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Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011

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Abstract

IMPORTANCE—Prescription and over-the-counter medicines and dietary supplements are commonly used, alone and together, among older adults. However, the effect of recent regulatory and market forces on these patterns is not known.

OBJECTIVES—To characterize changes in the prevalence of medication use, including concurrent use of prescription and over-the-counter medications and dietary supplements, and to quantify the frequency and types of potential major drug-drug interactions.

DESIGN, SETTING, AND PARTICIPANTS—Descriptive analyses of a longitudinal, nationally representative sample of community-dwelling older adults 62 to 85 years old. In-home interviews with direct medication inspection were conducted in 2005–2006 and again in 2010–2011. The

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Author Contributions: Dr Qato had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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dates of the analysis were March to November 2015. We defined medication use as the use of at least 1 prescription or over-the-counter medication or dietary supplement at least daily or weekly and defined concurrent use as the regular use of at least 2 medications. We used Micromedex to identify potential major drug-drug interactions.

MAIN OUTCOMES AND MEASURES—Population estimates of the prevalence of medication use (in aggregate and by therapeutic class), concurrent use, and major drug-drug interactions.

RESULTS—The study cohort comprised 2351 participants in 2005–2006 and 2206 in 2010–2011. Their mean age was 70.9 years in 2005–2006 and 71.4 years in 2010–2011. Fifty-three percent of participants were female in 2005–2006, and 51.6% were female in 2010–2011. The use of at least 1 prescription medication slightly increased from 84.1% in 2005–2006 to 87.7% in 2010–2011 ($P = .003$). Concurrent use of at least 5 prescription medications increased from 30.6% to 35.8% ($P = .02$). While the use of over-the-counter medications declined from 44.4% to 37.9%, the use of dietary supplements increased from 51.8% to 63.7%($P < .001$ for both). There were clinically significant increases in the use of statins (33.8% to 46.2%), antiplatelets (32.8% to 43.0%), and omega-3 fish oils (4.7% to 18.6%) ($P < .05$ for all). In 2010–2011, approximately 15.1% of older adults were at risk for a potential major drug-drug interaction compared with an estimated 8.4% in 2005–2006 ($P < .001$). Most of these interacting regimens involved medications and dietary supplements increasingly used in 2010–2011.

CONCLUSIONS AND RELEVANCE—In this study, the use of prescription medications and dietary supplements, and concurrent use of interacting medications, has increased since 2005, with 15% of older adults potentially at risk for a major drug-drug interaction. Improving safety with the use of multiple medications has the potential to reduce preventable adverse drug events associated with medications commonly used among older adults.

Most older adults in the United States use prescription and over-the-counter (OTC) medications and dietary supplements.[1–3] Older adults are also at increased risk for adverse drug events[4] and polypharmacy,[5,6] and many medications commonly used among older adults, such as antiplatelets, anticoagulants, statins, and nonsteroidal anti-inflammatory drugs (NSAIDs), have serious drug-drug interactions and may further increase this risk.[4,7]

Our group previously examined the use of prescription and OTC medications and dietary supplements among older adults in the United States.[8] Using the National Social Life, Health, and Aging Project (NSHAP), a nationally representative in-home survey that included direct medication visualization, we found that polypharmacy was common and that more than half of the older adults were concurrently using prescription and nonprescription medications in 2005–2006, including dietary supplements.[8] In addition, our group estimated that 4% of older adults were concurrently using interacting medications or dietary supplements and thus were potentially at risk for an adverse drug event from a serious drug-drug interaction.[8]

During the past decade, various regulatory and market events have taken place that may have affected medication use among older adults, including the implementation of Medicare Part D,[9] the introduction of dozens of new drugs to market,[10] and the increasing availability of generic[11,12] and OTC[13] products. In addition to these forces, a growing number of safety concerns associated with commonly used medications, including statins, [14–16] NSAIDs,[17,18]

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proton pump inhibitors,[19] and medication combinations,[20–24] have emerged that may also have affected medication and supplement use among older adults. A recent study[25] using the National Health and Nutrition Examination Survey (NHANES) indicates that the use of prescription medications and polypharmacy has increased between 1999 and 2012 among adults 65 years and older. However, these findings may underestimate medication use and potential adverse effects because they do not capture information on OTC medications and dietary supplements.

Herein, we use nationally representative data from Wave 2 (fielded in 2010–2011) of the NSHAP to update our estimates of medication use, concurrent use, and drug-drug interactions among community-dwelling older adults in the United States. In addition to comparing rates of medication use between the 2 periods, we also examined changes in the risk of drug-drug interactions.

Methods

Participants

The NSHAP is based on a nationally representative probability sample of community-dwelling adults born between 1920 and 1947 (57–85 years old in 2004–2005), including an over-sampling of blacks, Hispanics, men, and older individuals (75–85 years). As has been previously described,[26] a sample of 4400 individuals was drawn from households screened in 2004 (one individual per household), of whom 4017 were determined to be eligible and 3005 successfully interviewed between July 2005 and March 2006. The weighted response rate in this first wave (baseline), calculated using the American Association for Public Opinion Research's response rate 2, was 75.5%.[27] A second wave was fielded between August 2010 and May 2011, during which surviving Wave 1 respondents and their spouses or partners (if married or cohabiting) were interviewed. In addition, respondents sampled in Wave 1 but who declined to participate were approached again, with 161 (26%) being interviewed. The overall weighted response rate in Wave 2 was 74%, and the conditional response rate among those interviewed in Wave 1 was 89%. All respondents provided written informed consent. The institutional review boards of the University of Chicago and the National Opinion Research Center approved the NSHAP research protocol.

Key Points

Question

How has the use of prescription and over-the-counter medications and dietary supplements among older US adults changed between 2005 and 2011?

Finding

In this national population-based study, we found that older US adults were increasingly using multiple medications and supplements, with 36% regularly using 5 or more medications or supplements and 15% potentially at risk for a major drug-drug interaction.

Meaning

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Efforts that focus on improving the safe use of multiple medications have the potential to reduce preventable adverse drug events associated with medications commonly and increasingly used among older adults in the United States.

