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

Objectives: 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.

Method: We 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).

Results: 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 ($p < 0.001$).

Discussion: 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.

Keywords. Polypharmacy, cognitive impairment, medications, side effects.

I. Introduction

Background

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 consequences for individuals, families, and government programs (Hurd, Martorell, Delavande, Mullen, & Langa, 2013; Langa et al., 2008; Seeher, Low, Reppermund, & Brodaty, 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 (Kantor, Rehm, Haas, Chan, & Giovannucci, 2015). 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, Ozenberger, & Olfson, 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, Shannon, Valim, & Mandl, 2010; Marcum et al., 2012; Nguyen, Fouts, Kotabe, & Lo, 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, Paquette, Hilmer, Holroyd-Leduc, & Carnahan, 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, Bodmer, Jick, & Meier, 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[1].

Theoretical framework

In this study we 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 our 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 (J. 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

[1] Although there is no scientific consensus or clinical definition of polypharmacy, the term is typically used interchangeably to describe multiple, concurrent, excessive, unnecessary, or unindicated medication consumption.

develop delirium. Following this theoretical framework, we 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.

Research questions

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. Our 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?

II. Methods

Data

We 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). We 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, Crawford, & Phillips, 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, we 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, we 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, Guglielmo, Maselli, & Auerbach, 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. We 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 Appendix Table 1). We 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, we 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. We created a similar variable for the use of medications *without* known cognitive side effects.

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, Beydoun, & Wang, 2008; Cherbuin, Kim, & Anstey, 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, Spitzer, & Williams, 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)). We included a dummy variable for year to account for any trend in the outcome.

Statistical Analysis

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. We imputed missing data for all control variables using multiple imputation with chained equations. We 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, we considered a p-value of less than 0.05 as statistically significant and we did not correct for multiple testing due to the exploratory nature of this study.

III. Results

1. Trend in utilization of medications with cognitive side effects

Figure 1 presents the trend in utilization of medications with cognitive side effects from 1999-2000 to 2015-2016 for adults aged 60 and older. In 1999-2000, approximately 55.3% (95% CI, 51.3%-59.3%) of older adults did not consume any medications with cognitive side effects. 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. Appendix 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--

2. Descriptive Statistics

Table 1 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[2] in the last 30 days, and such use of opioids increased as respondents consumed more medications with cognitive side effects.[3] Consistently across all cognitive

[2] 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.

[3] Several studies found that the use of opioids was harmful to cognitive health (Kamboj, Tookman, Jones, & Curran, 2005; Sjøgren, Christrup, Petersen, & Højsted, 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

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 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 1 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.

3. Association between cognitive function and medications with side effects

Table 2 presents results from the adjusted multivariate analyses. We 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

cognitive impairment (Chapman, Byas-Smith, & Reed, 2002; Dublin et al., 2015). For information purposes, we included the prevalence of opioid use in the descriptive statistics table.

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). We 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, we 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 2 About Here--

In Table 3, we 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. See Appendix Tables 3 and 4 for the coefficients of all other covariates in the analyses.

In both Tables 2 and 3, we 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. We 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 2, and in this case the coefficients were smaller than the coefficients for three or more medications with side effects.

In Table 4, we 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 2 and 3, 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. We 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.

Finally, in Appendix Figures 1 to 5, we 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, we 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.

IV. Discussion

To our 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. We 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.

Our 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[4] 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

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

scored 0.6 to 0.8 standard deviations lower in various cognitive tests. Our 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 we included in our study many medications other than anticholinergics that had smaller incidence rates of cognitive impairment. Nonetheless, our 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. We 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 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, Stellhorn, Krasa, & Kostic, 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 our study, about 9% of older adults took three or more medications with cognitive side effects in the past 30 days. Kantor et al. (2015) found that the prevalence of older adults taking at least five medications increased by 81.8% from 1999-2000 to 2011-2012. 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. Prior research has shown that taking multiple medications is a risk factor for dementia and delirium, as well as other adverse events (Jyrkkä, Enlund, Lavikainen, Sulkava, & Hartikainen, 2011; Martin, Stones, Young, & Bédard, 2000). Research on the reasons for an increase in polypharmacy is limited, though prior studies points to the growing presence of comorbidity (Slabaugh, Maio, Templin, & Abouzaid, 2010), the failure to consider comorbidity in clinical practice guidelines (Tinetti, Bogardus Jr, & Agostini, 2004), visiting multiple providers (Col, Fanale, & Kronholm, 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, Appendix Table 5 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.

