance coverage, obesity, number of chronic conditions, whether had any pain that interfered with normal work outside the house or housework in the past 4 weeks, year and region fixed-effects.

[a]: Measured in round 2 for those in the 1st year of their panel, and round 4 for those in the 2nd year.

[b]: Measured in round 1 for those in the 1st year of their panel, and round 3 for those in the 2nd year.

Table 9. Adjusted Logit and Two-Part Model Regressions of Utilization/Cost of Mental Health Services on Medication Use for Adults Aged 25-84 With at Most One Chronic Condition. Data Source: MEPS 2004-2015.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
				Health services utilization [a]				
Outcome:	Whether had more visits for mental disorders at follow-up	Changes in number of visits for mental disorders between baseline and follow-up	Changes in cost for mental disorders between baseline and follow-up	Whether used more medications for mental disorders at follow-up	Whether used more antidepres-sants for mental disorders at follow-up	Whether used more anxiolytics, sedatives, or hypnotics for mental disorders at follow-up	Whether used more anticonvul-sants for mental disorders at follow-up	Whether used more antipsych-otics for mental disorders at follow-up
	Logit	Two-part model	Two-part model	Logit	Logit	Logit	Logit	Logit
	OR (SE)	Marginal effect (SE)	Marginal effect (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Number of medications WITH any insomnia, depression, suicidal, or anxiety side effects at baseline [b]								
None (reference)								
1 medication	1.447***	0.021	11.398	1.558***	1.392***	1.507***	1.235	0.925
	(0.091)	(0.014)	(8.728)	(0.098)	(0.096)	(0.148)	(0.139)	(0.125)
2 medications	1.994***	0.070**	38.634*	2.128***	1.921***	2.201***	1.939***	1.489**
	(0.162)	(0.023)	(15.156)	(0.181)	(0.184)	(0.254)	(0.261)	(0.227)
3+ medications	2.730***	0.158***	102.222***	2.989***	3.092***	3.049***	3.019***	2.129***
	(0.262)	(0.034)	(24.579)	(0.363)	(0.396)	(0.429)	(0.450)	(0.376)
Number of medications WITHOUT any insomnia, depression, suicidal, or anxiety side effects at baseline [b]								
None (reference)								
1 medication	0.990	0.013	4.757	0.987	0.988	0.986	0.946	0.999
	(0.055)	(0.014)	(8.268)	(0.050)	(0.050)	(0.077)	(0.076)	(0.091)

2 medications	0.914	-0.007	14.572	0.969	0.896	1.051	1.067	1.044
	(0.063)	(0.017)	(12.903)	(0.074)	(0.080)	(0.107)	(0.131)	(0.153)
3+ medications	0.936	0.008	2.130	0.816*	0.831	0.985	0.853	0.943
	(0.073)	(0.022)	(13.366)	(0.074)	(0.080)	(0.109)	(0.115)	(0.155)
Mean outcome	0.038	0.137	59.606	0.039	0.031	0.016	0.012	0.009
No. of persons	164,882	164,882	164,882	164,882	164,882	164,882	164,882	164,882

Note: * p<0.05, ** p<0.01, *** p<0.001

All analyses control for changes in the number of medications with and without side effects consumed between round 1 and round 2 (for those in the first year of their panel) and between round 3 and round 4 (for those in the second year of their panel), race/ethnicity, gender, age and age squared, marital status, education, poverty, health insurance coverage, obesity, number of chronic conditions, whether had any pain that interfered with normal work outside the house or housework in the past 4 weeks, year and region fixed-effects.

[a]: Measured in round 2 for those in the 1st year of their panel, and round 4 for those in the 2nd year.

[b]: Measured in round 1 for those in the 1st year of their panel, and round 3 for those in the 2nd year.

Table 10. Adjusted Linear Least-Squared and Logit Regressions of Mental Health on Medication Use for Adults Aged 25-84 Without Mental Disorders at Baseline. Data Source: MEPS 2004-2015.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	Overall K6 scale [a]		**Individual questions of the K6 scale (score >=3) [a]**						**Mental disorders [a]**
Outcome:	Raw score	Whether score >=13	Felt everything an effort	Felt hopeless	Felt nervous	Felt restless	Felt sad	Felt worthless	Any new mental disorders at follow-up
	OLS	Logit	Logit	Logit	Logit	Logit	Logit	Logit	Logit
	Coeff. (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Number of medications WITH any insomnia, depression, suicidal, or anxiety side effects at baseline [b]									
None (reference)									
1 medication	0.159***	1.060	1.068	1.043	1.119*	1.123*	1.012	0.975	1.341***
	(0.030)	(0.054)	(0.039)	(0.060)	(0.051)	(0.051)	(0.065)	(0.063)	(0.057)
2 medications	0.194***	1.157*	1.130*	1.051	1.118	1.173*	1.069	1.048	1.614***
	(0.050)	(0.072)	(0.066)	(0.085)	(0.080)	(0.075)	(0.089)	(0.091)	(0.099)
3+ medications	0.776***	1.550***	1.842***	1.277**	1.516***	1.664***	1.318*	1.257*	2.024***
	(0.086)	(0.120)	(0.132)	(0.120)	(0.129)	(0.136)	(0.144)	(0.122)	(0.161)
Number of medications WITHOUT any insomnia, depression, suicidal, or anxiety side effects at baseline [b]									
None (reference)									
1 medication	0.054	0.959	1.030	1.008	1.059	1.006	0.896	1.031	1.015
	(0.032)	(0.053)	(0.045)	(0.056)	(0.058)	(0.045)	(0.061)	(0.069)	(0.045)
2 medications	0.082	1.027	1.077	0.977	1.021	1.020	1.108	1.008	1.049
	(0.043)	(0.064)	(0.056)	(0.070)	(0.066)	(0.061)	(0.089)	(0.080)	(0.059)
3+ medications	0.144**	1.017	1.204**	0.981	1.012	1.080	1.039	1.193*	0.897
	(0.046)	(0.063)	(0.068)	(0.069)	(0.065)	(0.066)	(0.077)	(0.099)	(0.058)
Mean outcome	3.301	0.049	0.074	0.035	0.048	0.057	0.028	0.032	0.050

No. of persons	176,362	176,362	176,362	176,362	176,362	176,362	176,362	176,362	176,362

Note: * p<0.05, ** p<0.01, *** p<0.001

All analyses control for changes in the number of medications with and without side effects consumed between round 1 and round 2 (for those in the first year of their panel) and between round 3 and round 4 (for those in the second year of their panel), race/ethnicity, gender, age and age squared, marital status, education, poverty, health insurance coverage, obesity, number of chronic conditions, whether had any pain that interfered with normal work outside the house or housework in the past 4 weeks, year and region fixed-effects.

[a]: Measured in round 2 for those in the 1st year of their panel, and round 4 for those in the 2nd year.

[b]: Measured in round 1 for those in the 1st year of their panel, and round 3 for those in the 2nd year.

