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Impact of drug-drug and drug-disease interactions on gait speed in community-dwelling older adults

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Abstract

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Compliance with Ethical Standards

Conflicts of Interest

Jennifer Naples, Zachary Marcum, Subashan Perera, Anne Newman, Susan Greenspan, Shelly Gray, Douglas Bauer, Eleanor Simonsick, Ronald Shorr, and Joseph Hanlon declare that they have no conflict of interest relevant to the content of this review.

Ethical Approval

All participants provided written informed consent, and the Institutional Review Boards at both study sites approved all protocols.

Background—Gait speed decline, an early marker of functional impairment, is a sensitive predictor of adverse health outcomes in older adults. The effect of potentially inappropriate prescribing on gait speed decline is not well known.

Objective—To determine if potentially inappropriate drug interactions impair functional status as measured by gait speed.

Methods—The sample included 2,402 older adults with medication and gait speed data from the Health, Aging and Body Composition study. The independent variable was the frequency of drug-disease and/or drug-drug interactions at baseline and three additional years. The main outcome was a clinically meaningful gait speed decline ≥ 0.1 m/s the year following drug interaction assessment. Adjusted odds ratios and 95% confidence intervals were calculated using multivariate generalized estimating equations for both the overall sample and a sample stratified by gait speed at time of drug interaction assessment.

Results—The prevalence of drug-disease and drug-drug interactions ranged from 7.6–9.3% and 10.5–12.3%, respectively, with few participants (3.8–5.7%) having multiple drug interactions. At least 22% of participants had a gait speed decline of ≥ 0.1 m/s annually. Drug interactions were not significantly associated with gait speed decline overall or in the stratified sample of fast walkers. There was some evidence, however, that drug interactions increased the risk of gait speed decline among those participants with slower gait speeds, though p values did not reach statistical significance (adjusted odds ratio 1.22, 95% confidence intervals 0.96–1.56, $p=0.11$). Moreover, a marginally significant dose-response relationship was seen with multiple drug interactions and gait speed decline (adjusted odds ratio 1.40; 95% confidence intervals 0.95–2.04, $p=0.08$).

Conclusions—Drug interactions may increase the likelihood of gait speed decline among older adults with evidence of preexisting debility. Future studies should focus on frail elders with less physiological reserve who may be more susceptible to the harms associated with potentially inappropriate medications.

1. Introduction

Potentially inappropriate medications (PIM) have been associated with an increased risk of adverse drug reactions (ADRs) in older adults [1]. One major but preventable cause of ADRs involves drug interactions, an umbrella category comprised of both drug-disease interactions (DDxIs) and drug-drug interactions (DDIs) [2,3]. Up to 44% and 30% of the general population are estimated to have DDxIs and DDIs, respectively [3]. In older adults with age-related physiological impairments, there is potential concern that the impact of these drug interactions may exceed existing cardiopulmonary, neurological, musculoskeletal, or renal organ system reserves and manifest as a decline in functional status [4,5].

Functional status impairment may be detected by a change in mobility, evidenced by slowing gait speed [6,7]. Slower gait speed has been shown to predict incident disability, hospitalization, and mortality in older adults [8–10]. To date, only a few studies have examined the impact of PIM (e.g., benzodiazepines, higher doses of anticholinergic agents, multiple central nervous system [CNS] medications) on gait speed decline, and none specifically evaluate the role of DDxIs [11]. As such, the current study aims to investigate

the association of these two types of drug interactions, separately and in combination, with clinically-meaningful changes in gait speed in a sample of community-dwelling older adults.

2. Methods

2.1 Study Design, Setting, Source of Data, and Sample

This longitudinal study used four years of data from older adults participating in the Health, Aging and Body Composition (Health ABC) study [6]. At baseline, the Health ABC study enrolled 3,075 community-dwelling adults with no self-reported mobility limitations, recruited through population-based lists of Medicare enrollees from Pittsburgh, Pennsylvania, and Memphis, Tennessee [6]. The current study sample was restricted to 2,402 individuals with medication data at year 2 and 20-meter gait speed available at years 2 and 3. Between years 1 and 2 of the Health ABC study, 32 participants died, 3 withdrew, and 42 did not have information for a year 2 clinic visit. Of the 2,988 participants remaining at year 2, 596 were excluded because they did not have medication data ($n = 90$) or gait speed measures at either year 2 or year 3 ($n = 506$). Excluded individuals were more likely to be older, black, and hospitalized in the previous 12 months compared to the included sample ($p < 0.05$ for all factors). This is similar to a previous study evaluating functional mobility in this sample that found individuals unable to participate in gait speed measures were more likely to be older with more comorbidities [6]. All participants provided written informed consent, and the Institutional Review Boards at both study sites approved all protocols.