Finally, 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, Barnett, & Denham, 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, Cryer, & Triadafilopoulos, 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, Rubin, Campbell, Gwyther, & Clark, 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.

Limitations

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, we were 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. We addressed both of these 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. In addition, since NHANES only collected data on outpatient and over-the-counter medications, we lacked information on medications administered to inpatients at hospitals. To address some forms of unobserved heterogeneity, we followed another similar study and included in our models the number of medications *without* any known cognitive side effects (Qato et al., 2018). We 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.

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, Batty, Allerhand, & Deary, 2018).

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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Figure 1. 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.

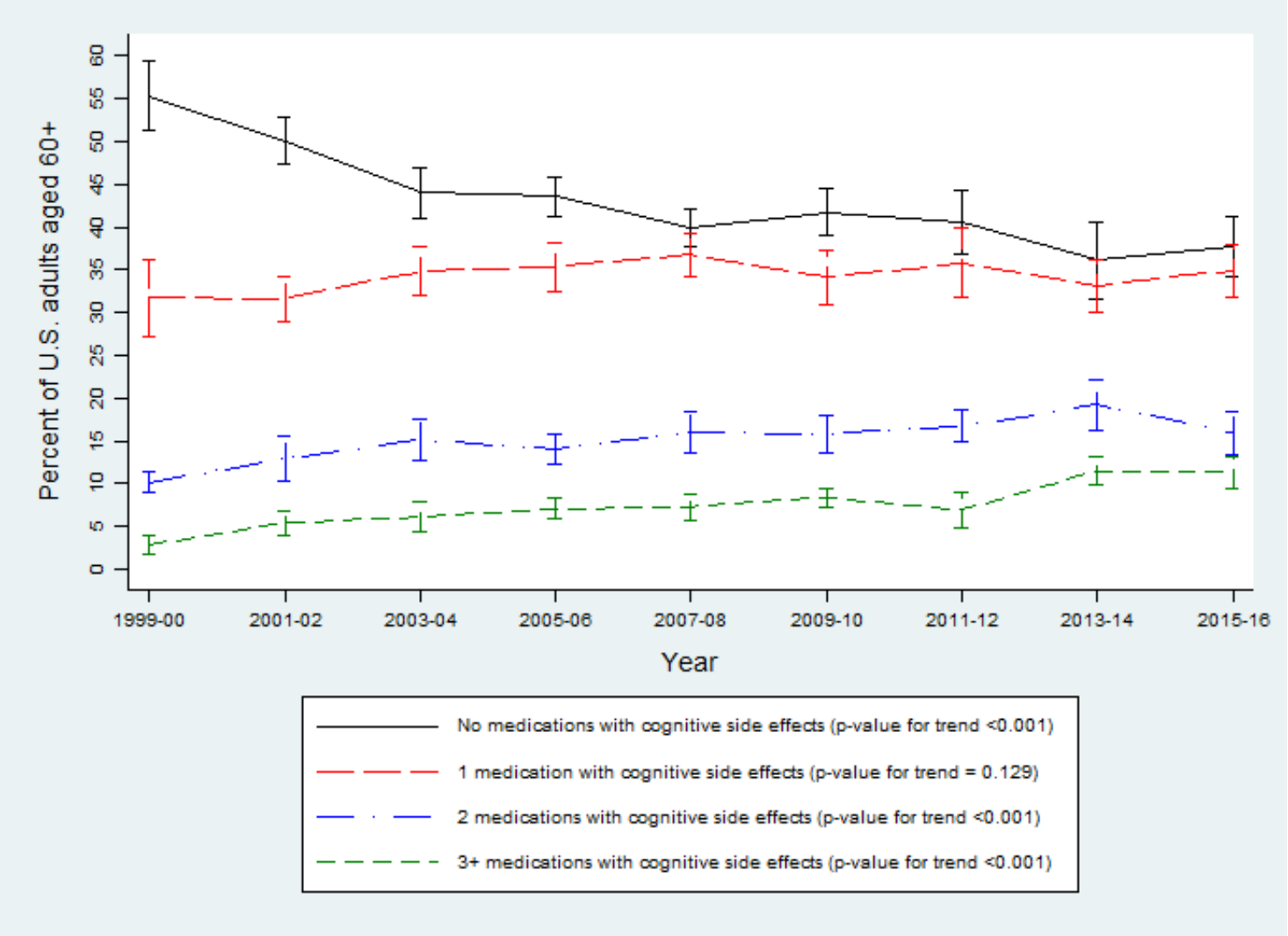


Table 1. Descriptive Statistics of Cognitive Function Measurements and Covariates Among U.S. Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.

	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 2. 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.

	Standardized test scores						**Composite measure**	
Outcome:	Word learning and recalls		Animal fluency		Digit symbol substitution		Average standardized score of the three tests	
	Coef. (S.E.)	p-value	Coef. (S.E.)	p-value	Coef. (S.E.)	p-value	Coef. (S.E.)	p-value
Whether taking medications WITH cognitive side effects								
None (reference)								