To facilitate comparisons between waves, we limited our analytic sample to respondents who were sampled in Wave 1 (ie, we excluded spouses and partners) and who were 62 to 85 years old at the time of the interview. These criteria yielded 2377 Wave 1 interviews and 2245 Wave 2 interviews, with 1555 respondents being interviewed at both waves.

Medication and Supplement Data

Field interviewers collected data on medication and supplement use during the household interview by direct observation using a computer-based medication log.[8] In brief, respondents were asked to show the containers of all medications, prescription and nonprescription, including OTC medicines and supplements used on a "regular schedule, like every day or every week." Medication and supplement names were then coded and linked by generic drug name to a proprietary drug database (Lexicon Plus; Cerner Multum, Inc) to facilitate analyses. Additional details on the internal and external validity of this method of data collection and coding have been previously described.[28]

Medications and supplements were defined by type (prescription or OTC medications or dietary supplements), therapeutic drug class (for prescription and OTC medications), and supplement type (nutritional product or alternative therapy). Nonprescription medications included OTC medications and dietary supplements. We defined any medication use as the regular use of at least 1 prescription, OTC, or dietary supplement. Similar to our group's previous analyses,[8] we defined concurrent use as the regular use of 2 or more medications at least daily or weekly. We also identified potentially major drug-drug interactions using a drug interaction software program (Micromedex; Truven Health Analytics) from a list of the 20 most commonly used prescription and OTC medications and the 20 most commonly used dietary supplements in 2010–2011.

Other Variables

Age at the time of the interview was calculated for all respondents based on date of birth. Race and Hispanic ethnicity were assessed via self-report. Respondents were then classified as non-Hispanic white, non-Hispanic black, Hispanic (any race), or other. Education was grouped into the following 4 mutually exclusive categories: less than high school, high school diploma or general equivalency diploma, some college, or bachelor's degree or higher. Household income was translated into a percentage of the federal poverty level (FPL) based on household size. Respondents were classified as poor if their household income was at or below 100% of the FPL, near poor if their household income was between 101% and 200% of the FPL, or nonpoor if their household income was above 200% of the FPL. Insurance status was measured using the question, "Are you currently covered by any of the following health insurance programs: Medicare, Medicaid, private insurance, Veterans Administration, or other?" Respondents were categorized as having a usual source of care if they responded affirmatively to the question, "Do you have a routine place you go when you

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are sick?" Respondents were also asked to rate their physical health using a standard 5-point scale with the responses excellent, very good, good, fair, or poor.

Statistical Analysis

The prevalence of use of any prescription medications, OTC medications, and dietary supplements, as well as specific medications, was estimated separately for each wave, both overall and separately by sex. In addition, the prevalence of use by therapeutic class and for the 20 most commonly used medications and supplements and interacting drug regimens was estimated. All prevalence estimates are weighted using the sample weights distributed with the data set to adjust for unequal probabilities of selection and differential nonresponse.[29] Variance estimates were obtained using the stratum and primary sampling unit variables distributed with the data set via the linearization method.[30] Confidence intervals were computed on the logit scale and then transformed to the corresponding prevalence.

Comparisons between waves were performed in 2 ways. Initially, a Wald test of the 2 prevalence estimates was conducted, which provides a test of the null hypothesis that the prevalence among those 62 to 85 years old is equal at both periods. However, because the use of many medications is associated with age, changes in the age distribution within the subpopulation 62 to 85 years old may affect the overall prevalence of use. To allow for this possibility, a logistic regression was fit to the pooled data set (ie, both waves), including age, wave, and an interaction between the 2. From the fitted model, age-specific differences in the predicted prevalence between waves were computed (on the logit scale) and averaged over the observed ages. The resulting predictive margin was tested against the null hypothesis that the population value was zero,[31] thus providing a comparison between waves unaffected by changes in the age distribution. Note that in both cases, the design-based covariance matrix of the estimators allows for the dependence between observations from the same respondent at both waves because both observations are taken from the same primary sampling unit.[32] The dates of the analysis were March to November 2015. All analyses were performed using statistical software (Stata, version 14.1; Stata-Corp LP). All *P* values are 2 sided, with a level of significance of .05.

Results

Among 2377 Wave 1 and 2245 Wave 2 interviews, only 26 (1.1%) and 39 (1.7%) respondents, respectively, declined to complete the medication log, yielding an analytic subsample of 4557 interviews. Table 1 lists the characteristics of this subsample, which correspond closely to those of respondents in the 2002 and 2012 Current Population Survey.[33] Compared with 2005–2006, older adults in 2010–2011 were more likely to be insured and have a usual source of care.

Use and Concurrent Use of Prescription and OTC Medications and Supplements

The Figure shows the prevalence of medication use in 2005–2006 and 2010–2011 overall and by the number and type of medication. The prevalence of prescription medication use among older adults 62 to 85 years old marginally increased from 84.1%(95%CI, 82.3%–

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85.7%) in 2005–2006 to 87.7%(95%CI, 85.6%–89.6%) in 2010–2011 (P= .003). Polypharmacy (concurrent use of ≥5 prescription medications) increased from 30.6% to 35.8% (P= .02). Concurrent use of 5 or more medications or supplements of any type increased substantially from 53.4% to 67.1% during this 5-year period (P< .001). The use of OTC medications declined from 44.4% (95% CI, 41.5%–47.4%) to 37.9% (95% CI, 35.3%–40.6%) (P< .001), while the use of dietary supplements increased from 51.8% (95% CI, 48.1%–55.4%)to 63.7%(95%CI, 60.6%–66.7%)(P< .001). Concurrent use of 2 or more dietary supplements increased from 31.6% to 47.0%(P< .001).

Among older adult prescription medication users, concurrent use of nonprescription medications (OTC or dietary supplements) marginally changed from 70.2% to 71.7%(P= .53) (eFigure in the Supplement). While concurrent use of OTC medications declined from 48.3% to 39.9%(P< .001), concurrent use of dietary supplements increased substantially from 53.9% to 65.7% (P< .001).