2.2 Data Collection and Management

Data collection and management processes used for the Health ABC study are described in detail elsewhere [6]. Briefly, comprehensive health evaluations and blood draws were completed by trained research assistants during annual clinic or home visits. Gait speed was measured at years 2–6 by having participants walk down an unobstructed 20-meter hallway; timing started with the first step over the starting line and ended at the first footfall over the finishing line [6]. Medication data were collected at years 2, 3, and 5 for both prescription and over-the-counter (OTC) medications using a state-of-the-art “brown bag” review method in which a trained interviewer recorded the drug name, strength, and frequency of use in the previous two weeks [12]. All medications were coded using the Iowa Drug Information System (IDIS) Drug Vocabulary and Thesaurus [13].

2.3 Independent Variables

Using explicit criteria developed through expert panel consensus, 24 DDxIs were studied [14]. For four conditions (i.e., falls in the previous year, heart failure, Parkinson’s disease, and syncope), reliable and valid self-reported information was collected directly from participants [15,16]. Renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min) was calculated with the CKD-EPI Cystatin C equation using serum cystatin C values from blood draws taken at years 1, 3, and 4 [17,18]. Cognitive impairment was defined as a Modified Mini-Mental Status (3MS) score less than 80 [19,20]. In participants with at least one of the six conditions, possible DDxIs involving inappropriate medications/classes were identified by IDIS codes.

Additionally, 30 DDIs based on expert panel consensus explicit criteria were studied [14,21,22]. For these DDIs, an object drug's systemic clearance could be decreased (e.g., digoxin and amiodarone) or pharmacodynamic sensitivity could be enhanced by an interacting medication (e.g., multiple anticholinergic agents).

2.4 Dependent Variable

The primary outcome variable was a gait speed decline ≥ 0.1 m/s during the year following drug interaction assessment. The 0.1 m/s criterion represents a substantial and meaningful change across varying subgroups of older adults, including those with baseline gait speed impairment [6,8,23].

2.5 Covariates

Several characteristics that may confound the association between PIM and gait speed were adjusted for in the analyses [6,24]. Demographic characteristics included age, sex, race, education, and study site. Health status characteristics included self-rated health, hospitalization in the previous 12 months, number of prescription and over-the-counter medications, and self-reported coronary heart disease, diabetes mellitus, osteoarthritis, osteoporosis, peripheral artery disease, pulmonary disease, and stroke. Depressive symptoms were identified using the valid and reliable Short Center for Epidemiologic Studies Depression (CES-D > 10) scale [24].

2.6 Statistical Analyses

Descriptive statistics were used to summarize participant characteristics. Additional tests included generalized estimating equations (GEEs) models with gait speed decline of ≥ 0.1 m/s as the dichotomous dependent variable; binomial distribution and a logit link function; separate, combinations and counts (0, 1, ≥ 2), in individual models, of DDxIs and DDIs as main independent variables of interest; and an exchangeable working correlation structure to account for multiple years of data from the same participants [25]. We added time-varying measures for age, self-rated health, hospitalization in the previous 12 months, and total number of prescription medications as additional independent covariates to obtain adjusted odds ratios (AORs) and their 95% confidence intervals (CI). These same analyses were again conducted for samples stratified by gait speed (i.e., "slow" versus "fast" walkers based on a median split at 1.15 m/s to ensure similar sample sizes in each group). All analyses were performed using SAS[®] software (version 9.3; SAS Institute Inc., Cary, NC).

3. Results

As seen in Table 1, the baseline sample was approximately 75 years old and well-educated, with more than three-quarters having at least a high-school diploma. There was an even distribution among sex and site, and one-third was black. Approximately half of participants rated their health as very good to excellent and only 14% were hospitalized in the previous year. On average, participants took slightly more than 3 prescription and nearly 2.5 over-the-counter medications..

The frequency of DDxIs increased slightly from year 2 to year 5 (Table 2). The most common DDxI involved benzodiazepine receptor agonists, opioid receptor agonists, or selective serotonin-reuptake inhibitors in participants with a recent history of falls. Similarly, the frequency of DDIs also increased over time (Table 3); the most frequent DDI involved angiotensin-converting enzyme inhibitors with other agents that may increase potassium. The proportion of participants experiencing either type of drug interaction also increased over time (16.3% in year 2; 16.4% in year 3; 19.2% in year 5). Few participants experienced multiple drug interactions in year 2 (4.4%, n=108), year 3 (3.8%, n = 81), or year 5 (5.7%, n = 105).