1 medication	-0.02 (0.06)	0.76	-0.04 (0.06)	0.55	0.00 (0.06)	0.99	-0.02 (0.05)	0.69
2 medications	-0.10 (0.06)	0.12	0.01 (0.08)	0.94	-0.03 (0.07)	0.70	-0.04 (0.05)	0.46
3+ medications	-0.24 (0.09)	0.02	-0.15 (0.09)	0.10	-0.27 (0.07)	0.001	-0.22 (0.06)	< 0.001
Whether taking medications WITHOUT cognitive side effects								
None (reference)								
1 medication	0.00 (0.07)	0.96	-0.10 (0.08)	0.19	-0.11 (0.08)	0.17	-0.07 (0.05)	0.21
2 medications	-0.10 (0.06)	0.15	-0.05 (0.08)	0.53	-0.07 (0.07)	0.33	-0.07 (0.05)	0.20
3+ medications	-0.07 (0.05)	0.19	-0.07 (0.08)	0.37	-0.17 (0.06)	0.01	-0.10 (0.05)	0.04
No. of observations	2,908		2,908		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.

Table 3. 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 test scores are more than 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 (S.E.)	p-value	OR (S.E.)	p-value	OR (S.E.)	p-value	OR (S.E.)	p-value
Whether taking medications WITH cognitive side effects								
None (reference)								
1 medication	1.38 (0.22)	0.05	0.77 (0.12)	0.09	1.20 (0.18)	0.22	0.88 (0.15)	0.48
2 medications	1.55 (0.28)	0.02	0.85 (0.13)	0.28	1.34 (0.29)	0.18	1.38 (0.23)	0.06
3+ medications	2.04 (0.64)	0.03	1.59 (0.39)	0.07	2.82 (0.67)	< 0.001	2.10 (0.54)	0.01
Whether taking medications WITHOUT cognitive side effects								
None (reference)								
1 medication	0.68 (0.15)	0.10	1.10 (0.27)	0.71	0.98 (0.24)	0.92	0.92 (0.23)	0.72
2 medications	1.08 (0.25)	0.74	0.98 (0.25)	0.95	0.61 (0.14)	0.04	0.82 (0.21)	0.46
3+ medications	0.83 (0.18)	0.40	1.41 (0.33)	0.16	1.22 (0.28)	0.39	1.28 (0.27)	0.26
No. of observations	2,908		2,908		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.

Table 4. Adjusted Linear and Logistic Regressions of Composite Cognitive Measures on Utilization of Medications with Cognitive Side Effects and Duration of Using Such Medications for Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.