Use of Specific Therapeutic Classes, Medications, and Supplements

Table 2 summarizes increases in the use of several therapeutic classes, including statins (33.8% to 46.2%, P< .001), antiplatelets (32.8% to 43.0%, P< .001), NSAIDs (10.1% to 13.7%, P< .001), and proton pump inhibitors (15.7% to 18.5%, P= .05). The prevalence of the use of antihypertensives increased slightly (60.9% to 65.1%, P= .01), driven largely by increases in angiotensin-converting enzyme inhibitors (24.5% to 30.4%, P< .001), which were as commonly used as diuretics (29.5%) and β-blockers (31.2%) in 2010–2011.

The use of many individual medications among older adults increased from 2005 to 2011, including simvastatin (10.3% to 22.5%), aspirin (30.2% to 40.2%), lisinopril (12.9% to 19.9%), and omeprazole (8.2% to 14.2%) (P< .001 for all) (Table 3). By contrast, there was a significant decline in the use of atorvastatin calcium (13.8% to 9.7%, P< .001) and no significant changes in the use of other medications, such as warfarin sodium, furosemide, and acetaminophen.

Multivitamin or mineral supplements and calcium were the most commonly used supplements in both 2005–2006 and 2010–2011 (Table 3). There were clinically and statistically significant increases in the use ofomega-3 fish oils (4.7% to 18.6%), vitamin D (4.6% to 15.6%), and coenzyme Q_{10} (1.5% to 3.0%) between 2005–2006 and 2010–2011 (P < .05 for all). While the use of vitamin E (9.0% to 7.0%) and folic acid (5.9% to 4.2%) significantly declined (P< .05 for both), the use of several common dietary supplements, specifically potassium (7.5% to 8.5%), niacin (2.0% to 2.3%), and vitamin C (9.3% to 9.5%), remained constant.

Use of Potentially Interacting Drug Regimens

Using Micromedex, we identified 93 potential drug-drug interactions that involved prescription and OTC medications and supplements based on the 20 most commonly used medications and 20 most commonly used supplements (40 products in total). Among these 20 products, 15 interacting combinations were classified as potentially of major or life-threatening severity, all of which were used by at least 1 respondent in our sample (Table 4).

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Approximately 15.1%(95%CI, 13.2%–17.1%) of older adults 62 to 85 years old were using medication combinations with the potential for a major drug-drug interaction in 2010–2011, which reflected an increase from an estimated 8.4%(95%CI, 7.2%–9.8%) of the older population similarly at risk in 2005–2006 ($P < .001$). In both periods, men (19.8%) were significantly more likely than women(11.7%) to use interacting medications. Furthermore, in 2010–2011, 4.2% of older adults were using multiple (≥2) potentially interacting drug regimens, an approximately 3-fold greater proportion than the 1.6% estimated to be at risk in 2005–2006 ($P < .05$).

Preventive cardiovascular medications and supplements were increasingly used concurrently in interacting drug regimens. The use of both amlodipine and simvastatin was the most commonly used interacting drug regimen involving concurrent use of prescription medications and significantly increased from 1.0% to 3.9% between 2005–2006 and 2010–2011 ($P < .001$). This potentially major interaction was significantly more common in older adult men than women. Concurrent use of aspirin with clopidogrel bisulfate increased by almost 2-fold from 2.3% to 4.6% during this 5-year period. The use of warfarin concurrently with omega-3 supplements, an alternative therapy, increased substantially from 0.1% in 2005–2006 to 0.8% in 2010–11 ($P < .001$). In addition, concurrent use of aspirin and naproxen (both OTC medications) significantly increased from 0.9% to 2.2% between 2005–2006 and 2010–2011 ($P = .001$).

Discussion

We used in-home interviews with direct medication inspection to examine prescription and OTC medication use and dietary supplement use among a nationally representative sample of older adults in the United States in 2010–2011. Similar to a recent study[25] of the US population using the NHANES, we found that more than 1 in 3 older adults use 5 or more prescription medications concurrently. We also found that more than two-thirds of older adults concurrently use prescription medications with OTC medications or dietary supplements. Since 2005–2006, concurrent use of interacting medications and supplements has almost doubled, with approximately 1 in 6 older adults potentially at risk for a major drug-drug interaction. Most of these interacting drug regimens involve medications and dietary supplements increasingly used in 2010–2011.

We identified increases in the use of many therapeutic classes, including statins, NSAIDs, and antiplatelets, that were particularly noteworthy. Our findings for prescription-only medications, such as statins, were similar to those observed in the recent NHANES study,[25] which substantially underestimates the use of and changes in the use of antiplatelets and NSAIDs (commonly used OTC medications). These changes, which persisted in age-adjusted analyses, demonstrate the potential for large secular changes in the use of many prescription and OTC products and therapeutic classes over short periods. Although our investigation was not designed to determine the specific causes of changes that we identify, several contributing factors may account for increases we observed, including the implementation of Medicare Part D,[10,34] changes to clinical guidelines,[35,36] and market dynamics, such as new therapies brought to market as well as patent expirations.[13,37–40]

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Despite no evidence of any clinical benefits,[41] dietary supplement use is increasingly common among older adults, with almost a 50% increase in the use of multiple supplements. The almost 4-fold increase in the use of omega-3 fish oils over a 5-year period is particularly noteworthy considering their limited cardiovascular benefits.[42] We also identified an almost 3-fold increase in the use of vitamin D, which may be due to increased reports supporting possible cognitive benefits in older adults.[43] However, vitamin E use has declined, coinciding with the US Preventive Services Task Force recommendation against its use for the prevention of cardiovascular disease and cancer.[44]

While concurrent use of prescription and nonprescription medications remains common, concurrent use of interacting medications among older adults has almost doubled since 2005–2006, with approximately 1 in 6 older adults in the United States potentially at risk for a major drug-drug interaction. Most of these interactions involved medications and supplements increasingly used in 2010–2011 and indicate that commonly used medications are often concurrently used in combinations that may potentially contribute to and worsen avoidable adverse drug events in older adults,[7] including renal failure and hemorrhagic complications.[4,21–23] These findings suggest that the unsafe use of multiple medications among older adults is a growing public health problem. Therefore, health care professionals should carefully consider the adverse effects of commonly used prescription and nonprescription medication combinations when treating older adults and counsel patients about these risks.