Table 11. Adjusted Logit and Two-Part Model Regressions of Utilization/Cost of Mental Health Services on Medication Use for Adults Aged 25-84 Without Mental Disorders at Baseline. Data Source: MEPS 2004-2015.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
				Health services utilization [a]				
Outcome:	Whether had more visits for mental disorders at follow-up	Changes in number of visits for mental disorders between baseline and follow-up	Changes in cost for mental disorders between baseline and follow-up	Whether used more medications for mental disorders at follow-up	Whether used more antidepres-sants for mental disorders at follow-up	Whether used more anxiolytics, sedatives, or hypnotics for mental disorders at follow-up	Whether used more anticonvul-sants for mental disorders at follow-up	Whether used more antipsych-otics for mental disorders at follow-up
	Logit	Two-part model	Two-part model	Logit	Logit	Logit	Logit	Logit
	OR (SE)	Marginal effect (SE)	Marginal effect (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Number of medications WITH any insomnia, depression, suicidal, or anxiety side effects at baseline [b]								
None (reference)								
1 medication	1.565***	0.017**	4.430	1.545***	1.425***	1.584***	1.270	0.914
	(0.110)	(0.006)	(3.384)	(0.104)	(0.106)	(0.168)	(0.174)	(0.165)
2 medications	2.056***	0.032**	18.500*	2.121***	1.949***	2.152***	1.864***	1.082
	(0.232)	(0.010)	(7.229)	(0.189)	(0.202)	(0.322)	(0.330)	(0.302)
3+ medications	1.857***	0.043*	17.742	3.143***	2.935***	3.042***	2.544***	1.548
	(0.275)	(0.019)	(9.680)	(0.360)	(0.400)	(0.489)	(0.531)	(0.507)
Number of medications WITHOUT any insomnia, depression, suicidal, or anxiety side effects at baseline [b]								
None (reference)								
1 medication	0.959	0.006	-3.324	1.041	1.021	1.020	0.976	1.180
	(0.077)	(0.006)	(3.258)	(0.063)	(0.066)	(0.112)	(0.133)	(0.214)

2 medications	0.983	-0.002	2.231	1.028	0.923	1.220	1.326	1.226
	(0.098)	(0.006)	(5.504)	(0.082)	(0.089)	(0.155)	(0.217)	(0.262)
3+ medications	0.886	-0.004	-6.508	0.792**	0.773**	0.961	0.936	1.138
	(0.097)	(0.007)	(4.688)	(0.068)	(0.072)	(0.127)	(0.163)	(0.289)
Mean outcome	0.045	0.158	76.465	0.050	0.040	0.022	0.017	0.012
No. of persons	176,362	176,362	176,362	176,362	176,362	176,362	176,362	176,362

Note: * p<0.05, ** p<0.01, *** p<0.001
All analyses control for changes in the number of medications with and without side effects consumed between round 1 and round 2 (for those in the first year of their panel) and between round 3 and round 4 (for those in the second year of their panel), race/ethnicity, gender, age and age squared, marital status, education, poverty, health insurance coverage, obesity, number of chronic conditions, whether had any pain that interfered with normal work outside the house or housework in the past 4 weeks, year and region fixed-effects.
[a]: Measured in round 2 for those in the 1st year of their panel, and round 4 for those in the 2nd year.
[b]: Measured in round 1 for those in the 1st year of their panel, and round 3 for those in the 2nd year.

Table 12. Adjusted Linear Least-Squared and Logit Regressions of Mental Health on Medication Use for Adults Aged 25-84 With Mental Disorders at Baseline. Data Source: MEPS 2004-2015.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	Overall K6 scale [a]		**Individual questions of the K6 scale (score >=3) [a]**						**Mental disorders [a]**
Outcome:	Raw score	Whether score >=13	Felt everything an effort	Felt hopeless	Felt nervous	Felt restless	Felt sad	Felt worthless	Any new mental disorders at follow-up
	OLS	Logit	Logit	Logit	Logit	Logit	Logit	Logit	Logit
	Coeff. (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Number of medications WITH any insomnia, depression, suicidal, or anxiety side effects at baseline [b]									
None (reference)									
1 medication	0.100	1.056	1.000	0.963	0.916	1.171	0.913	0.985	1.164
	(0.121)	(0.079)	(0.072)	(0.078)	(0.068)	(0.095)	(0.084)	(0.081)	(0.121)
2 medications	0.552***	1.240*	1.149	1.149	1.091	1.369***	1.101	1.099	1.422**
	(0.148)	(0.110)	(0.091)	(0.108)	(0.094)	(0.120)	(0.123)	(0.106)	(0.173)
3+ medications	1.837***	2.078***	1.983***	1.859***	1.650***	1.912***	1.742***	1.814***	1.837***
	(0.169)	(0.196)	(0.175)	(0.179)	(0.146)	(0.188)	(0.198)	(0.176)	(0.249)
Number of medications WITHOUT any insomnia, depression, suicidal, or anxiety side effects at baseline [b]									
None (reference)									
1 medication	-0.108	0.940	1.052	0.966	0.989	1.012	0.909	0.946	1.077
	(0.110)	(0.058)	(0.064)	(0.066)	(0.067)	(0.066)	(0.067)	(0.069)	(0.092)
2 medications	-0.305*	0.866*	0.937	0.894	0.934	0.923	0.886	0.866	1.032
	(0.131)	(0.060)	(0.062)	(0.078)	(0.069)	(0.067)	(0.079)	(0.074)	(0.104)
3+ medications	-0.364**	0.864*	1.037	0.837*	0.838*	0.884	0.738***	0.844	1.016
	(0.139)	(0.064)	(0.067)	(0.071)	(0.060)	(0.062)	(0.062)	(0.074)	(0.098)

Mean outcome	6.656	0.170	0.199	0.116	0.158	0.163	0.094	0.109	0.075
No. of persons	35,189	35,189	35,189	35,189	35,189	35,189	35,189	35,189	35,189

Note: * p<0.05, ** p<0.01, *** p<0.001

All analyses control for changes in the number of medications with and without side effects consumed between round 1 and round 2 (for those in the first year of their panel) and between round 3 and round 4 (for those in the second year of their panel), race/ethnicity, gender, age and age squared, marital status, education, poverty, health insurance coverage, obesity, number of chronic conditions, whether had any pain that interfered with normal work outside the house or housework in the past 4 weeks, year and region fixed-effects.

[a]: Measured in round 2 for those in the 1st year of their panel, and round 4 for those in the 2nd year.

[b]: Measured in round 1 for those in the 1st year of their panel, and round 3 for those in the 2nd year.

Table 13. Adjusted Logit and Two-Part Model Regressions of Utilization/Cost of Mental Health Services on Medication Use for Adults Aged 25-84 With Mental Disorders at Baseline. Data Source: MEPS 2004-2015.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Health services utilization [a]							
Outcome:	Whether had more visits for mental disorders at follow-up	Changes in number of visits for mental disorders between baseline and follow-up	Changes in cost for mental disorders between baseline and follow-up	Whether used more medications for mental disorders at follow-up	Whether used more antidepres-sants for mental disorders at follow-up	Whether used more anxiolytics, sedatives, or hypnotics for mental disorders at follow-up	Whether used more anticonvul-sants for mental disorders at follow-up	Whether used more antipsych-otics for mental disorders at follow-up
	Logit	Two-part model	Two-part model	Logit	Logit	Logit	Logit	Logit
	OR (SE)	Marginal effect (SE)	Marginal effect (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Number of medications WITH any insomnia, depression, suicidal, or anxiety side effects at baseline [b]								
None (reference)								
1 medication	1.184*	0.069	68.206	1.165*	1.047	1.169	1.180	0.952
	(0.084)	(0.085)	(60.799)	(0.087)	(0.081)	(0.108)	(0.123)	(0.116)
2 medications	1.489***	0.119	152.039	1.368***	1.210*	1.533***	1.580***	1.349*
	(0.122)	(0.110)	(90.350)	(0.116)	(0.117)	(0.154)	(0.182)	(0.181)
3+ medications	2.101***	0.660***	534.938***	1.927***	1.873***	2.126***	2.386***	2.014***
	(0.192)	(0.125)	(126.322)	(0.209)	(0.199)	(0.245)	(0.321)	(0.282)
Number of medications WITHOUT any insomnia, depression, suicidal, or anxiety side effects at baseline [b]								
None (reference)								