The average gait speed for the overall sample was 1.15 m/s at year 2, 1.16 m/s at year 3, and 1.12 m/s at year 5. For the stratified samples, the mean \pm standard deviation (range) for slow and fast walkers, respectively, were: 0.98 ± 0.14 m/s (0.05 to 1.15) and 1.31 ± 0.13 m/s (1.15 to 2.03) at year 2; 0.99 ± 0.13 m/s (0.38 to 1.15) and 1.33 ± 0.13 m/s (1.15 to 1.97) at year 3; and 0.98 ± 0.15 m/s (0.18 to 1.15) and 1.30 ± 0.12 m/s (1.15 to 1.92) at year 3. At least 22% of participants experienced a gait speed decline of ≥ 0.1 m/s each year (22.4% between years 2–3; 22.6% between years 3–4; 23.9% between years 5–6). In multivariate analyses of the entire sample, drug interactions (DDxI, DDI, or either) were not associated with gait speed decline in either the crude analyses (Model 1), demographic-adjusted analyses (Model 2), or fully-adjusted analyses (Model 3) (Table 4). Additionally, there was no apparent dose-response relationship with number of drug interactions in any model.

As seen in Table 5, similar results were seen in the stratified sample of “fast” walkers. There was some evidence, however, that these two types of DIs (alone or in combination) increased the risk of gait speed decline among those participants with slower gait speeds, though *p* values did not reach statistical significance. Moreover, a marginally significant dose-response relationship was seen, with the likelihood of gait speed decline increasing from 16% in participants with 1 drug interaction to 40% in those with ≥ 2 drug interactions. We also conducted a sensitivity analysis in which the baseline sample was stratified by a gait speed of 1.0 m/s and found similar results (data not shown).

4. Discussion

Overall, this study indicates that drug interactions do not increase the likelihood of a large meaningful decline in gait speed among high-functioning older adults. These results are consistent with another study that found DDIs among Hispanic community-dwelling elders were not associated with lower extremity functional limitation, including gait speed [26]. However, gait speed decline may be associated with DDIs or DDxIs, alone or in combination, in those participants with evidence of preexisting debility as evidenced by slow gait speed. There was also the suggestion of a dose-response relationship, which supports the contention that older adults with slower gait speeds may have less resilience to respond to additional physiologic stressors such as drug interactions [4]. Because slow gait speed is a consistent predictor of disability, health services utilization, and mortality among older adults, it may be especially important to ensure appropriate medication use to improve this modifiable risk factor for elderly patients with baseline functional impairment [8,10].

This study is among the first to evaluate the frequency and prevalence of both types of drug interactions [3]. Few (if any) participants with heart failure, Parkinson's disease, or a history of syncope had a DDxI in this study. Rather, DDxIs were seen more frequently among older adults with chronic kidney disease, cognitive impairment, and a history of falls. These latter three conditions are also included in the National Committee for Quality Assurance (NCQA) Criteria for Potentially Harmful Drug-Disease Interactions, affirming their importance as targets for quality of care measurement [27].

Interestingly, the most common DDIs in this study involved the use of multiple anticholinergic and CNS medications, a pharmacodynamic drug interaction. Previous studies have shown that increasing anticholinergic and/or CNS burden is associated with adverse events, including functional status decline, incident dementia and recurrent falls [11,16,28]. Unfortunately, pharmacodynamic drug-drug interactions are rarely included in commercially-available computerized physician order entry or pharmacy dispensing software. Moreover, this study is one of the first to evaluate drug interactions while including over-the-counter (OTC) medications [3]. Over one-third of drug interactions in this study involved an OTC agent (data not shown). The proportion of OTC medications implicated in these drug interactions reinforces the importance of asking about the use of these drugs as part of a comprehensive medication reconciliation review.