Improving the safe use of medications is particularly important among older adults using preventive cardiovascular medications and supplements. Most of the interacting regimens we identified involved statins, antiplatelets (eg, clopidogrel and aspirin), NSAIDs, or omega-3 fish oils, which may not only lead to adverse drug events due to drug-drug interactions but also worsen cardiovascular risk.[20–24,42] For example, the use of clopidogrel in combination with omeprazole or NSAIDs is associated with an increased risk of myocardial infarction, hemorrhagic complications, or cardiovascular death.[20,22–24] However, according to our analyses, approximately 1.8% of older adults (or 1 million) regularly use clopidogrel in interacting combinations.

Recent implementation of treatment guidelines promoting statins in the primary prevention of cardiovascular disease,[45] as well as the availability of both clopidogrel and atorvastatin as generics,[46,47] may further increase the use of these interacting regimens. Therefore, efforts are needed that focus on increasing patient and health care professional awareness of the risks associated with concurrent use of interacting medications among older adults, particularly for statins and antiplatelets. These efforts may include incorporation of the interaction effects of commonly used medications, including OTC medications and dietary supplements, in treatment guidelines.

Our study has several limitations. First, the risk-benefit profile of a potentially interacting drug regimen may vary between patients, and we examined the potential for drug interactions. Our study was not designed to evaluate health outcomes directly, including adverse drug events. Second, there is a broad range of factors that influence adverse drug events, such as liver and kidney function, type of interaction, dosage, timing of concurrent

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use, and disease severity, and our data were not designed to evaluate these factors. Third, we used the Micromedex drug interaction software to identify potential interactions in our sample, and alternative sources of such information may yield greater or lesser estimates of the prevalence of specific types of drug-drug interactions. Fourth, our data were limited to medications used regularly rather than occasionally and thus exclude medications commonly used for acute conditions, such as antibiotics for acute bronchitis, that may potentially interact with medications regularly used. We also restricted our analyses to the 20 most commonly used medications and supplements; therefore, our findings may underestimate the potential risk of major drug-drug interactions among older adults.

Conclusions

Older adults are increasingly using multiple medications and dietary supplements, and the use of interacting medication regimens has increased over time. Approximately 1 in 6 older adults may be at risk for a major drug-drug interaction. Efforts that focus on improving the safe use of multiple medications have the potential to reduce preventable adverse drug events associated with medications commonly and increasingly used among older adults in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Gu Q, Dillon CF, Burt VL. Prescription drug use continues to increase: U.S. prescription drug data for 2007–2008. NCHS Data Brief. 2010; (42):1–8.
2. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med. 2002; 162(20):2269–2276. [PubMed: 12418941]
3. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012; 60(4):616–631. [PubMed: 22376048]
4. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA. 2006; 296(15):1858–1866. [PubMed: 17047216]
5. Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther. 2009; 85(1):86–88. [PubMed: 19037203]
6. Leiss W, Méan M, Limacher A, et al. Polypharmacy is associated with an increased risk of bleeding in elderly patients with venous thromboembolism. J Gen Intern Med. 2015; 30(1):17–24. [PubMed: 25143224]

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7. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011; 365(21):2002–2012. [PubMed: 22111719]
8. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA. 2008; 300(24):2867–2878. [PubMed: 19109115]
9. Briesacher BA, Zhao Y, Madden JM, et al. Medicare Part D and changes in prescription drug use and cost burden: national estimates for the Medicare population, 2000 to 2007. Med Care. 2011; 49(9):834–841. [PubMed: 21544002]
10. Aitken M, Berndt ER, Cutler DM. Prescription drug spending trends in the United States: looking beyond the turning point. Health Aff (Millwood). 2009; 28(1):w151–w160. [PubMed: 19088102]
11. Alldredge BK, Kayser SR. Bending the curve toward increased use of generic drugs. JAMA Intern Med. 2013; 173(3):233–234. [PubMed: 23303368]
12. IMS Institute for Healthcare Informatics. [Accessed February 1, 2016] The use of medicines in the United States: review of 2011. https://www.imshealth.com/files/web/IMSH%20Institute/Reports/The%20Use%20of%20Medicines%20in%20the%20United%20States%202011/IHII_Medicines_in_U.S_Report_2011.pdf
13. Simonson W. Implications of over-the-counter proton pump inhibitors for patient counseling by pharmacists. Am J Ther. 2013; 20(6):676–684. [PubMed: 21642828]
14. Kelley BJ, Glasser S. Cognitive effects of statin medications. CNS Drugs. 2014; 28(5):411–419. [PubMed: 24504830]
15. Dormuth CR, Filion KB, Paterson JM, et al. Canadian Network for Observational Drug Effect Studies Investigators. Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. BMJ. 2014; 348:g3244. [PubMed: 24874977]
16. Desai CS, Martin SS, Blumenthal RS. Non-cardiovascular effects associated with statins. BMJ. 2014; 349:g3743. [PubMed: 25035309]
17. Hsu CC, Wang H, Hsu YH, et al. Use of nonsteroidal anti-inflammatory drugs and risk of chronic kidney disease in subjects with hypertension: nationwide longitudinal cohort study. Hypertension. 2015; 66(3):524–533. [PubMed: 26169048]
18. U.S. Food and Drug Administration. [Accessed August 1, 2015] FDA drug safety communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm. Published July 9, 2015
19. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. PLoS One. 2015; 10(6):e0124653.doi: 10.1371/journal.pone.0124653 [PubMed: 26061035]
20. Leonard CE, Bilker WB, Brensinger CM, et al. Comparative risk of ischemic stroke among users of clopidogrel together with individual proton pump inhibitors. Stroke. 2015; 46(3):722–731. [PubMed: 25657176]
21. Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. Kidney Int. 2015; 88(2):396–403. [PubMed: 25874600]
22. Shehab N, Sperling LS, Kegler SR, Budnitz DS. National estimates of emergency department visits for hemorrhage-related adverse events from clopidogrel plus aspirin and from warfarin. Arch Intern Med. 2010; 170(21):1926–1933. [PubMed: 21098354]
23. Lamberts M, Lip GY, Hansen ML, et al. Relation of nonsteroidal anti-inflammatory drugs to serious bleeding and thromboembolism risk in patients with atrial fibrillation receiving antithrombotic therapy: a nationwide cohort study. Ann Intern Med. 2014; 161(10):690–698. [PubMed: 25402512]
24. Schjerning Olsen AM, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA. 2015; 313(8):805–814. [PubMed: 25710657]
25. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999–2012. JAMA. 2015; 314(17):1818–1831. [PubMed: 26529160]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