1 medication	0.980	-0.014	29.979	0.878*	0.911	0.901	0.906	0.968
	(0.049)	(0.084)	(60.331)	(0.053)	(0.058)	(0.063)	(0.067)	(0.077)
2 medications	0.938	-0.097	6.955	0.883	0.805*	0.950	0.929	0.965
	(0.058)	(0.103)	(63.331)	(0.074)	(0.071)	(0.079)	(0.094)	(0.104)
3+ medications	0.777***	-0.184	40.054	0.714***	0.748***	0.946	0.873	0.875
	(0.046)	(0.098)	(65.025)	(0.053)	(0.062)	(0.070)	(0.073)	(0.080)
Mean outcome	0.232	0.810	360.470	0.206	0.167	0.101	0.084	0.069
No. of persons	35,189	35,189	35,189	35,189	35,189	35,189	35,189	35,189

Note: * p<0.05, ** p<0.01, *** p<0.001
All analyses control for changes in the number of medications with and without side effects consumed between round 1 and round 2 (for those in the first year of their panel) and between round 3 and round 4 (for those in the second year of their panel), race/ethnicity, gender, age and age squared, marital status, education, poverty, health insurance coverage, obesity, number of chronic conditions, whether had any pain that interfered with normal work outside the house or housework in the past 4 weeks, year and region fixed-effects.
[a]: Measured in round 2 for those in the 1st year of their panel, and round 4 for those in the 2nd year.
[b]: Measured in round 1 for those in the 1st year of their panel, and round 3 for those in the 2nd year.

Figure 3: Association Between Baseline Medications with Side Effects and K6 Score by Age Groups

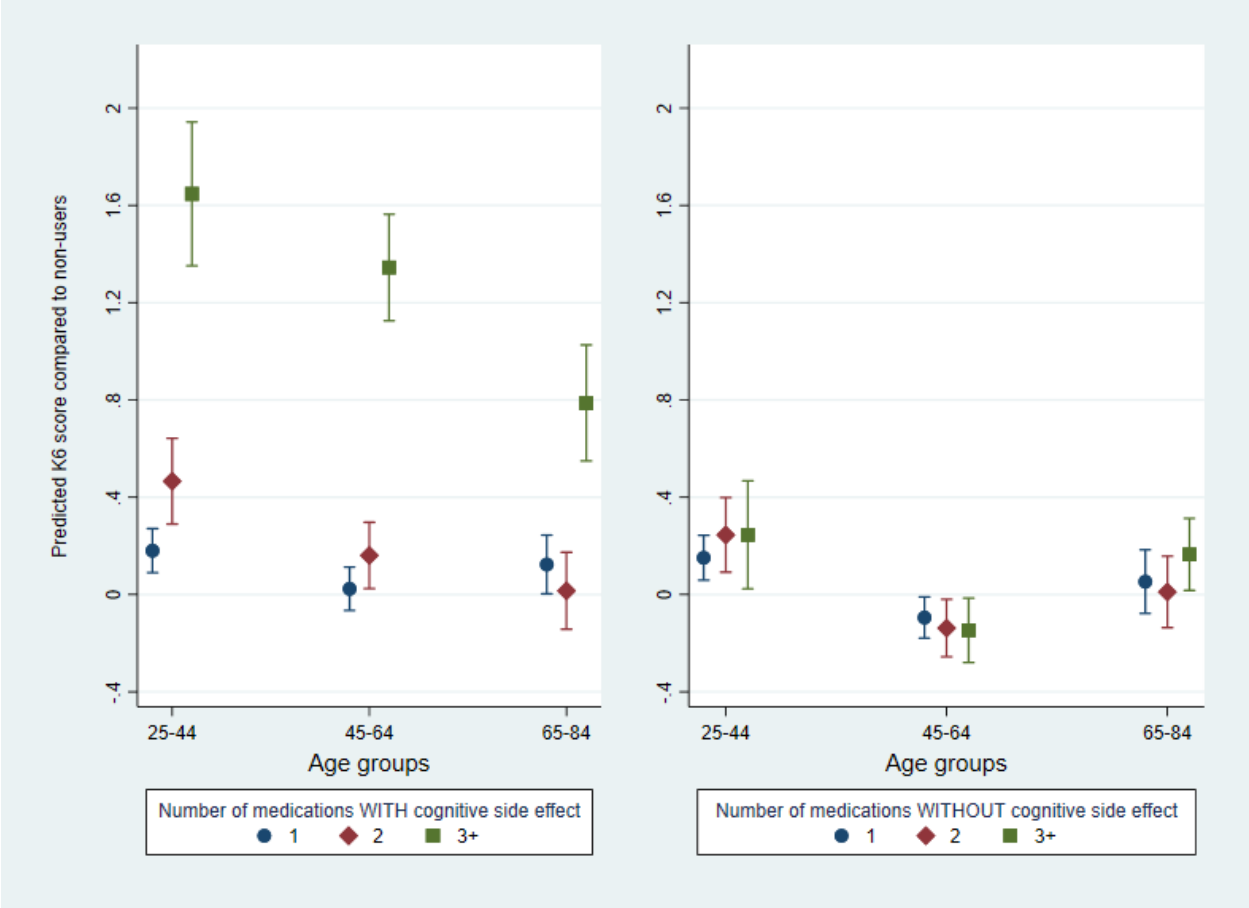


Figure 4: Association Between Baseline Medications with Side Effects and Mental Distress (K6 >= 13) by Age Groups