Outcome:	**Global cognitive measures**			
	Average standardized score of the three tests		Whether 2+ test scores are more than one standard deviation below the mean	
	Coef. (SE)	p-value	OR (SE)	p-value
Whether taking medications WITH cognitive side effects and duration of using such medications				
None (reference)				
1 medication				
At most one year	-0.03 (0.06)	0.67	0.83 (0.24)	0.54
More than one year	-0.01 (0.05)	0.76	0.89 (0.15)	0.49
2 medications				
At most one year	-0.12 (0.09)	0.18	1.28 (0.47)	0.51
More than one year	-0.03 (0.05)	0.58	1.39 (0.23)	0.05
3+ medications				
At most one year	-0.63 (0.21)	0.005	10.89 (8.11)	0.003
More than one year	-0.20 (0.06)	0.002	1.83 (0.51)	0.04
Whether taking medications WITHOUT cognitive side effects and duration of using such medications				
None (reference)				
1 medication				
At most one year	-0.09 (0.06)	0.14	1.16 (0.43)	0.7
More than one year	-0.06 (0.07)	0.39	0.83 (0.21)	0.47
2 medications				
At most one year	-0.02 (0.08)	0.8	0.49 (0.24)	0.16
More than one year	-0.08 (0.06)	0.19	0.86 (0.23)	0.58
3+ medications				
At most one year	-0.07 (0.15)	0.64	1.90 (0.83)	0.15
More than one year	-0.10 (0.05)	0.03	1.22 (0.26)	0.35
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.

Appendix 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		

Appendix 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. of observations	1834	1872	1901	1570	2154	2073	1791	1841	1901		

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

Appendix Table 3. 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
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.

Appendix Table 4. 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.

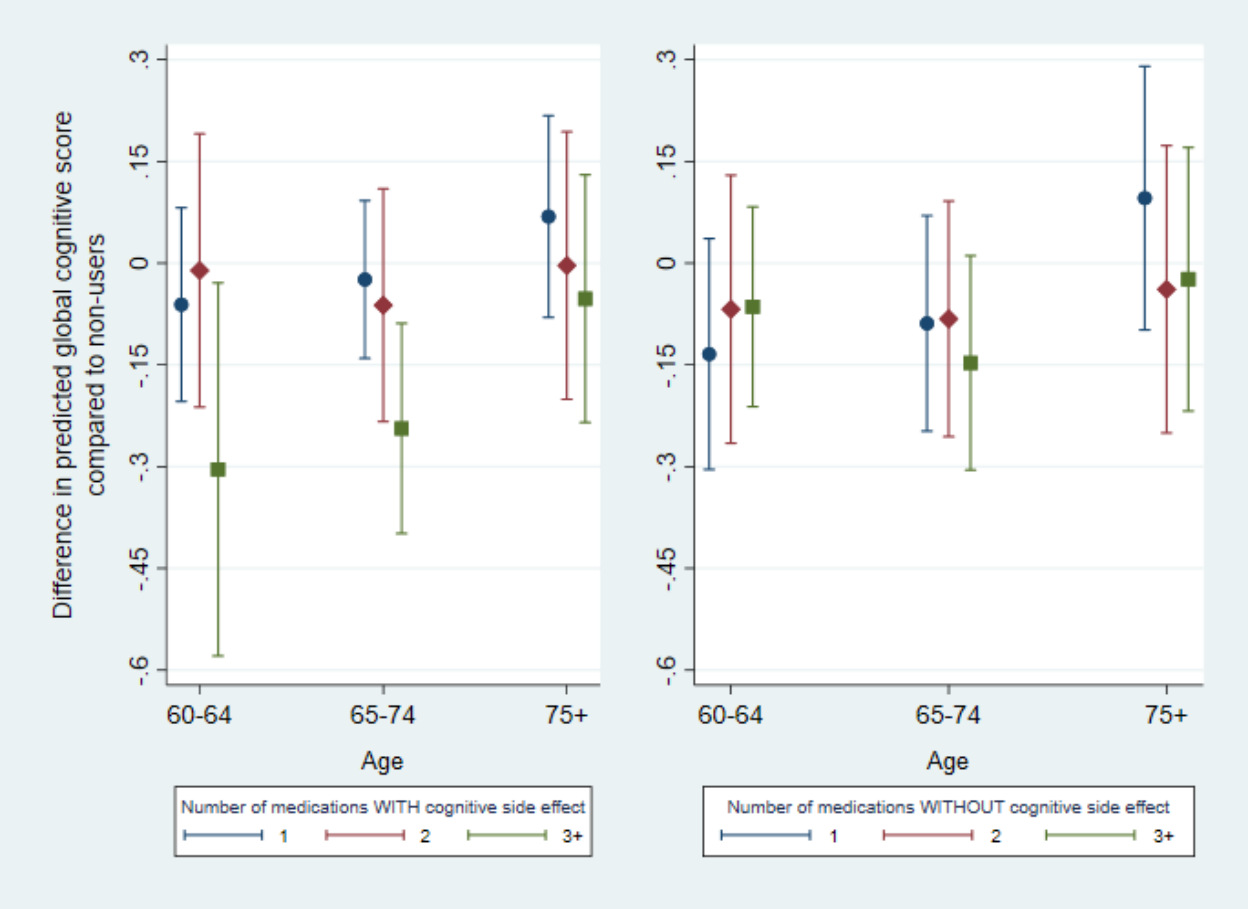
	Whether scores are one standard deviation below the mean			Composite measure
Outcome:	Word learning and recalls	Animal Fluency	Digit Symbol Substitution	Whether 2+ test scores are more than one standard deviation below the mean
	OR (SE)	OR (SE)	OR (SE)	OR (SE)
Whether taking medications WITH cognitive 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.