26. O'Muircheartaigh C, English N, Pedlow S, Kwok PK. Sample design, sample augmentation, and estimation for Wave 2 of the NSHAP. J Gerontol B Psychol Sci Soc Sci. 2014; 69(suppl 2):S15–S26. [PubMed: 25360016]
27. American Association for Public Opinion Research. Standard Definitions: Final Dispositions of Case Codes and Outcome Rates for Surveys. 5. Lenexa, KS: American Association for Public Opinion Research; 2008.
28. Qato DM, Schumm LP, Johnson M, Mihai A, Lindau ST. Medication data collection and coding in a home-based survey of older adults. J Gerontol B Psychol Sci Soc Sci. 2009; 64(suppl 1):i86–i93. [PubMed: 19491196]
29. National Archive of Computerized Data on Aging. [Accessed March 2015] National Social Life, Health, and Aging Project (NSHAP). http://www.icpsr.umich.edu/icpsrweb/NACDA/
30. Binder DA. On the variances of asymptotically normal estimators from complex surveys. Int Stat Rev. 1983; 51:279–292.
31. Graubard BI, Korn EL. Predictive margins with survey data. Biometrics. 1999; 55(2):652–659. [PubMed: 11318229]
32. Wolter, KM. Introduction to Variance Estimation. New York, NY: Springer-Verlag; 1985.
33. United States' Census Bureau. [Accessed November 22, 2015] Current population survey, annual social and economic supplement. 2012. http://www.census.gov/population/age/data/2012.html. Published December 2013
34. Basu A, Yin W, Alexander GC. Impact of Medicare Part D on Medicare-Medicaid dual-eligible beneficiaries' prescription utilization and expenditures. Health Serv Res. 2010; 45(1):133–151. [PubMed: 20002765]
35. Introduction: the American Diabetes Association's (ADA) evidence-based practice guidelines, standards, and related recommendations and documents for diabetes care. Diabetes Care. 2012; 35(suppl 1):S1–S2. [PubMed: 22187466]
36. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014; 311(5):507–520. [published correction appears in *JAMA*. 2014;311(17):1809]. [PubMed: 24352797]
37. Zhou M, Daubresse M, Stafford RS, Alexander GC. National trends in the ambulatory treatment of hypertension in the United States, 1997–2012. PLoS One. 2015; 10(3):e0119292.doi: 10.1371/journal.pone.0119292 [PubMed: 25738503]
38. Turner LW, Nartey D, Stafford RS, Singh S, Alexander GC. Ambulatory treatment of type 2 diabetes in the U.S., 1997–2012. Diabetes Care. 2014; 37(4):985–992. [PubMed: 24198301]
39. Wang B, Choudhry NK, Gagne JJ, Landon J, Kesselheim AS. Availability and utilization of cardiovascular fixed-dose combination drugs in the United States. Am Heart J. 2015; 169(3):379–386. e1. DOI: 10.1016/j.ahj.2014.12.014 [PubMed: 25728728]
40. Holtmann G, Bigard MA, Malfertheiner P, Pounder R. Guidance on the use of over-the-counter proton pump inhibitors for the treatment of GERD. Int J Clin Pharm. 2011; 33(3):493–500. [PubMed: 21472476]
41. Guallar E, Stranges S, Mulrow C, Appel LJ, Miller ER III. Enough is enough: stop wasting money on vitamin and mineral supplements. Ann Intern Med. 2013; 159(12):850–851. [PubMed: 24490268]
42. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA. 2012; 308(10):1024–1033. [PubMed: 22968891]
43. Dickens AP, Lang IA, Langa KM, Kos K, Llewellyn DJ. Vitamin D, cognitive dysfunction and dementia in older adults. CNS Drugs. 2011; 25(8):629–639. [PubMed: 21790207]
44. Moyer VA. U.S. Preventive Services Task Force. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 160(8):558–564. [PubMed: 24566474]
45. Stone NJ, Robinson JG, Lichtenstein AH, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American

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College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014; 129(25 suppl 2):S1–S45. [PubMed: 24222016]

46. Doll J, Zeitler E, Becker R. Generic clopidogrel: time to substitute? JAMA. 2013; 310(2):145–146. [PubMed: 23839745]
47. Kennally WC III. Generic atorvastatin and health care costs. N Engl J Med. 2012; 366(15):1451. [PubMed: 22494136]