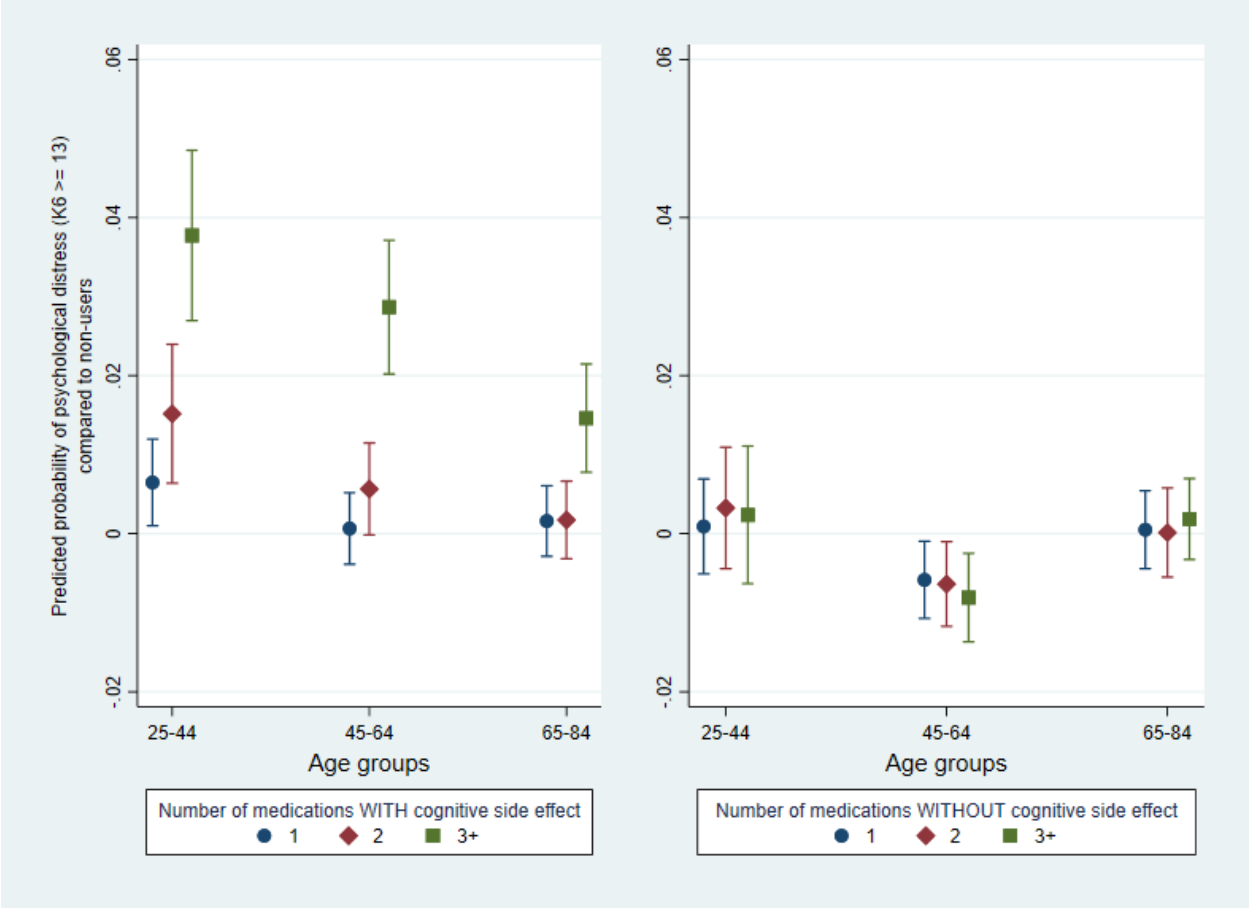


Figure 5: Association Between Baseline Medications with Side Effects and Whether Having a New Mental Disorder at Follow-up by Age Groups

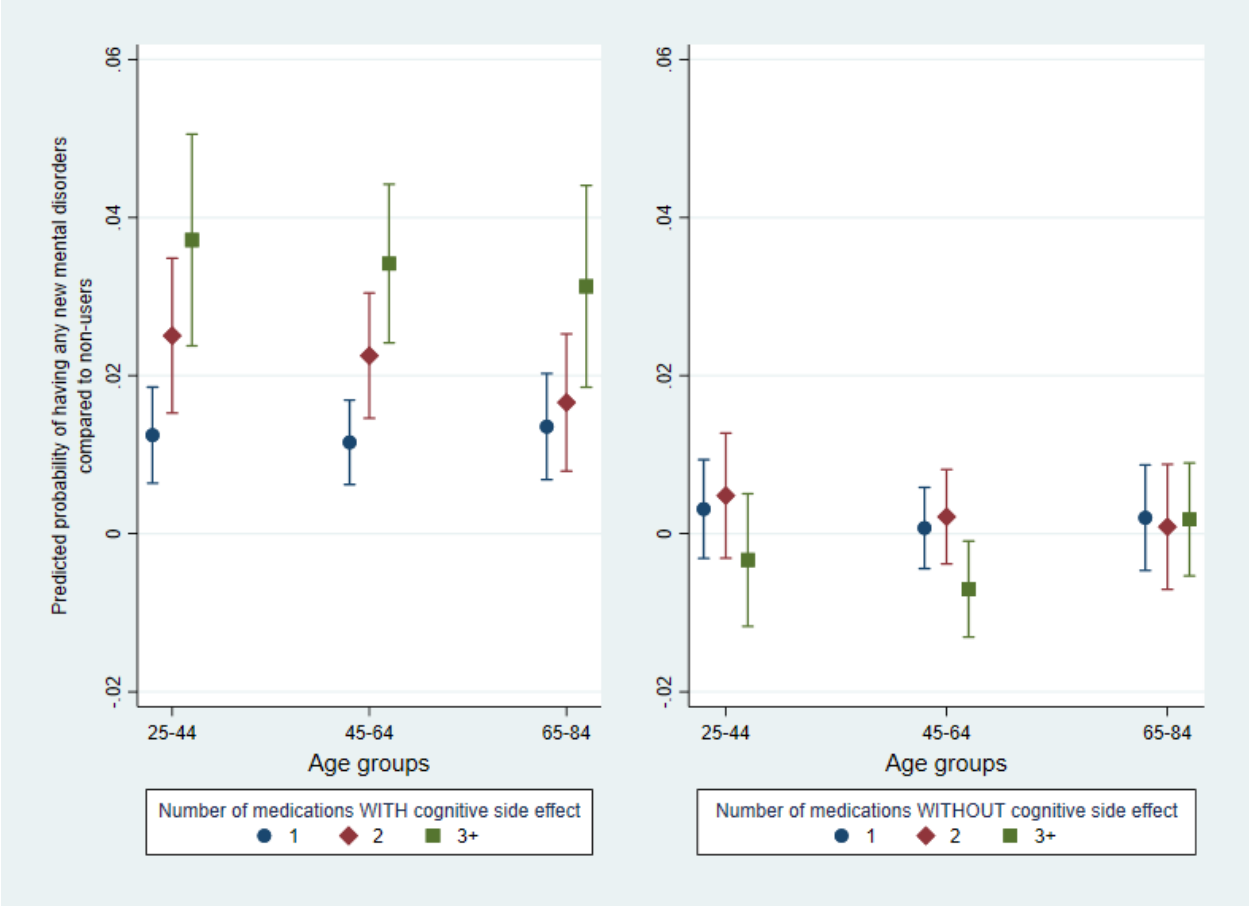


Figure 6: Association Between Baseline Medications with Side Effects and Whether Have More Visits for Mental Disorders at Follow-up by Age Groups