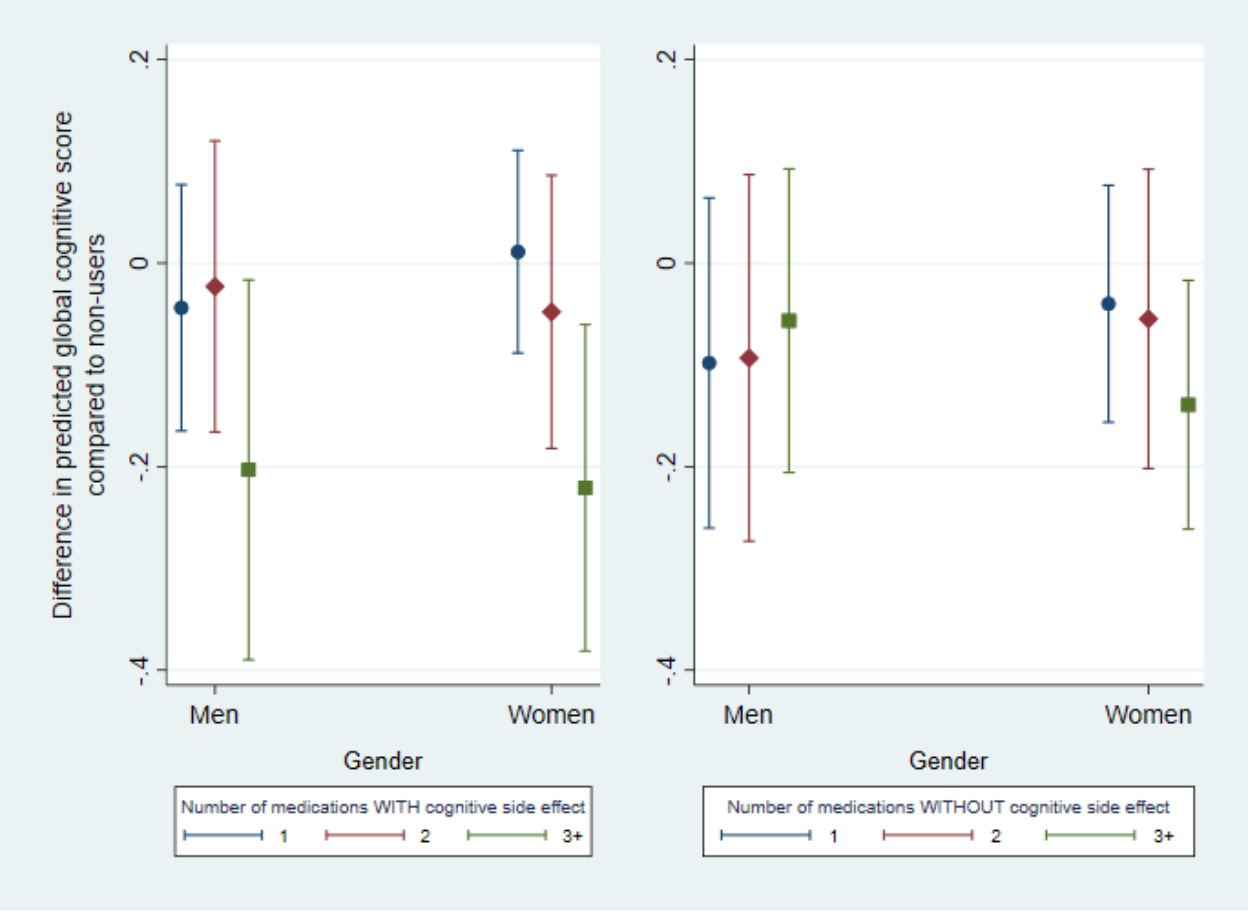
*p<0.05, **p<0.01, ***p<0.001. Standard errors are in parentheses. All analyses were weighted using survey weights.

