

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
	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016		
Survey cycles:											
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 heart 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.

Outcome:	Whether scores are one standard deviation below the mean			Composite measure
	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)

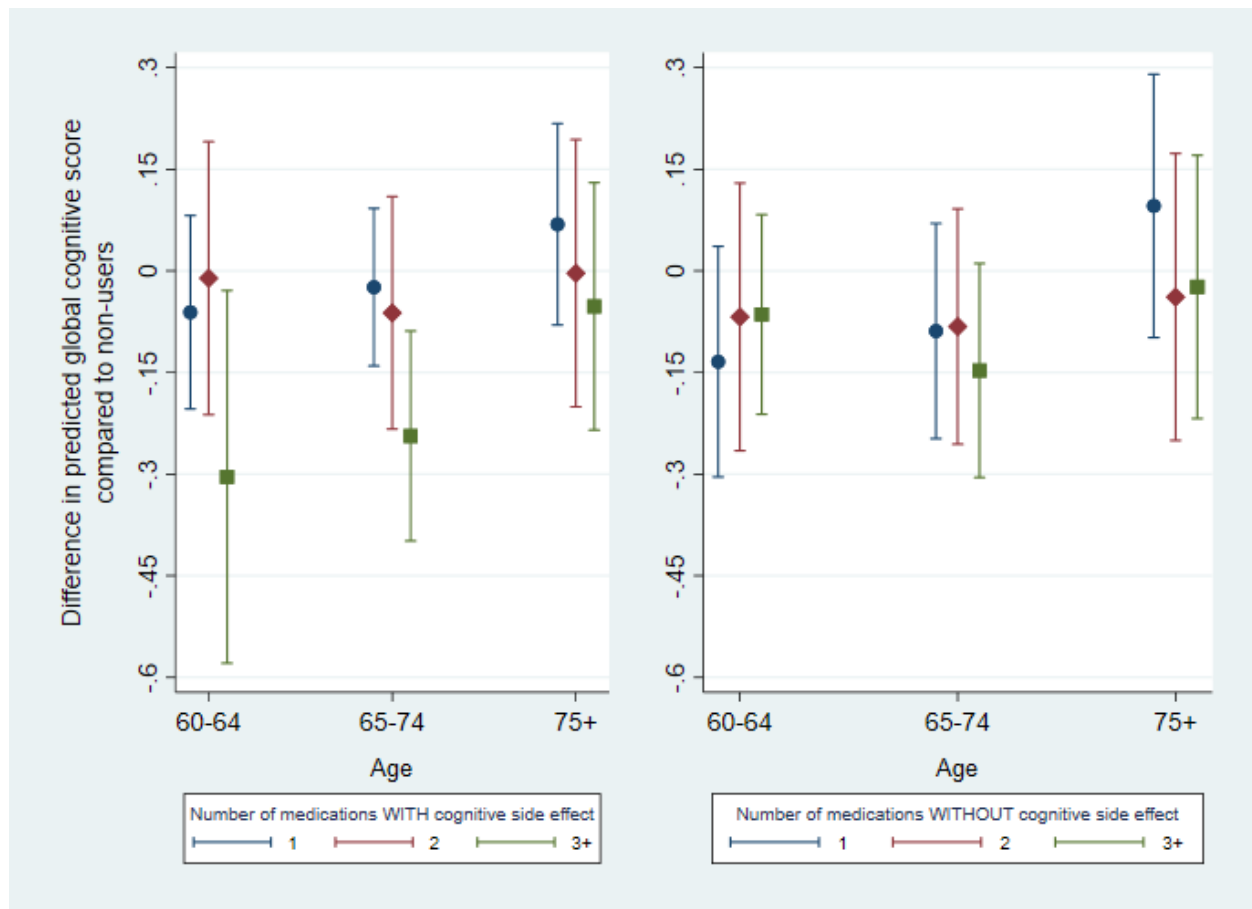
Smoking

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 heart failure, coronary heart disease, heart attack, angina, emphysema, bronchitis, stroke, diabetes, hypertension, and sleep disorder.