As with any study there are some limitations that must be considered. It is possible this study may have had limited power to detect statistically significant risk of functional status decline due to the small sample size. However, the authors believe the elevated odds ratio point estimate represents the best approximation of the true magnitude of the association, which is further supported by the higher risk found in those individuals with slower baseline gait speed who had two or more drug interactions. Second, selection bias may exist. Not including potentially frailer participants in our sample may have limited our ability to elicit statistically significant associations in the "slow" stratum, as those missing data were likely to have poorer function resulting in a declining gait speed. The trends we report, however, are despite this limitation, and would likely be stronger if we had complete data. A third potential limitation is that gait speed was measured in one-year intervals that may have missed transient changes within the 12 month period. Similarly, although accurate, the yearly brown bag technique captures only medication use in the previous 2 weeks. Finally, as with all observational studies, potential issues with unmeasured residual confounding and generalizability must be considered. Specifically, the individuals recruited for the Health ABC study were healthy older adults with no baseline mobility concerns from two US cities. Consequently, extrapolation must be done cautiously.

5. Conclusion

Despite the limitations mentioned in the previous section, the results from this study suggest drug interactions may increase the likelihood of gait speed decline among older adults with evidence of preexisting debility, though the point estimates only reached marginal significance. Future studies should focus on frail elders with less physiological reserve who may be more susceptible to the harms associated with potentially inappropriate medications.

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Key Points

- Drug-drug and drug-disease interactions, which can arise from two types of potentially inappropriate prescribing, may lead to declines in gait speed in those individuals with baseline functional impairment.
- Future studies should focus on frail elders with less physiological reserve who may be more susceptible to the harms associated with potentially inappropriate medications.

Table 1

Characteristics of the sample at baseline (n=2,402)

Variables		n (%)
<i>Demographics</i>	Age, mean (\pm SD) ^a	74.6 (\pm 2.9)
	Female	1232 (51.3)
	Black	897 (37.3)
	High school graduate	1871 (78.1)
	Site (Pittsburgh)	1257 (52.3)
<i>Health Status</i> ^b	Very good/excellent self-rated health ^a	1127 (46.9)
	Hospitalized in the previous 12 months ^a	339 (14.1)
	Coronary heart disease	340 (14.2)
	Diabetes mellitus	383 (16.0)
	Osteoarthritis	592 (24.7)
	Osteoporosis	152 (6.4)
	Peripheral arterial disease	111 (4.7)
	Pulmonary disease	247 (10.3)
	Stroke	99 (4.1)
	Depression (Short CES-D > 10)	91 (3.8)
	Number of prescription medications, mean (\pm SD) ^a	3.2 (\pm 2.7)
	Number of over-the-counter medications, mean (\pm SD) ^a	2.4 (\pm 2.6)

^aIndicates a time-varying variable.^bParticipants could report more than one chronic condition.

Abbreviations: CES-D = Center for Epidemiologic Studies-Depression scale; SD = standard deviation.

Table 2

Clinically important drug-disease interactions overall and by organ system^a

Interaction	Year 2 (n = 2,402) n (%)	Year 3 (n = 2,136) n (%)	Year 5 (n = 1,842) n (%)
Any drug-disease interaction	183 (7.62)	163 (7.63)	172 (9.34)
Cognitive impairment/dementia (any)	40 (1.67)	61 (2.86)	49 (2.66)
Anticholinergics	22 (0.92)	33 (1.54)	27 (1.47)
Antiemetics	1 (0.04)	6 (0.28)	3 (0.16)
Antidepressants	8 (0.33)	8 (0.37)	9 (0.49)
Antihistamines	8 (0.33)	13 (0.61)	4 (0.22)
Anti-Parkinson agents	0 (0.00)	0 (0.00)	0 (0.00)
Antipsychotics	2 (0.08)	1 (0.05)	2 (0.11)
Gastrointestinal antispasmodics	3 (0.12)	1 (0.05)	1 (0.05)
Urinary antispasmodics	1 (0.04)	2 (0.09)	8 (0.43)
Miscellaneous	2 (0.08)	3 (0.14)	1 (0.05)
BZD receptor agonists	9 (0.37)	20 (0.94)	7 (0.38)
H ₂ receptor antagonists	18 (0.75)	22 (1.03)	21 (1.14)
Falls (any)	120 (5.00)	83 (3.89)	110 (5.97)
Anticonvulsants	15 (0.62)	19 (0.89)	24 (1.30)
Antipsychotics	4 (0.17)	1 (0.05)	4 (0.22)
BZD receptor agonists	43 (1.79)	24 (1.12)	34 (1.85)
Opioid receptor agonists	37 (1.54)	23 (1.08)	30 (1.63)
SSRIs	27 (1.12)	33 (1.54)	42 (2.28)
TCAs	21 (0.87)	10 (0.47)	10 (0.54)
Heart failure (any)	24 (1.00)	21 (0.98)	21 (1.14)
Diltiazem	9 (0.37)	7 (0.33)	5 (0.27)
NSAIDs	13 (0.54)	12 (0.56)	14 (0.76)
TZDs	0 (0.00)	0 (0.00)	1 (0.05)
Verapamil	3 (0.12)	3 (0.14)	3 (0.16)
Parkinson's disease	0 (0.00)	0 (0.00)	0 (0.00)
Antipsychotics ^b , metoclopramide, prochlorperazine, or promethazine			
Renal impairment (eGFR < 30 mL/min)	0 (0.00)	1 (0.05)	2 (0.11)
NSAIDs			
Syncope history (any)	11 (0.46)	8 (0.37)	8 (0.43)
AChEs	0 (0.00)	0 (0.00)	2 (0.11)
Alpha blockers (peripheral)	9 (0.37)	6 (0.28)	4 (0.22)
Chlorpromazine	0 (0.00)	0 (0.00)	0 (0.00)
Olanzapine	0 (0.00)	0 (0.00)	1 (0.05)