Appendix Figure 1: Marginal Effects 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.



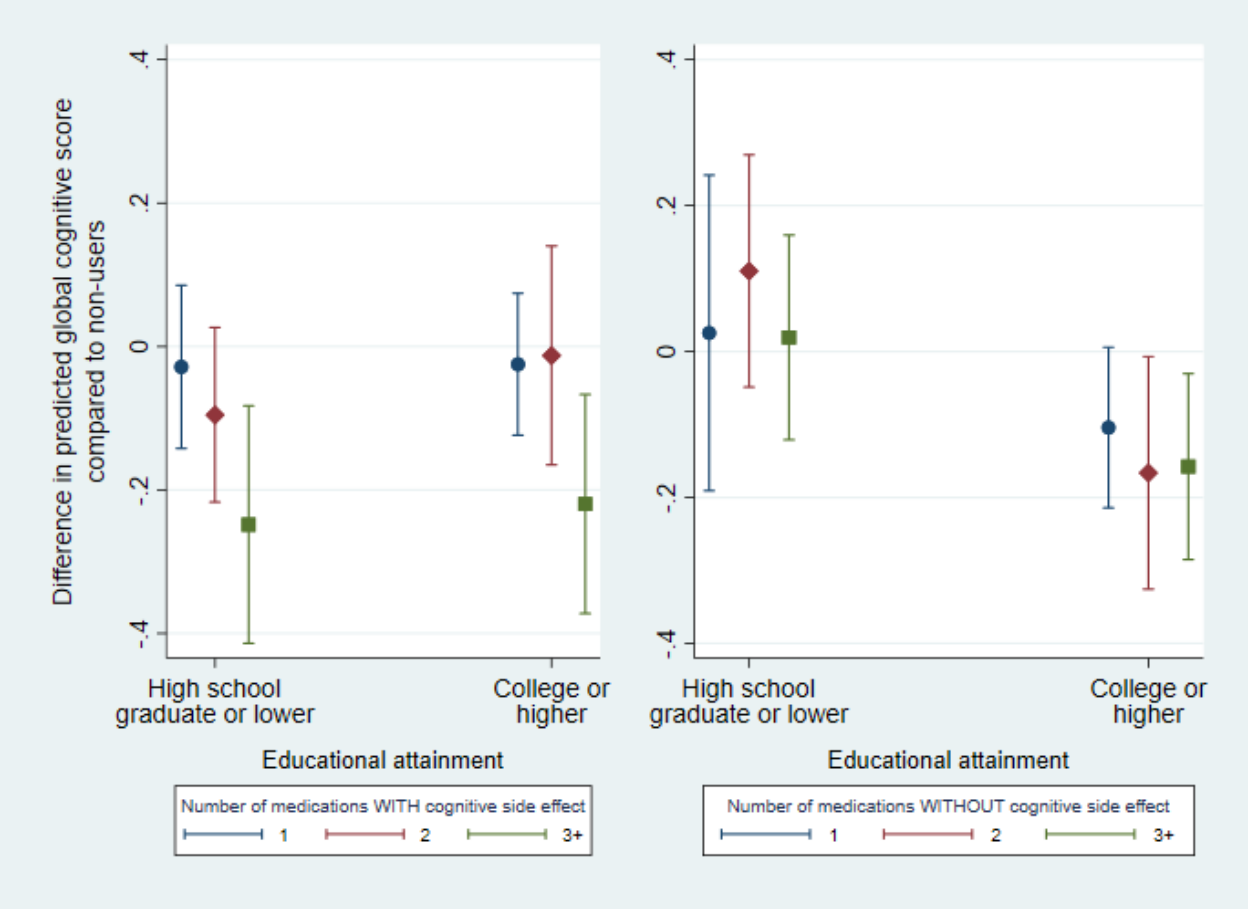
Notes: The marginal effects were calculated from the linear regression of the global cognitive score (average of the three standardized cognitive assessment scores) on the interactions between medications with/without cognitive side effects and age groups (60-64, 65-74, and 75+), while controlling for 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.