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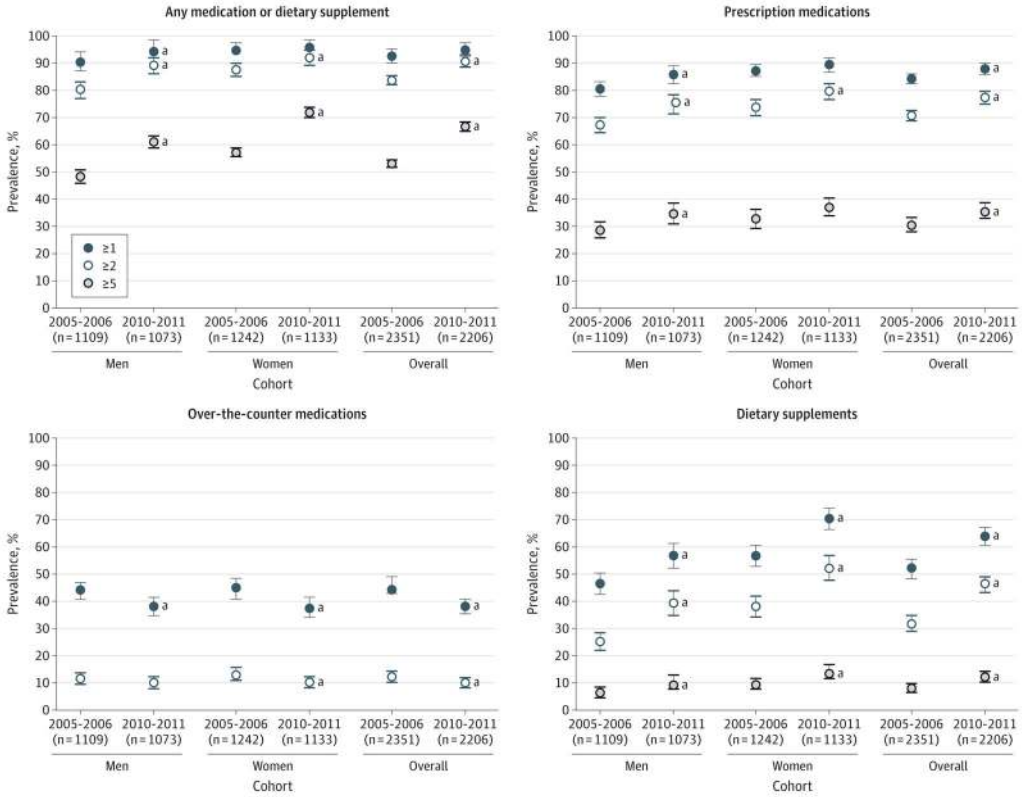

Figure. Weighted Prevalence Estimates of Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States

Error bars indicate 95% CIs. *P* values are based on a Wald test of the predictive margin calculated by averaging the age-specific differences in predicted prevalence (on the logit scale) between waves over the observed ages in the sample and by using a design-based estimate of variance.

[a] $P < .05$.

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Table 1

Sociodemographic, Health, and Health Care Characteristics of Older US Adults[a]

Variable	Weighted Distribution, % (95% CI)		*P* Value[b]
	Wave 1, 2005–2006 (n = 2351)	Wave 2, 2010–2011 (n = 2206)	
Sex			
Men	46.7 (44.3–49.2)	48.4 (45.8–51.4)	.04
Women	53.3 (50.8–55.7)	51.6 (48.9–54.2)	.04
Education			
<High school	20.3 (17.3–23.7)	15.9 (12.7–19.6)	<.001
High school diploma or GED	28.1 (25.5–30.8)	25.2 (22.5–27.9)	.02
≥Some college	51.6 (48.1–55.2)	59.0 (54.9–63.2)	.27
Race/ethnicity			
Non-Hispanic white	81.3 (77.4–84.8)	80.1 (76.2–83.4)	.16
Non-Hispanic black	9.9 (7.9–12.4)	10.4 (8.2–13.2)	.52
Hispanic, any race	6.4 (3.9–10.3)	6.9 (4.4–10.8)	.21
Other	2.4 (1.7–3.4)	2.6 (1.7–3.9)	.56
Household income			
Poor	9.7 (7.0–13.2)	7.7 (5.6–10.6)	.07
Near poor	20.9 (18.1–24.0)	19.1 (16.4–22.0)	.19
Nonpoor	69.4 (65.1–73.4)	73.2 (68.9–77.1)	.01
Health insurance			
None	4.4 (3.4–5.6)	2.7 (2.0–3.6)	<.001
Medicare	72.1 (68.9–75.1)	73.4 (69.5–77.0)	.35
Private only	16.8 (14.3–19.6)	14.2 (11.1–17.9)	.34
Medicaid/VA/other, no Medicare	6.7 (5.3–8.3)	9.7 (8.1–11.6)	.01
Have usual source of care	91.2 (89.5–92.6)	94.5 (93.2–95.6)	.001
Self-reported health			
Poor	6.8 (5.4–8.5)	5.9 (4.3–8.1)	.66
Fair	18.3 (16.4–20.3)	18.7 (16.5–21.1)	.71
Good	30.7 (28.1–33.4)	31.2 (28.4–34.2)	.91
Very good	31.4 (28.9–33.9)	31.5 (29.2–33.8)	.78
Excellent	12.9 (10.8–15.3)	12.7 (10.3–15.6)	>.99
Medication use			
No medication use	7.2 (5.9–8.6)	4.9 (3.6–6.6)	.02
Prescription	84.1 (82.3–85.7)	87.7 (85.6–89.6)	.003
OTC	44.4 (41.5–47.4)	37.9 (35.3–40.6)	<.001
Dietary supplement[c]	51.8 (48.1–55.4)	63.7 (60.6–66.7)	<.001

Abbreviations: GED, general equivalency diploma; OTC, over the counter; VA, Veterans Administration.

[a]The mean (range) age of the study cohort was 70.9 years (70.6–71.3 years) in 2005–2006 and 71.4 years (70.9–71.9 years) in 2010–2011 (*P* = .06).

[b] *P* values are based on a Wald test of the predictive margins calculated by averaging the age-specific differences in predicted prevalence (on the logit scale) between waves over the observed ages in the sample and by using a design-based estimate of variance.

[c] Dietary supplements include the use of nutritional products and alternative therapies.