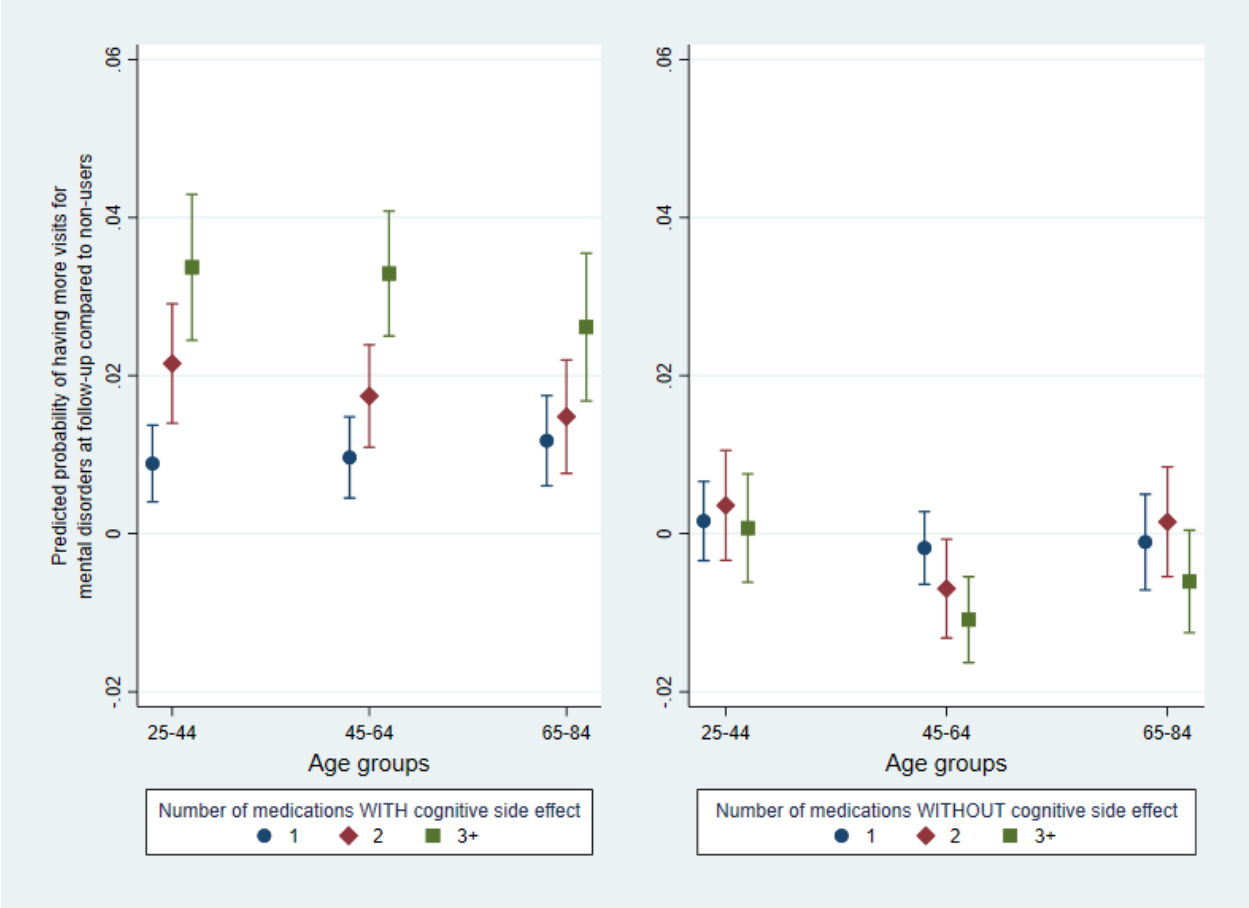


Figure 7: Association Between Baseline Medications with Side Effects and Whether Used More Psychotropic Medications for Treatment of Mental Disorders at Follow-up by Age Groups

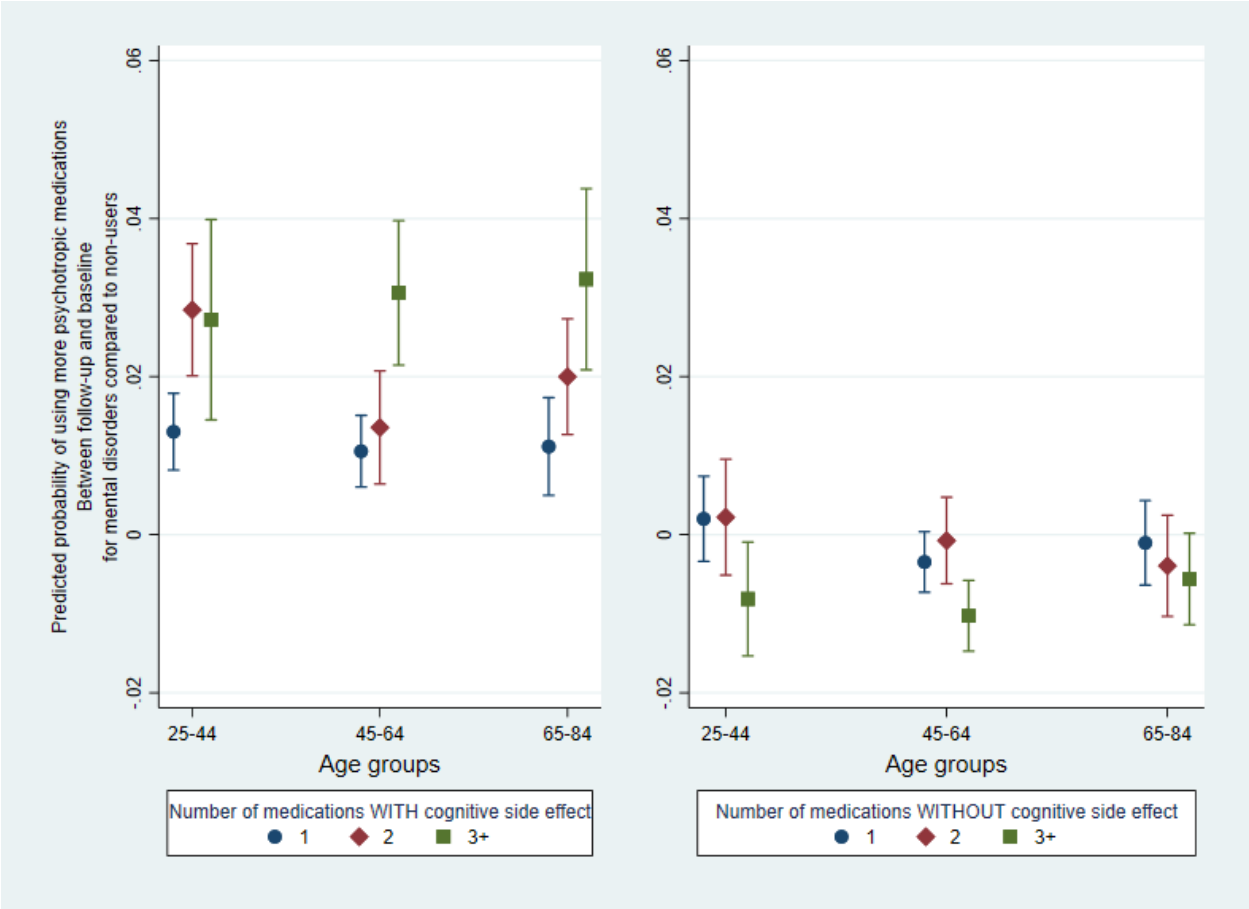


Figure 8: Association Between Baseline Medications with Side Effects and Changes in Number of Visits for Mental Disorders Between Baseline and Follow-up by Age Groups