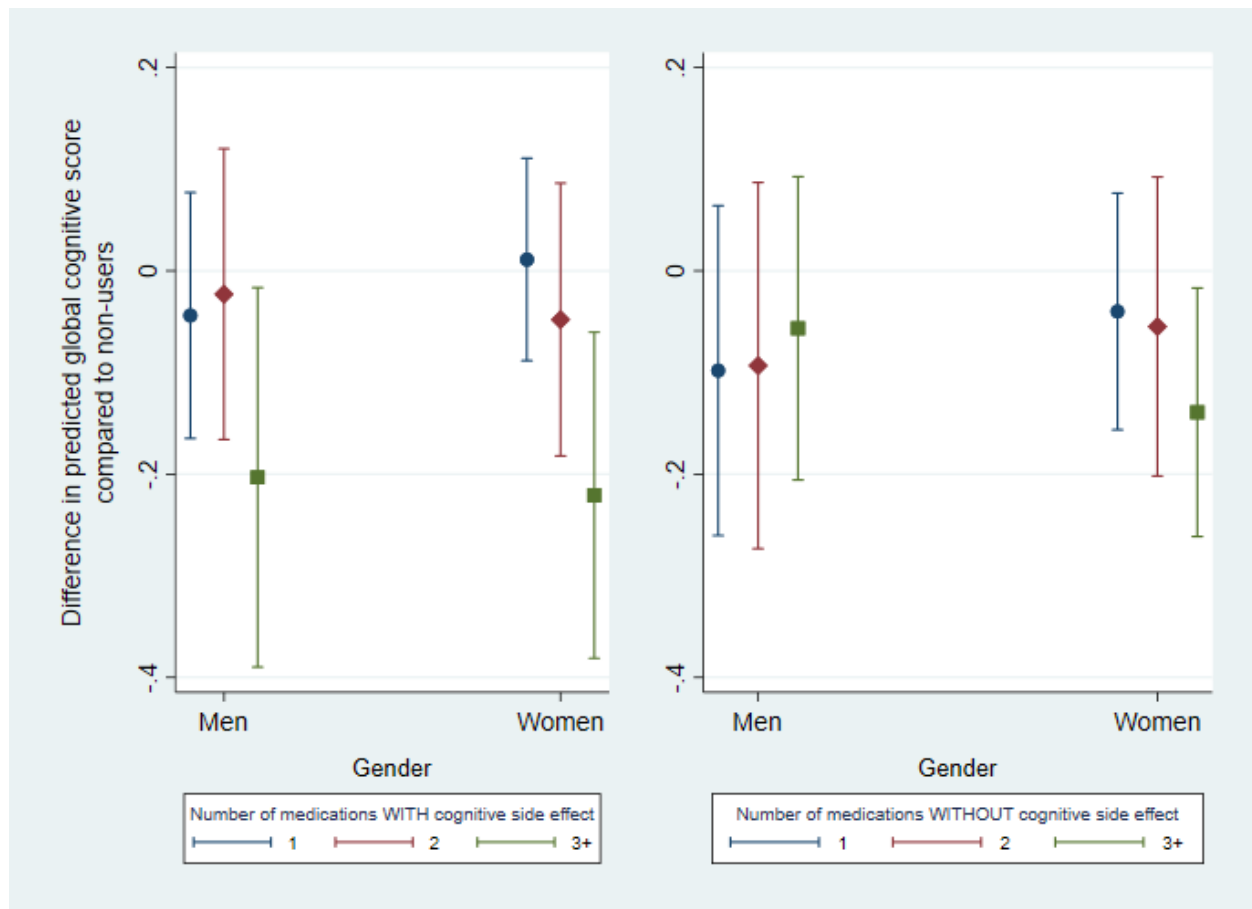
*p<0.05, **p<0.01, ***p<0.001. Standard errors are in parentheses. All analyses were weighted using survey weights.