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Table 2

Weighted Prevalence Estimates of the Most Commonly Used Therapeutic Classes Among Older Adults in the United States

Variable	Estimated Prevalence, % (95% CI)		*P* Value[a]
	2005–2006 (n = 2351)	2010–2011 (n = 2206)	
Antihyperlipidemics	37.3 (34.6–40.1)	50.1 (47.1–53.0)	<.001
Statins	33.8 (31.3–36.4)	46.2 (43.3–49.2)	<.001
Antihyperlipidemic combinations	2.6 (1.9–3.6)	2.7 (1.9–3.7)	.89
Antihypertensives	60.9 (58.3–63.6)	65.1 (62.3–67.9)	.01
ACE inhibitors	24.5 (22.7–26.4)	30.4 (27.5–33.4)	<.001
Angiotensin II antagonists	13.5 (12.0–15.3)	13.2 (11.4–15.2)	.39
Diuretics	27.4 (24.9–30.1)	29.5 (26.5–32.8)	.22
Calcium channel blockers	17.8 (16.2–19.5)	19.5 (17.2–22.2)	.84
β-Blockers	27.1 (24.9–29.5)	31.2 (29.0–33.4)	.03
Antihypertensive combinations	10.7 (9.1–12.7)	12.4 (10.3–14.8)	.12
Antidiabetic agents	16.6 (14.6–18.8)	17.8 (15.7–20.1)	.47
Insulins	3.5 (2.6–4.7)	4.0 (3.0–5.3)	.35
Sulfonylureas	8.5 (7.1–10.2)	7.9 (6.5–9.5)	.38
Nonsulfonylureas	9.3 (8.1–10.7)	12.5 (11.1–14.1)	<.001
Thiazolidinediones	4.4 (3.5–5.7)	3.0 (2.4–3.8)	.006
Antidiabetic combinations	1.6 (1.1–2.3)	0.9 (0.6–1.4)	.01
Coagulation modifiers	36.9 (34.1–39.8)	47.6 (45.2–50.1)	<.001
Coumarins and indandiones	5.3 (4.6–6.2)	6.4 (5.3–7.7)	.45
Antiplatelets	32.8 (29.9–35.8)	43.0 (40.6–45.6)	<.001
Analgesics	44.3 (41.7–47.2)	54.3 (51.5–57.0)	<.001
Narcotic analgesics	4.9 (4.0–5.9)	6.7 (5.4–8.3)	.01
Nonsteroidal anti-inflammatory drugs	10.1 (9.0–11.4)	13.7 (12.3–15.1)	<.001
Salicylates	30.3 (27.5–33.3)	40.4 (37.8–43.0)	<.001
COX-2 inhibitors	2.3 (1.7–3.1)	1.3 (0.9–1.9)	.001
Narcotic analgesics combinations	3.6 (2.8–4.5)	4.2 (3.2–5.6)	.22
Analgesics combinations	0.6 (0.3–0.09)	0.4 (0.2–0.8)	.46
Respiratory agents	15.3 (13.6–17.3)	19.6 (17.4–22.0)	.002
Adrenergic bronchodilators	5.9 (4.6–7.5)	7.3 (6.0–8.8)	.17
Inhaled corticosteroids	4.4 (3.5–5.6)	6.5 (5.3–7.9)	.02
Anticholinergic bronchodilators	2.4 (1.8–3.2)	2.8 (2.1–3.7)	.73
Respiratory combinations	3.5 (2.7–4.4)	5.0 (4.1–6.2)	.07
Proton pump inhibitors	15.7 (14.0–17.5)	18.5 (16.5–20.6)	.05
Thyroid hormones	14.8 (13.1–16.7)	15.8 (14.2–17.6)	.91
Anxiolytics, sedatives, and hypnotics	8.5 (7.5–9.4)	12.5 (10.6–14.8)	<.001
Benzodiazepines	5.8 (5.0–6.7)	7.6 (6.2–9.3)	.06

Abbreviations: ACE, angiotensin-converting enzyme; COX-2, cyclooxygenase 2.

[a] *P* values are based on a Wald test of the predictive margin calculated by averaging the age-specific differences in predicted prevalence (on the logit scale) between waves over the observed ages in the sample and by using a design-based estimate of variance.

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Table 3

Weighted Prevalence Estimates of the Most Commonly Used Prescription and Over-the-Counter (OTC) Medications and Dietary Supplements Among US Older Adults

Variable	Estimated Prevalence, % (95% CI)		*P* Value[a]
	2005–2006 (n = 2351)	2010–2011 (n = 2206)	
Prescription and OTC medications			
Aspirin OTC[b]	30.2 (27.4–33.1)	40.2 (37.7–42.8)	<.001
Simvastatin[c]	10.3 (9.0–11.7)	22.5 (20.4–24.9)	<.001
Lisinopril	12.9 (11.3–14.8)	19.9 (17.7–22.4)	<.001
Hydrochlorothiazide	17.1 (14.9–19.5)	19.3 (16.8–22.0)	.06
Levothyroxine sodium	14.3 (12.6–16.3)	15.4 (13.7–17.2)	.86
Metoprolol	11.7 (10.1–13.6)	14.9 (12.9–17.3)	.02
Amlodipine[c]	8.5 (7.5–9.7)	13.4 (11.6–15.5)	.001
Metformin	9.3 (8.0–10.7)	12.6 (11.3–14.2)	<.001
Omeprazole OTC[b]	8.2 (7.1–9.4)	14.2 (12.6–16.1)	<.001
Atorvastatin calcium	13.8 (11.9–16.0)	9.7 (8.4–11.2)	<.001
Acetaminophen OTC[b]	8.1 (6.7–10.0)	8.7 (7.3–10.4)	.92
Atenolol	9.5 (8.1–11.1)	8.5 (7.3–9.9)	.12
Furosemide	7.3 (6.1–8.6)	8.2 (7.2–9.4)	.83
Clopidogrel bisulfate	4.5 (3.6–5.8)	7.1 (5.5–9.2)	.04
Warfarin sodium	5.3 (4.6–6.2)	6.4 (5.3–7.7)	.45
Carvedilol	2.3 (1.7–3.2)	4.5 (3.1–6.5)	.02
Pravastatin sodium[c]	2.8 (2.1–3.7)	4.9 (4.0–6.1)	.002
Rosuvastatin calcium	1.1 (0.1–1.6)	4.9 (3.9–6.2)	<.001
Naproxen OTC[b]	3.5 (2.9–4.3)	4.7 (3.7–6.0)	.045
Ezetimibe	5.6 (4.6–6.8)	4.6 (3.7–5.7)	.13
Dietary supplements			
Multivitamin/minerals	29.0 (25.5–32.6)	34.9 (32.2–37.7)	.03
Calcium	18.9 (17.0–21.0)	24.1 (22.0–26.5)	.009
Omega-3 fish oil	4.7 (3.4–6.3)	18.6 (16.7–20.6)	<.001
Vitamin D	4.6 (3.7–5.6)	15.6 (13.9–17.6)	<.001
Any vitamin B[d]	8.1 (6.8–10.0)	9.8 (8.1–11.7)	.34
Vitamin C	9.3 (8.0–11.0)	9.5 (8.2–11.0)	.59
Chondroitin sulfate sodium–glucosamine	7.3 (6.2–8.7)	8.5 (6.9–10.5)	.29
Potassium	7.5 (6.5–8.7)	8.5 (7.4–9.7)	.28
Vitamin E	9.0 (7.3–11.1)	7.0 (5.8–8.5)	.04
Iron	1.5 (1.1–2.1)	1.8 (1.3–2.4)	.39
Folic acid	5.9 (4.8–7.2)	4.2 (3.2–5.4)	.01