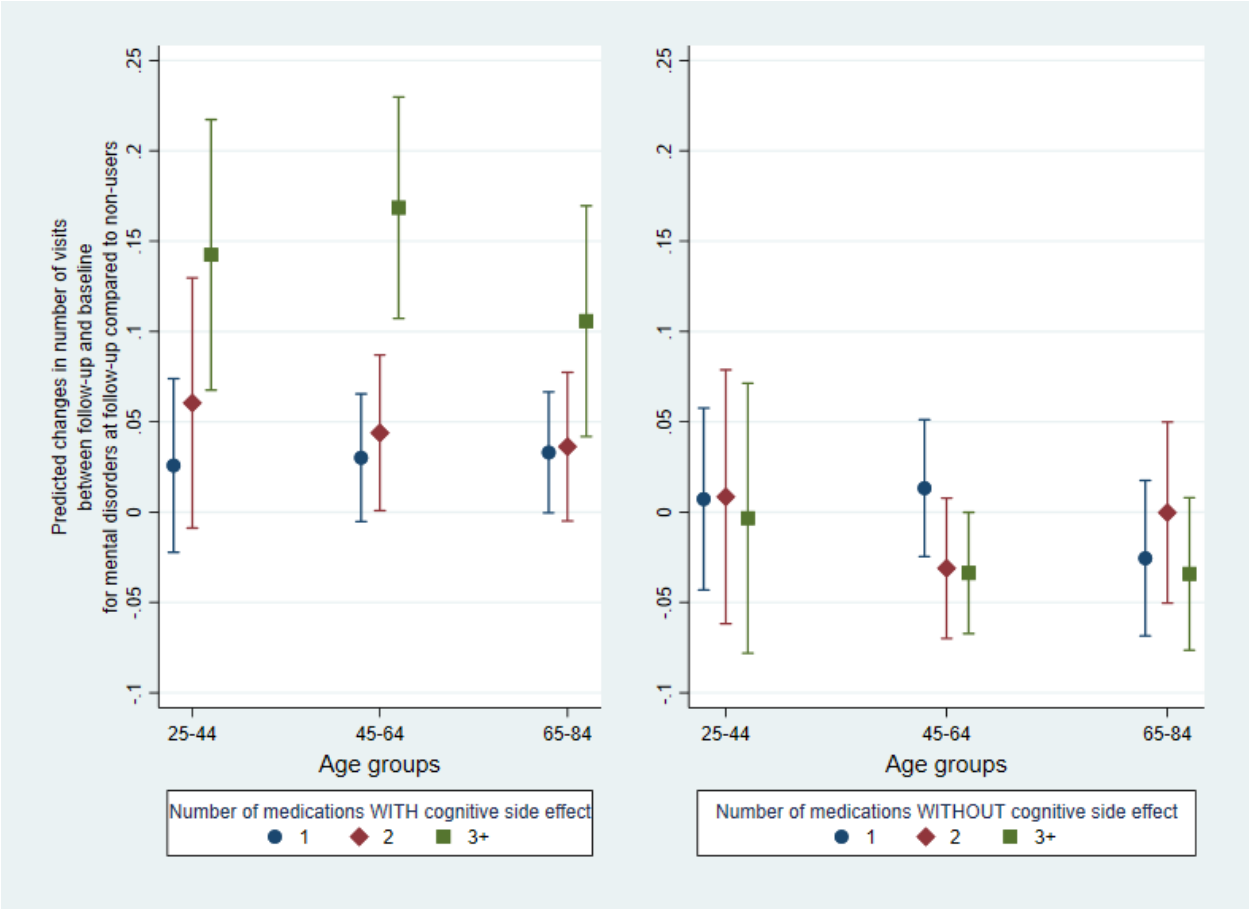
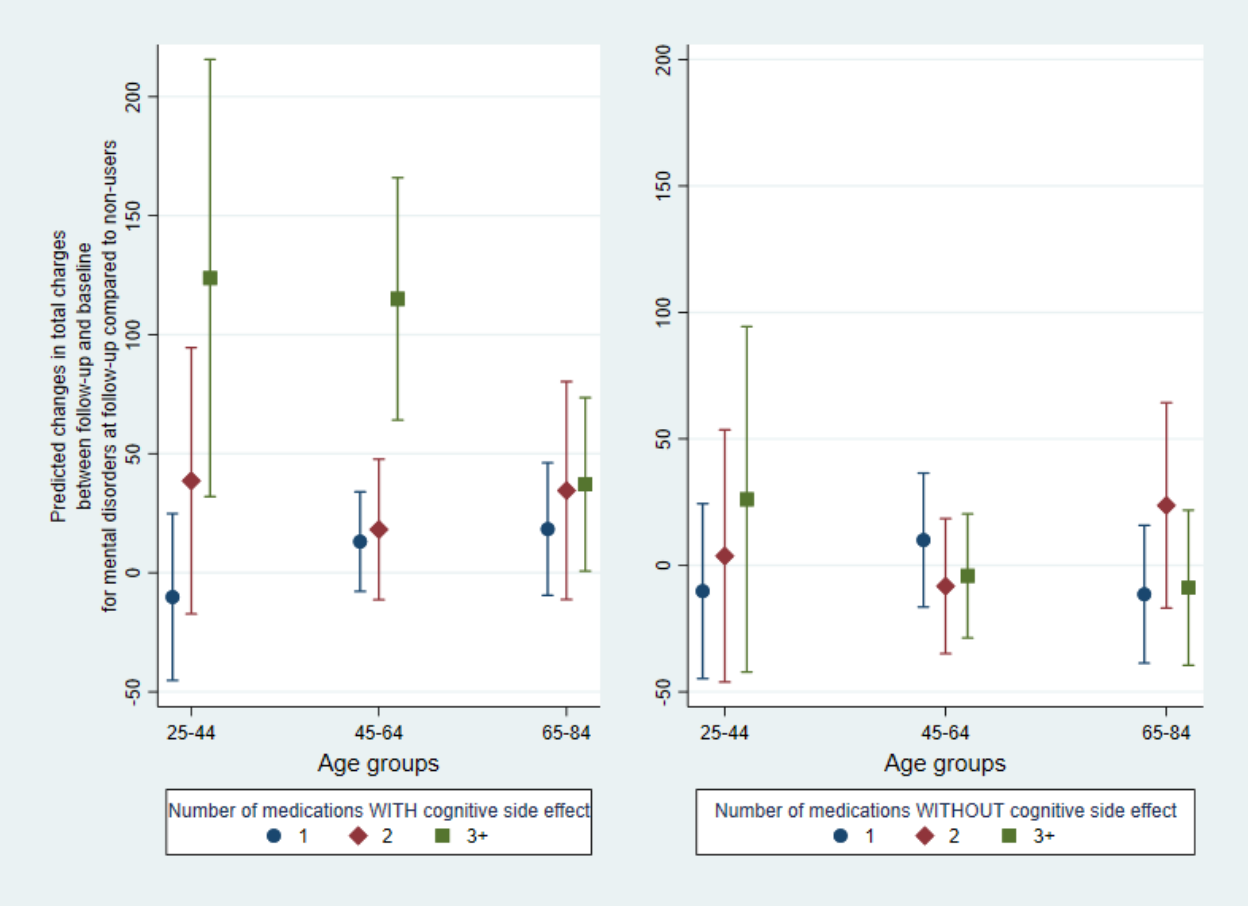


Figure 9: Association Between Baseline Medications with Side Effects and Changes in Costs for Mental Disorders Between Baseline and Follow-up by Age Groups



CHAPTER 5:

Discussion

Summary

This dissertation investigated the causes and health consequences of polypharmacy. In the first chapter, I provided strong evidence that while the expansion of Medicare Part D increased access to affordable and life-saving medications for older adults, it had a substantial impact on polypharmacy. An increase at this margin introduced a potential moral hazard, given that the additional research conducted in my dissertation showed significant adverse effects for emotional and cognitive well-being associated with polypharmacy. To the extent that these results are generalizable to other health insurance programs, expanding Medicaid under the Affordable Care Act in 2014 or implementing a Medicare-for-All program might produce similar effects on polypharmacy. Therefore, policies that reduce polypharmacy by promoting proper prescribing practices following an insurance expansion program can potentially alleviate adverse medical outcomes associated with polypharmacy. In the second chapter, I showed that the concurrent use of three or more medications with cognitive impairment side effects among U.S. older adults increased three-fold in the past two decades. Further, I found that concurrent use of three or more of these medications was associated with reductions in the global cognitive score, performance on the word learning and recall assessment, and performance on the digit symbol substitution assessments. In contrast, medications without known cognitive side effects were not associated with a decline in cognitive function. Finally, in my third chapter, I assessed trends in the use of medications with mental health side effects and their consequences for mental health and the use/costs of mental health services. My results showed a growth of 36% in the concurrent use of three of more of these

medications among U.S. adults in the past two decades. I also found that the concurrent use of mediations with mental health side effects was associated with an increase in psychiatric symptoms and the use/costs of mental health services. Patterns in medication use observed in the second and third chapters were potentially due to overconfidence in medicine as a solution to disease, a focus on single disease outcomes rather than comorbidity, and the spillover effect of treating chronic physical disease to mental disease. The results also highlighted the impact of polypharmacy. The most significant side effects documented in this dissertation were limited to individuals taking three or more medications with cognitive or mental health side effects. Polypharmacy may present unique risks for side effects, amplifying the effects of each of the medications in a set. Further, polypharmacy also increases the risk of drug-drug interactions that may lead to adverse cognitive and psychiatric disorders.