Interaction	Year 2 (n = 2,402) n (%)	Year 3 (n = 2,136) n (%)	Year 5 (n = 1,842) n (%)
TCA (tertiary)	1 (0.04)	2 (0.09)	1 (0.05)
Thioridazine	1 (0.04)	0 (0.00)	0 (0.00)

^aParticipants could have > 1 potentially inappropriate drug-disease interaction;

^bDoes not include clozapine or quetiapine.

Abbreviations: AChEIs = acetylcholinesterase inhibitors; BZD = benzodiazepine; eGFR = estimated glomerular filtration rate; NSAIDs = non-steroidal anti-inflammatory drugs; H = histamine; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; TZDs = thiazolidinediones.

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Table 3

Clinically important drug-drug interactions overall and by organ system^a

Interaction	Year 2 (n = 2,402) n (%)	Year 3 (n = 2,136) n (%)	Year 5 (n = 1,842) n (%)
Any drug-drug interaction	251 (10.45)	220 (10.30)	227 (12.32)
ACE inhibitors (any)	79 (3.29)	72 (3.37)	83 (4.51)
Amiloride	2 (0.08)	2 (0.09)	2 (0.11)
Potassium supplements	60 (2.50)	55 (2.57)	63 (3.42)
Triamterene	25 (1.04)	22 (1.03)	23 (1.25)
Angiotensin receptor blockers (any)	13 (0.54)	21 (0.98)	40 (2.17)
Amiloride	0 (0.00)	0 (0.00)	1 (0.05)
Potassium supplements	11 (0.46)	20 (0.94)	29 (1.57)
Triamterene	2 (0.08)	3 (0.14)	13 (0.71)
Digoxin(any)	31 (1.29)	22 (1.03)	18 (0.98)
Amiodarone	3 (0.12)	2 (0.09)	2 (0.11)
Quinidine	7 (0.29)	4 (0.19)	3 (0.16)
Propafenone	3 (0.12)	3 (0.14)	2 (0.11)
Verapamil	18 (0.75)	13 (0.61)	11 (0.60)
Disopyramide (any)	0 (0.00)	0 (0.00)	0 (0.00)
Cimetidine			
Potassium supplements (any)	26 (1.08)	22 (1.03)	22 (1.19)
Amiloride	3 (0.12)	4 (0.19)	5 (0.27)
Triamterene	23 (0.96)	18 (0.84)	17 (0.92)
Procainamide (any)	0 (0.00)	0 (0.00)	0 (0.00)
Amiodarone, cimetidine, or ranitidine			
Quinidine (any)	0 (0.00)	0 (0.00)	0 (0.00)
Cimetidine			
Theophylline (any)	0 (0.00)	0 (0.00)	0 (0.00)
Cimetidine or fluvoxamine			
Anticholinergic (any)	58 (2.41)	44 (2.06)	38 (2.06)
Another anticholinergic			
Carbamazepine (any)	0 (0.00)	0 (0.00)	1 (0.05)
Cimetidine	0 (0.00)	0 (0.00)	1 (0.05)
Diltiazem, propoxyphene, or verapamil	0 (0.00)	0 (0.00)	0 (0.00)
CNS agent (any)	12 (0.50)	7 (0.33)	8 (0.43)
2 other CNS agents ^b			

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Interaction	Year 2 (n = 2,402) n (%)	Year 3 (n = 2,136) n (%)	Year 5 (n = 1,842) n (%)
Lithium (any)	0 (0.00)	0 (0.00)	0 (0.00)
ACE inhibitors or loop diuretics			
Statins (any)	62 (2.58)	52 (2.43)	48 (2.61)
Diltiazem ^c	46 (1.92)	37 (1.73)	33 (1.79)
Gemfibrozil	3 (0.12)	3 (0.14)	2 (0.11)
Verapamil ^c	13 (0.54)	13 (0.61)	13 (0.71)

^aParticipants could have > 1 potentially inappropriate drug-drug interaction;

^bCNS agents include opioids, antipsychotics, benzodiazepine receptor agonists;

^cOnly statins metabolized through cytochrome P450 isoenzyme 3A4 (i.e., atorvastatin, lovastatin, simvastatin).