Appendix Figure 2: Marginal Effects 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.



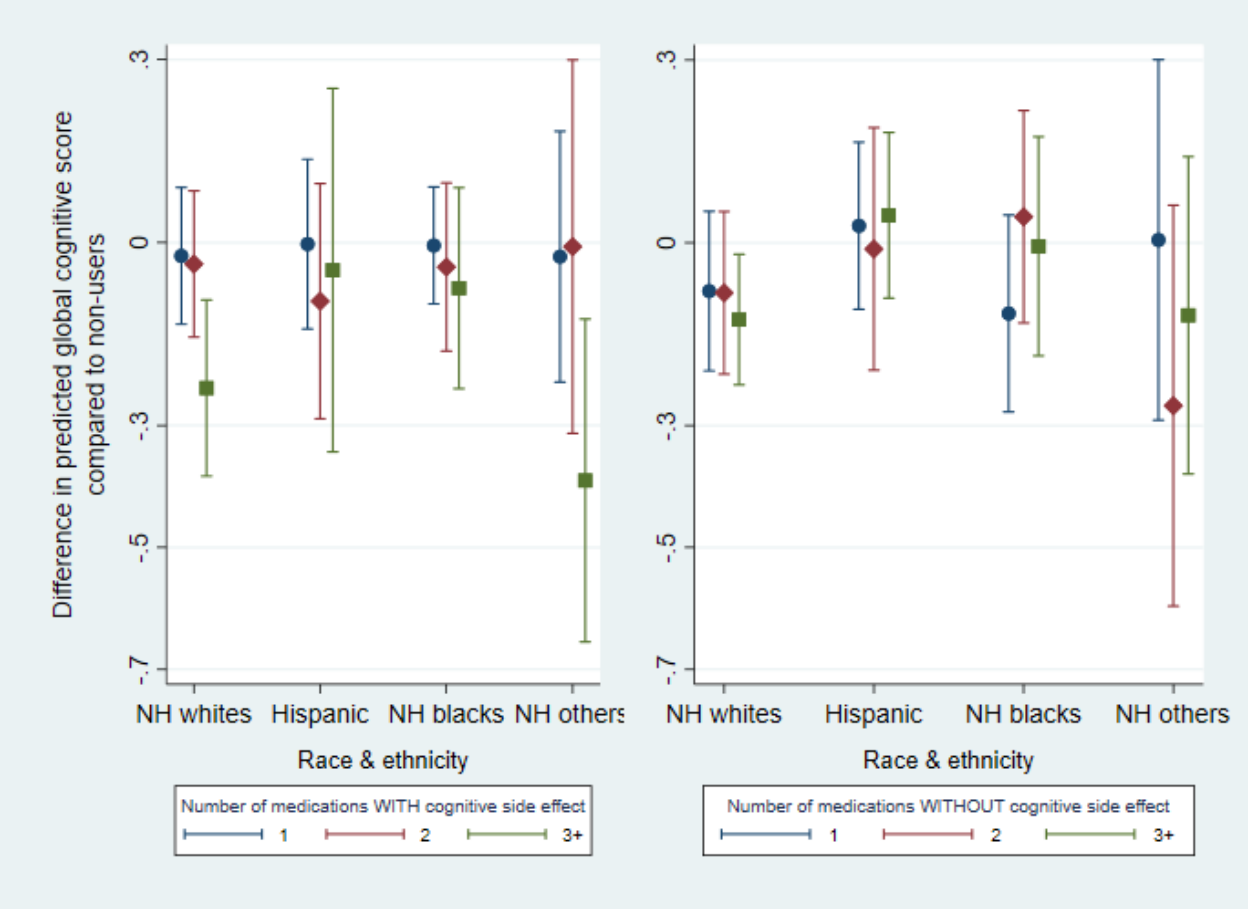
Notes: The marginal effects were calculated from the linear regression of the global cognitive score (average of the three standardized cognitive assessment scores) on the interactions between medications with/without cognitive side effects and gender, while controlling for other covariates such as race, 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.