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 heart 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.

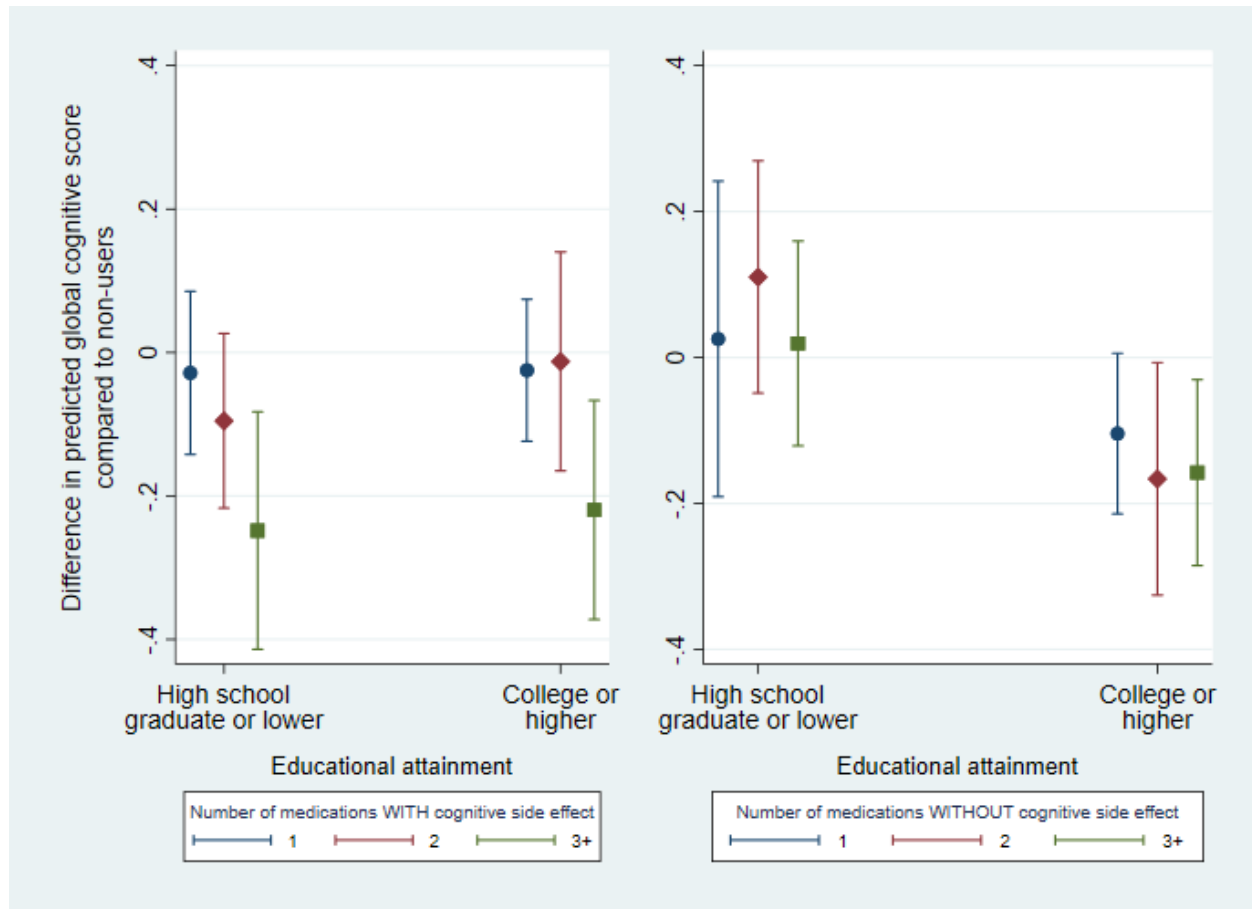
Appendix Figure 2: Marginal Effects of Medications With/Without Cognitive Side Effects on Global Cognitive Score by Gender Among Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.



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 heart 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.