Given the growing prevalence of polypharmacy and its adverse consequences on population health, it is important to understand how people are initially exposed to medication use and polypharmacy, and how the overuse of medications can potentially lead to larger social problems. In this chapter, I use the theoretical frameworks of medicalization and pharmaceuticalization to better understand the potential causes of polypharmacy and the increasing use of medications with cognitive and mental health side effects. Medicalization is a process in which previously non-medical problems are defined as illnesses or disorders, and are treated using medical interventions (Conrad, 1992). Pharmaceuticalization is defined as “the process by which social, behavioural or bodily conditions are treated or deemed to be in need of treatment, with *medical drugs* by

doctors or patients" (Abraham, 2010b). Despite the overlap, there are marked differences between two theories (Abraham, 2010b). Although medicalization increases patients' exposure to medical interventions, the treatment does not necessarily involve the use of prescription medications. Moreover, some medications can be used to treat established medical conditions, without transforming a non-medical problem to a medical one. In addition, whereas studies on medicalization focus on the interactions between physicians and patients when defining an illness, they pay less attention to the increasingly important role of the pharmaceutical industry in shaping and influencing medical treatments (Conrad & Leiter, 2004). Although these agents remain unchanged under both theoretical frameworks (i.e. physicians, patients, and the pharmaceutical industry), the key player is different. Guided by these two interrelated theories, I first demonstrate the extent to which physicians, the pharmaceutical industry, and patients contribute to the rise in medication use. I then examine how the processes of medicalization and pharmaceuticalization vary across subgroups in the population, resulting in disparities in medication use. Finally, I discuss the implication of disparities in medication usage across subgroups for population-level health disparities.

The roles of medicalization and pharmaceuticalization in increased medication use

Physicians. Prior studies have emphasized the ways that medical professionals organized to create demand in order to generate new markets for their services (Larson & Larson, 1979). In order to achieve professional dominance, it was crucial for medical professionals to become major players in the social construction of disease, including controlling the meanings, interpretations, and diagnoses of illnesses. These efforts can be

traced back to the medicalization of menopause in the 1930s and 1940s (Bell, 1987). A small number of elite physicians created a medical vocabulary for menopause and used it to define menopause as a deficiency disease instead of a normal process of aging (Moynihan, 2002). As a result, it was recommended that all menopausal women, not just some women, should consult physicians for appropriate treatment, making menopause a medical problem. The medicalization of menopause was successful in part due to the approval and availability of a new estrogen medication in 1938 (Bell, 1987). As a result, estrogen sales doubled and tripled in the mid-1960s and 1970s (Stefanick, 2005). By 2000, approximately 25% of women aged 40 and older were current estrogen therapy users (Brett & Reuben, 2003). While estrogen therapy can resolve symptoms of menopause and lower the risk of osteoporosis, they can also increase the risks of depression, suicide, and anxiety, as demonstrated in the third chapter of this dissertation. In fact, almost half of prescription medications with depression as a common or serious side effect are hormone/estrogen therapies (Qato et al., 2018). In some additional analyses not presented in this dissertation, I found that women were more likely to use medications with depression or suicide as potential side effects and were more likely to experience polypharmacy than men, in part due to their frequent consumption of hormone/estrogen medications. The dominant role of medical professionals in defining disease has also been documented in other historical examples of mental illness, alcoholism, opiate addiction, homosexuality, hyperactivity, delinquency, and crime (Conrad, 2005; Conrad & Schneider, 2010; Moynihan, 2002). Although advances in medicine allow physicians to improve the standards of medical care deliveries, they also

preserve the central role of physicians in pushing the boundaries of disease as wide as possible to expand markets for their services.

Pharmaceutical industry. Although previous analyses of medicalization designated physicians as the key drivers of the social construction of disease, recent studies of pharmaceuticalization have increasingly focused on the pharmaceutical industry (Abraham, 2010a; Conrad, 2005). Part of this shift was due to recent changes in the organization of medical care – including the introduction of managed care, the emphasis on consumer advocacy and accountability, and the advancement of pharmaceutical innovations (Abraham, 2010a; Conrad, 2005). Studies found that the pharmaceutical industry drove the process of pharmaceuticalization mainly through three channels, including (1) pharmaceutical detailing, (2) direct-to-consumer advertising, and (3) marketing diseases (Conrad, 2005; Conrad & Leiter, 2004; Williams et al., 2011). *First*, while pharmaceutical marketing varies widely in types, more than half of marketing expenditure directly targets physicians through detailing (Campbell, 2009). Aggressive detailing efforts from pharmaceutical representatives have resulted in almost 94% of physicians having some type of financial ties to the industry, most of which are by ways of free meals or gifts at the workplace (Campbell et al., 2007). Using various sources of exogenous shocks such as detailing regulations, drug patent expirations, or the migration of patients, prior studies have established a robust and positive association between receiving detailing payments and the quantity of drugs prescribed (Carey et al., 2017; Grennan et al., 2018; Manchanda & Honka, 2005; Spurling et al., 2010). Physicians with greater contact with drug sales representatives are also more likely to prescribe brand-

name medications that are clinically equivalent to other more-affordable or generic substitutes (Greenway & Ross, 2017). *Second*, the rise in direct-to-consumer advertising (DTCA) of prescription medications in the U.S. has generated a controversial debate on the extent to which DTCA has substantial effects on consumer behavior. Following a policy change that relaxed restrictions on DTCA in 1997, spending on DTCA has increased from $150 million in 1993 to $6 billion in 2016 (Dave, 2013; Schwartz & Woloshin, 2019). While DTCA may drive demand for expensive pharmaceutical treatments despite the clinical effectiveness of other existing alternatives (market stealing), it can also increase pharmaceutical usage and spending by getting undiagnosed individuals to doctor's office (market expansion). A handful of studies supported the effects of DTCA on market expansion (Bradford et al., 2006; Iizuka & Jin, 2005; Rosenthal et al., 2003) rather than market stealing (Dave, 2013; Wosinska, 2002), implying that DTCA tends to increase individuals' exposure to pharmaceutical therapies. *Third*, pharmaceutical companies are not just advertising medication, but are also selling sickness by reframing disease as having a pharmaceutical solution and by promoting the use of medication for non-medical purposes. Using a case study of erectile dysfunction, Lexchin (2006) demonstrated how Pfizer – one of the world's largest pharmaceutical companies – turned Viagra from an effective product for erectile dysfunction due to organic causes, such as diabetes or prostate surgery, to a legitimate lifestyle medication[14] for almost all men. Pfizer redefined the prevalence and psychological effects of erectile dysfunction by extrapolating results from a non-nationally-representative study to argue that more than half of men aged 40 and older experienced erectile dysfunction and that

[14] Medications that treat non–life-threatening or non-painful conditions.

erectile dysfunction led to psychological distress (Lexchin, 2006). By convincing men that Viagra should be the first choice of therapy for any degree of erectile dysfunction, regardless of the patient's age or the sources of the problem, Pfizer pharmaceuticalized a normal process of aging and turned it to a medical condition that required pharmaceutical interventions. Prior studies have also documented similar marketing strategies for the cases of restless leg syndrome (Woloshin & Schwartz, 2006), excessive sleepiness (Kroll-Smith, 2003), or male pattern baldness (Moynihan, Heath, & Henry, 2002). Taken together, aggressive marketing strategies employed by the pharmaceutical industry – either through detailing physicians, direct-to-consumer marketing, or redefining disease – can potentially contribute to patients' reliance on medications and increase the risk of polypharmacy. While the pharmaceutical industry has increasingly become an important player in the social construction of illness, it is important to not deemphasize the role of physicians. In fact, physicians remain as gatekeepers to most medical resources in the U.S., including prescription medications. The growth of the pharmaceutical industry, if any, may just help physicians reinforce their ability to transform non-medical problems to ones that have a pharmaceutical solution.