Appendix Figure 3: Marginal Effects 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.

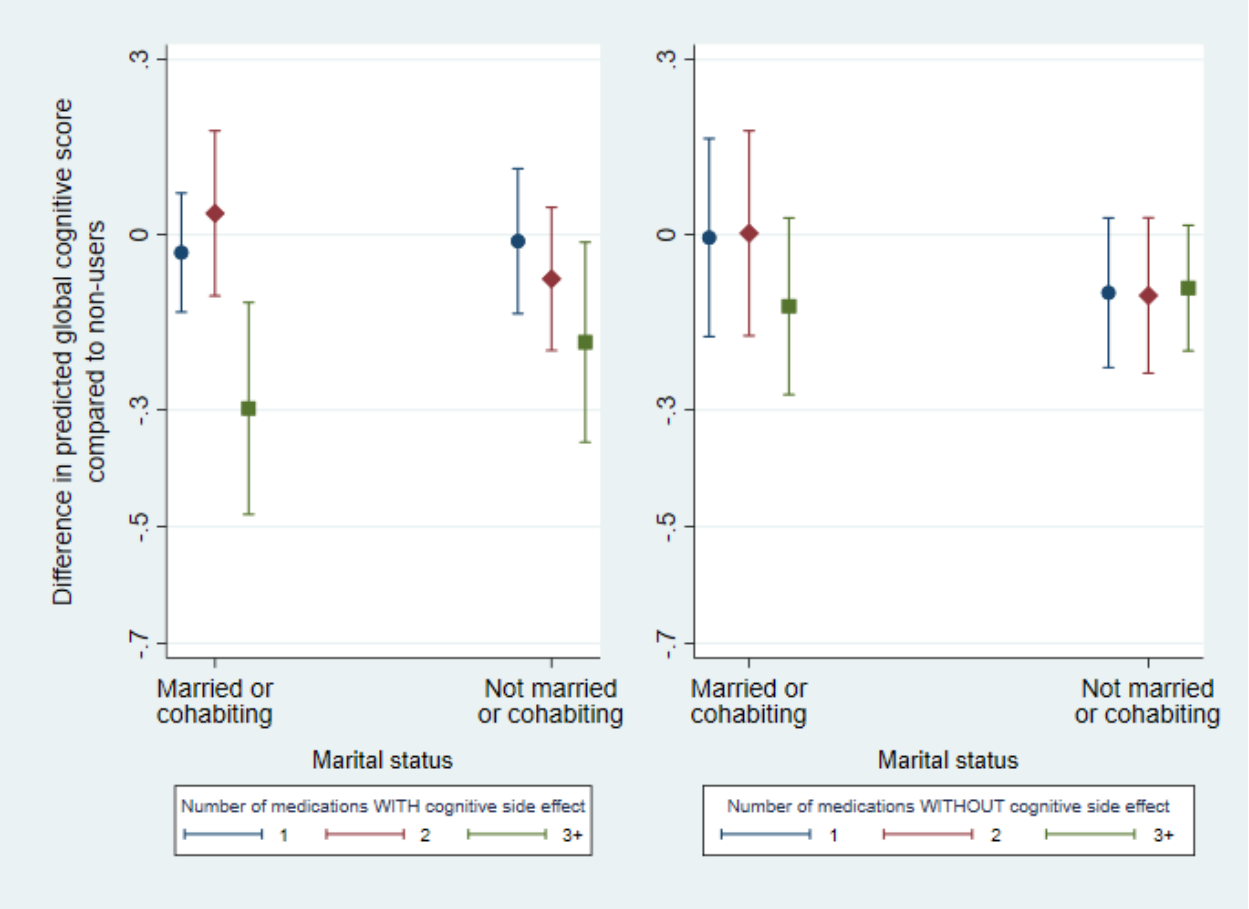
Appendix Figure 4: Marginal Effects of Medications With/Without Cognitive Side Effects on Global Cognitive Score by Race/Ethnicity Among Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.



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.

Appendix Figure 5: Marginal Effects 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.

Appendix Table 5. 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.