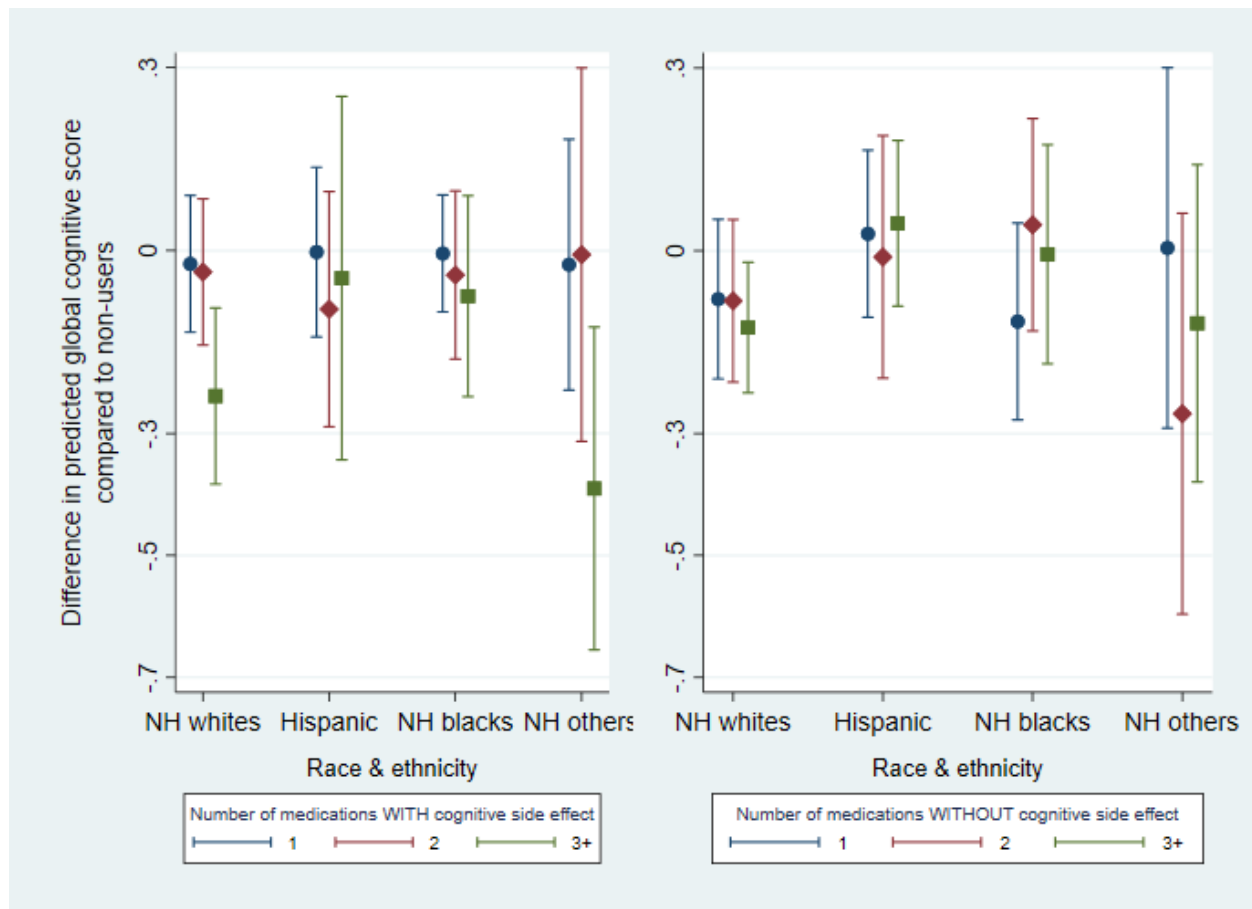
Appendix Figure 3: Marginal Effects of Medications With/Without Cognitive Side Effects on Global Cognitive Score by Educational Attainment Among Adults Aged 60+. Data

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 heart 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.