Patients. While physicians and pharmaceutical companies define or broaden the boundaries of illnesses to increase the demand for their services, these agents also respond to the markets that patients create (Conrad, 2005; Riessman, 1983). Barsky and Borus (1995) noted that the public's tolerance for mild symptoms and the threshold at which patients seek medical interventions have lowered in recent decades. Approximately 25 to 50% of patients in primary care complain about symptoms that have

no pathophysiological explanation or organic causes (Burton, 2003; Escobar et al., 2010; olde Hartman et al., 2009). These patients tend to overuse medical care, have higher medical expenditures, and undergo unnecessary procedures (Barsky et al., 2005). Using an example of sleeplessness, Moloney et al. (2011) reported that the number of office visits that involved complains for sleeplessness had more than doubled between 1993 and 2007 from 2.7 million to 5.7 million. In response, the diagnosis of sleeplessness and the prescription of nonbenzodiazepine sedative hypnotics increased by 7.6-fold and 30-fold, respectively (Moloney et al., 2011). As such, complains about mild symptoms in part contribute to the medicalization of physical distress in which uncomfortable bodily states are considered disease that require medical or pharmaceutical interventions.

The roles of medicalization and pharmaceuticalization in medication use disparities

Although the processes of medicalization and pharmaceuticalization might have significantly contributed to the rise in medication use and polypharmacy, these processes did not affect every individual equally. For instance, women's bodies were more vulnerable to medicalization and pharmaceuticalization than men's bodies due to normal bodily conditions such as childbirth, premenstrual syndrome, and menopause (Bell, 1987; Riessman, 1983). As a result, women are more likely to consume prescription medications and are at a higher risk of polypharmacy than men (Kantor et al., 2015). In the second and third chapters of this dissertation, I found that women were more likely than men to use medications that have cognitive impairment and mental health side effects. Many medications with these side effects were estrogen or hormone therapies, which was partly a result of the medicalization of menopause in the 1930s and 1940s

(Bell, 1987). In addition, there are substantial racial/ethnic disparities in the use of prescription medications and polypharmacy (Han & Liu, 2005; Kantor et al., 2015; Wang et al., 2007). While a majority of studies attributed the racial/ethnic gap in medication use to unequal access to health care and socioeconomic status (Wang et al., 2007), a growing literature focuses on minority patients' reluctance to medicalization and pharmaceuticalization as a reason for racial/ethnic disparities in medication use (Adams et al., 2018; Gaskin et al., 2006; Schnittker, 2003). One study has shown that minority patients are more likely than non-Hispanic White patients to have concerns about the side effects of diabetes-related medications and the potential reliance on medication, and are more reluctant to adding more medications to their treatment plans (Huang et al., 2009). Similarly, the use of clozapine – the first-choice medication for refractory illness – is significantly lower among Hispanic and non-Hispanic Black patients, compared to non-Hispanic Whites, in part due to concerns about serious side effects of the medication such as loss of white blood cells or instabilities of serum glucose levels (Copeland et al., 2003). Schnittker (2003) found that neither socioeconomic status, knowledge, religion, nor trust in medicine explained black patients' reluctance against the use of psychiatric medications, but rather their concerns towards serious side effects and efficacy of these medications. Minorities who are resistant to pharmaceuticals tend to adopt complementary and alternative medicine or healthy lifestyle changes, especially among less acculturated minorities (Adams et al., 2018). Therefore, even though medicalization and pharmaceuticalization might have increased the dependence on pharmaceutical treatments, they affected some groups more than others.

Implications for population-level health disparities

Disparities in medication use – either due to the heterogeneous effects of medicalization and pharmaceuticalization or other factors such as disparities in access to health care or socio-demographic status – can have substantial implications for population-level health disparities. On the one hand, medication underuse may lead to medical complications associated with undertreatment. For example, the underuse of diabetes-related medications among minority patients may in part explain for their higher rates of diabetes-related complications relative to non-Hispanic White patients (Huang et al., 2009), such as renal disease, retinopathy, blindness, amputations, amputation-related mortality, and diabetes-related mortality (Carter et al., 1996; Emanuele et al., 2005; Harris et al., 1998; Lanting et al., 2005; Lustman et al., 2000; National Center for Health Statistics, 2008). Similarly, women's and minorities' underuse and non-adherence of medications for prevention of cardiovascular disease (Lewey et al., 2013; Qato et al., 2010), despite growing evidence for their effectiveness (Weisman & Graham, 2002), may contribute to marked gender and racial/ethnic disparities in cardiovascular disease (Davis et al., 2007; Mensah et al., 2005; Qato et al., 2010; Sheifer et al., 2000).

On the other hand, minorities' resistance from medication usage, relative to non-Hispanic Whites, may have protective effects against certain medication side effects and may help explain for their lower prevalence of medical conditions associated with medication side effects. For instance, social scientists have found it difficult to explain the racial/ethnic paradox in mental health: that minorities often report better mental health than non-Hispanic Whites despite social and environmental conditions that are detrimental to

mental health (Budhwani et al., 2015; McGuire & Miranda, 2008). Enormous efforts have attempted to uncover the sources of this paradox, including socioeconomic status, discrimination, social networks, and religious involvement – and for the most part – have been unsuccessful. Schnittker and Do (2020) argue that the minority paradox in mental health is in part rooted in the disparity of medication use: the more frequent use of medications with depression or suicidal side effects among the non-Hispanic White population helps explain its higher rates of psychiatric symptoms than that of minorities. In addition, the use of medications with side effects may also be related to the migration paradox in mental health. The paradox implies that migrants, especially newly arrived migrants, often report fewer psychiatric symptoms than native-born Americans, despite numerous theories suggesting their disadvantages (Budhwani et al., 2015; Foo et al., 2018). In a preliminary analysis using the National Health and Nutrition Examination Survey (NHANES), I found that migrants were less likely to use medications with depression and suicide as side effects than native-born Americans. In analytic models that controlled for the use of these medications, the migrant disparity in depression was reduced to statistical insignificance. In addition, I found that pharmaceutical acculturation plays an important role in the relationship between medication usage and the migrant disparity in health. As migrants come to resemble the pharmaceutical culture in the U.S. and consume more medications with depressive or suicidal side effects, their reported prevalence of depressive symptoms increases and becomes similar to that of the native-born population. Moreover, the use of medication with depression or suicidal side effects can also help explain the gender disparities in mental health. In additional analyses not presented here, I found that the higher prevalence of psychiatric symptoms among

women, relative to men, can be partially explained by the use of medications with depression and suicidal side effects. More than half of these medications are estrogen or hormone therapies that resulted from the medicalization of menopause in the 1930s and 1940s (Bell, 1987; Qato et al., 2018). Collectively, these findings suggest a new explanation for differences in health outcomes: that much can be explained by the side effects of commonly used medications.

Conclusion

While the processes of medicalization and pharmaceuticalization may have improved the standard of medical care in the United States, they have also contributed tremendously to the rise in medication use and polypharmacy. These processes did not affect every individual equally, which in part resulted in vast disparities in medication use across subgroups. Although the underuse of medications among certain demographic groups might have led to medical complications associated with undertreatment, it also had protective effects against serious medication side effects. A handful of studies has focused on the former to explain for population-level disparities in health, whereas the role of medication side effect has likely been underappreciated, especially under the condition of polypharmacy. Therefore, the investigation of medication side effects is an important frontier for future social science research and could help explain important trends in health disparities. Moreover, conceptualizing how people are initially exposed to the use of medications with side effects will shed light on patterns and disparities in population health and speak directly to the role of broader social, economic, cultural, and institutional inequalities in generating and maintaining health disparities.

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