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Variable	Estimated Prevalence, % (95% CI)		*P* Value[a]
	2005–2006 (n = 2351)	2010–2011 (n = 2206)	
Eye vitamins	2.9 (2.2–3.8)	3.8 (3.0–4.8)	.52
Magnesium	2.7 (1.9–3.8)	2.9 (2.1–4.0)	.82
Coenzyme Q_{10}	1.5 (0.1–2.3)	3.0 (2.2–3.9)	.03
Flax	1.5 (0.1–2.5)	2.4 (1.7–3.5)	.15
Niacin	2.0 (1.5–2.7)	2.3 (1.7–3.1)	.43
Saw palmetto	3.4 (2.2–5.3)	2.1 (1.3–3.2)	.09
Methlysulfonylmethane	2.0 (1.5–3.2)	1.5 (1.0–2.2)	.06
Zinc	2.5 (1.7–3.6)	1.5 (1.0–2.2)	.03
Garlic	1.5 (1.0–2.4)	1.3 (1.0–1.8)	.63

[a] *P* values are based on a Wald test of the predictive margin calculated by averaging the age-specific differences in predicted prevalence (on the logit scale) between waves over the observed ages in the sample and by using a design-based estimate of variance.

[b] Medication is available as both prescription only and OTC depending on formulation and strength.

[c] Prescription medication was available in generic formulation between 2006 and 2011.

[d] Any vitamin B includes vitamin B_{12}, vitamin B_6, vitamin B complex, and unspecified vitamin B.

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Table 4

Weighted Prevalence Estimates of Potentially Major Drug-Drug Interactions Among US Older Adults

Variable	Estimated Prevalence, % (95% CI)		*P* Value[a]	Potential Adverse Drug Event
	2005–2006 (n = 2351)	2010–2011 (n = 2206)		
Prescription-prescription	2.5 (1.9–3.3)	6.3 (5.2–7.7)	<.001	NA
Amlodipine-simvastatin	1.0 (0.7–1.6)	3.9 (3.2–4.9)	<.001	Increased risk of myopathy or rhamdomyolysis, renal failure
Warfarin sodium–simvastatin	0.9 (0.6–1.3)	1.7 (1.3–2.3)	.046	Increased risk of bleeding or rhamdomyolysis, renal failure
Amlodipine–clopidogrel bisulfate	0.7 (0.4–1.3)	1.3 (0.8–2.0)	.68	Increased risk of thrombotic event
Warfarin sodium–clopidogrel bisulfate	0.1 (0.1–0.2)	0.2 (0.1–0.5)	.71	Increased risk of bleeding
Prescription-nonprescription	5.7 (4.7–6.9)	9.4 (7.9–11.2)	.002	NA
Aspirin–clopidogrel bisulfate	2.3 (1.6–3.3)	4.6 (3.3–6.3)	.009	Increased risk of bleeding
Lisinopril-potassium	1.2 (0.9–1.7)	2.1 (1.5–2.9)	.03	Increased risk of hyperkalemia
Warfarin sodium–aspirin	1.1 (0.6–1.8)	1.6 (1.1–2.2)	.71	Increased risk of bleeding
Warfarin sodium–omega-3 fish oil	0.1 (0.0–0.3)	0.8 (0.6–1.3)	<.001	Increased risk of bleeding
Warfarin sodium–naproxen	0.1 (0.0–0.4)	0.0 (0.1–0.5)	.03	Increased risk of bleeding
Warfarin sodium–garlic	0.0 (0.0–0.4)	0.0 (0.0–0.2)	.63	Increased risk of bleeding
Clopidogrel bisulfate–omeprazole	0.7 (0.4–1.2)	0.8 (0.4–1.2)	.87	Increased risk of thrombotic event
Clopidogrel bisulfate–naproxen	0.1 (0.0–0.3)	0.7 (0.3–1.8)	.003	Increased risk of bleeding
Niacin–atorvastatin calcium	0.6 (0.3–1.0)	0.5 (0.2–0.9)	.81	Increased risk of myopathy or rhamdomyolysis, renal failure
Niacin-simvastatin	0.4 (0.2–0.8)	0.5 (0.3–0.8)	.85	Increased risk of myopathy or rhamdomyolysis, renal failure
Niacin–rosuvastatin calcium	0.04 (0.0–0.3)	0.2 (0.1–0.5)	.15	Increased risk of myopathy or rhamdomyolysis, renal failure
Nonprescription-nonprescription	0.9 (0.6–1.3)	2.2 (1.5–3.3)	.001	NA
Aspirin-naproxen	0.9 (0.6–1.3)	2.2 (1.5–3.3)	.001	Increased risk of bleeding, ulceration, or perforation
Any major drug interaction	8.4 (7.2–9.8)	15.1 (13.2–17.1)	<.001	NA
≥2 Major interactions	1.6 (1.0–2.5)	4.2 (3.1–5.6)	.002	NA

Abbreviation: NA, not applicable.

[a] *P* values are based on a Wald test of the predictive margin calculated by averaging the age-specific differences in predicted prevalence (on the logit scale) between waves over the observed ages in the sample and by using a design-based estimate of variance.