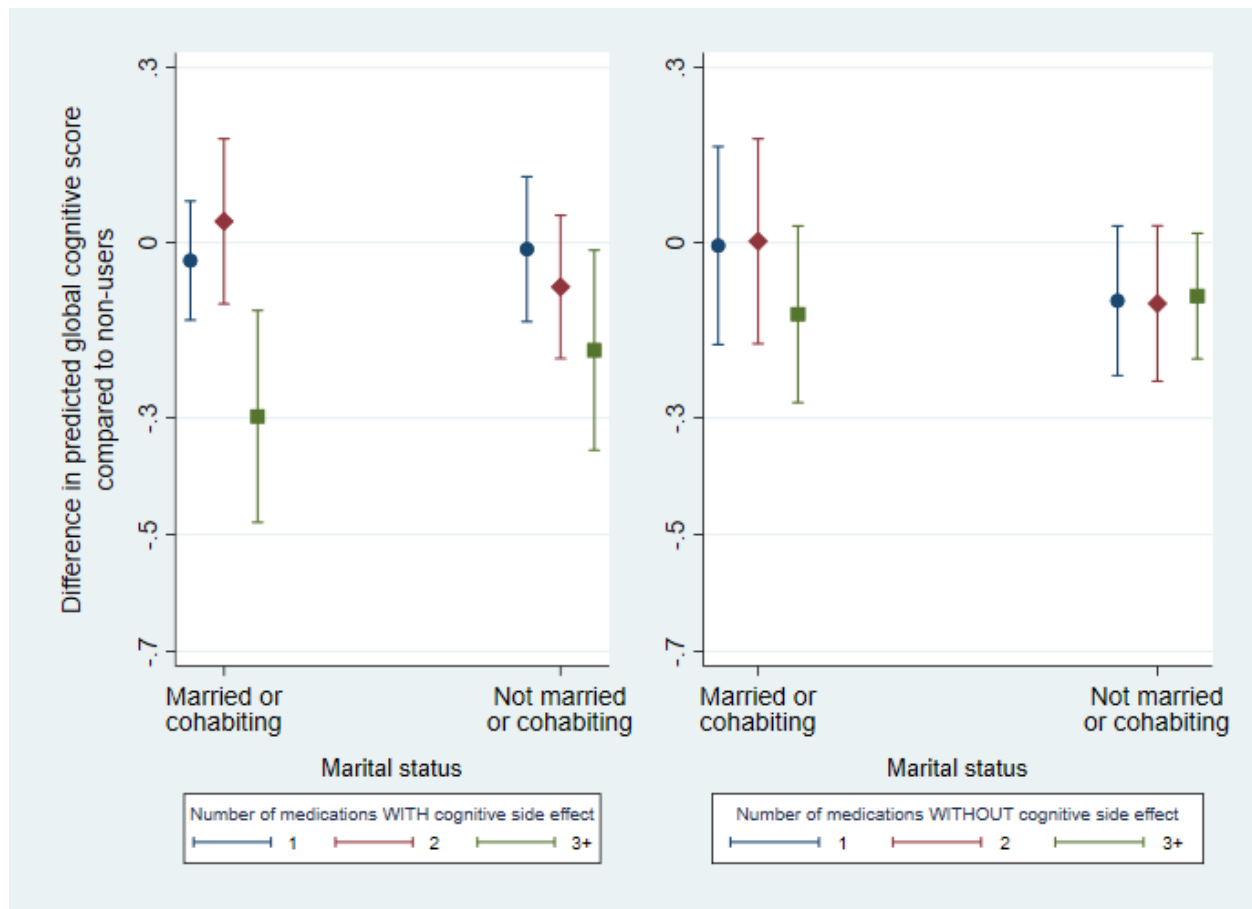
Appendix Figure 4: Marginal Effects of Medications With/Without Cognitive Side Effects on Global Cognitive Score by Race/Ethnicity Among Adults Aged 60+. Data Source: NHANES 2011-2012 and 2013-2014.



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 heart 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 heart 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.