Abbreviations: ACE = angiotensin-converting enzyme; CNS = central nervous system.

Table 4Multivariate analyses of drug interactions with gait speed decline 0.1 m/s in the overall sample^a

Variables	Model 1 ^a	Model 2 ^b	Model 3 ^c
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Any DDxI	1.13 (0.92, 1.39)	1.14 (0.92, 1.40)	1.13 (0.90, 1.41)
Any DDI	1.04 (0.87, 1.25)	1.06 (0.89, 1.27)	1.02 (0.84, 1.24)
Either type of interaction	1.06 (0.92, 1.24)	1.08 (0.93, 1.26)	1.06 (0.90, 1.24)
Total number of interactions			
0	[referent]	[referent]	[referent]
1	1.06 (0.89, 1.27)	1.07 (0.90, 1.28)	1.05 (0.88, 1.27)
2	1.07 (0.82, 1.39)	1.09 (0.84, 1.43)	1.06 (0.79, 1.41)

^aNot adjusted for any covariates.^bAdjusted for baseline sex, race, education, site, and time-varying age.^cAdjusted for baseline sex, race, education, site, coronary heart disease, diabetes, osteoarthritis, osteoporosis, peripheral arterial disease, pulmonary disease, stroke, depression, and time-varying age, self-rated health, hospitalizations in the past 12 months, total prescription and total over-the-counter medications.

Abbreviations: CI = confidence interval; DDI = drug-drug interaction; DDxI = drug-disease interaction; OR = odds ratio.

Table 5

Multivariate analyses of drug interactions with gait speed decline 0.1 m/s stratified by gait speed^a

Variables	Model 1 ^b			Model 2 ^c			Model 3 ^d		
	OR (95% CI)			OR(95% CI)			OR(95% CI)		
	Slow walkers	Fast walkers	Slow walkers	Fast walkers	Slow walkers	Fast walkers	Slow walkers	Fast walkers	Fast walkers
Any DDxI	1.32 (1.01, 1.73)	1.29 (0.91, 1.82)	1.29 (0.98, 1.70)	1.23 (0.86, 1.74)	1.24 (0.93, 1.67)	1.10 (0.76, 1.58)			
Any DDI	1.26 (0.98, 1.63)	1.08 (0.83, 1.41)	1.27 (0.99, 1.65)	1.09 (0.84, 1.42)	1.23 (0.93, 1.63)	0.97 (0.74, 1.28)			
Either type of interaction	1.28 (1.03, 1.58)	1.15 (0.92, 1.44)	1.27 (1.02, 1.57)	1.13 (0.90, 1.42)	1.23 (0.97, 1.55)	1.03 (0.81, 1.31)			
Total number of interactions	[referent]	[referent]	[referent]	[referent]	[referent]	[referent]			
0	1.22 (0.94, 1.57)	1.18 (0.91, 1.51)	1.21 (0.94, 1.56)	1.16 (0.90, 1.49)	1.16 (0.89, 1.52)	1.09 (0.84, 1.41)			
1	1.43 (1.02, 2.00)	1.06 (0.67, 1.67)	1.41 (1.00, 1.99)	1.04 (0.66, 1.64)	1.40 (0.96, 2.05)	0.84 (0.53, 1.34)			

^a Slow versus fast walkers based on a median split at 1.15 m/s.

^b Not adjusted for any covariates.

^c Adjusted for baseline sex, race, education, site and time-varying age.

^d Adjusted for baseline sex, race, education, site, coronary heart disease, diabetes, osteoarthritis, osteoporosis, peripheral arterial disease, pulmonary disease, stroke, depression, and time-varying age, self-rated health, hospitalizations in the past 12 months, total prescription and total over-the-counter medications.

Abbreviations: CI = confidence interval; DDI = drug-drug interaction; DDxI = drug-disease interaction; OR = odds ratio.