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Polypharmacy and Gait Performance in Community Dwelling Older Adults

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Abstract

Background—While polypharmacy is associated with adverse outcomes in older adults such as falls, frailty, disability, and mortality, its effect on locomotion in community-dwelling older adults is not well known.

Design—Cross-sectional

Setting—Community

Participants—482 community-dwelling older adults

Objective—Examine the relationship between polypharmacy and gait performance during simple (normal walk(NW)) and complex (Walking While Talking (WWT)) locomotion.

Measurements—Polypharmacy defined as the use of ≥5 medications, and a cohort specific alternate definition of ≥8 medications was examined. Velocity (cm/s) measured quantitatively during normal pace walking and WWT conditions.

Results—The 164 participants (34%) with polypharmacy (≥5) were older (77 ± 6.6 vs. 76.0 ± 6.4 years), and more likely to have hypertension, CHF, diabetes, MI, higher BMI, and fall within the last year compared to the remaining 318 without polypharmacy. The polypharmacy group walked 6 cm/s slower (p=0.004) during NW, and 4 cm/s slower during WWT (p=0.068) adjusting for age, sex, and education. Group differences were not statistically significant after adjusting for comorbidities. Prevalence of polypharmacy (≥8) was 10%. This polypharmacy group walked 11 cm/s slower p<.001 during NW and 8.59 cm/s slower during WWT (p=0.015); adjusted for age, sex, and education. Polypharmacy (≥8) participants had slower NW (8.5 cm/s; p=0.010), and slower WWT (6.9 cm/s; p=0.06) adjusting for comorbidities. Adjustments for BMI, high risk drugs, falls, and comorbidities yielded slower NW (15.9cm/s, p=0.005), and slower WWT (8.2 cm/s, p=0.03).

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Conclusion—Our results suggest an association between polypharmacy and locomotion, which was only partly explained by medical comorbidities.

Keywords

Polypharmacy; Physical Performance; Gait

Introduction

Polypharmacy is the use of more medications than is clinically indicated[1]. Current data suggests that the use of five or more medications is an acceptable definition of polypharmacy, and this cut point is associated with increased risk of adverse outcomes such as falls, frailty, disability, and mortality in older adults[2]. The mechanism for the influence of polypharmacy on adverse outcomes is multifactorial. Polypharmacy predisposes patients to adverse drug events (ADEs), drug interactions, medication non-adherence, and decreased functional capacity [3]. The impact is amplified in older adults who are more prone to medication side effects and outcomes such as falls, which can lead to hospitalization and further functional decline.

The ability to ambulate is a marker of independence and an indicator of good health status in older patients. While specific classes of medications have been linked to impaired mobility and its consequences such as falls [4]; the role of polypharmacy on locomotion is not well established. Human locomotion can be studied under simple conditions or complex conditions. Simple locomotion or normal walk (NW) in community dwelling older adults ranges from 0.8 – 1.2 cm/s[5](ref). Complex locomotion such as walking while performing a secondary cognitive activity like reciting alternate letters of the alphabet (Walking While Talking (WWT))ref), have been helpful in revealing early age related decline in gait and cognition,[67] and decline in performance on WWT has been linked to falls in community dwelling older adults. [7,8] Norms for WWT was considered to be within 1 standard deviation below group means. WWT provides the opportunity for early detection and intervention in people who are at risk and whose decreased function might not be evident by examining normal walk velocity alone. Given the link between polypharmacy and negative outcomes such as falls, exploring the relationship between and WWT performance in community dwelling older adults who are free of major cognitive or functional impairments is of importance. There is a paucity of data regarding this relationship.

To address the knowledge gap regarding polypharmacy effects on simple (normal pace walking) and complex (WWT) locomotion, we conducted this cross-sectional study in 482 community dwelling older adults. Polypharmacy is modifiable and if our results show a relationship of polypharmacy with locomotion, then we may be able to improve mobility and decrease the risk of adverse outcomes such as falls in older adults.

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MATERIALS AND METHODS

Participants

We performed a cross sectional study in 482 community dwelling adults age 65 years and older enrolled in the "Central Control of Mobility in Aging" (CCMA) study, a longitudinal study at Albert Einstein College of Medicine in the Bronx, New York. The main aim of the CCMA study is to determine cognitive processes and underlying brain substrates or neuronal structures responsible for mobility in aging. Study design has been previously reported[9]. In brief, participants are initially screened by telephone with cognitive screeners (AD8 Dementia Screening interview[10] and the Memory Impairment Screen[11]) to exclude participants with dementia. Participants who pass the screen and express interest in the study are invited for further in-person testing in our research center. Participants were included if they are aged 65 and older, English speaking, ambulatory, reside in the community and plan to be in the area for the next three years. Exclusion criteria for the parent study included presence of dementia (self-reported, detected on the CCMA telephone cognitive screen, or diagnosed by study clinicians at in-house visits), inability to walk independently, history of severe neurological or psychiatric disorders, significant loss of vision or hearing, recent or planned surgical procedures that could affect mobility, or serious chronic or acute illnesses. All eligible participants provided informed consent. The study protocol was approved by the Institutional review board.

Medication history

Medication use by participants was ascertained by the study clinician using both a structured questionnaire as well as an informal interview at the in-person visit. Medication history was further confirmed by review of medication bottles, interviewing family members when available, and any available medical records. Over the Counter (OTC) supplements, herbal agents, and prescription medications use was documented. We have previously reported moderate to high medication adherence in the same cohort.[12] Polypharmacy was defined as the use of 5 or more medications (regardless of class of medication) based upon widely used operational definition in the literature [2]. High risk drugs were defined based upon the American Geriatrics Society Beers Criteria for potentially inappropriate medication use.[13]

Quantitative gait assessments

Gait parameters were quantitatively assessed using the GAITRite system (CIR Systems, Havertown, PA). Participants walked on a 20-foot instrumented walkway, which also included four feet of non-recording surface at either end to account for initial acceleration and terminal deceleration. None of the participants included in this analysis used an assistive device during their walking trial or had any attached monitors. This system has been used in our previous studies and has excellent reliability.[14]

Our dependent variable was velocity (cm/s) measured during normal pace walking and WWT conditions in steady state. Participants were instructed to walk at their normal pace during normal walk for one trial. During WWT participants were instructed to walk while reciting alternate letters of the alphabet such as A, C, and E, etc. Our previous studies have

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reported that WWT velocity predicts falls, frailty and mortality in community dwelling older adults.[8,15]

Clinical evaluations

Participants received detailed clinical, cognitive, and mobility assessments at their baseline in-house visit and at yearly follow-up visits. They were also interviewed about medical conditions, cognitive status, and had neurological examinations performed by the study clinician. As previously reported[9], presence or absence of physician diagnosed chronic illnesses (depression, Parkinson's disease, chronic obstructive lung disease, or severe arthritis) and vascular diseases (diabetes, heart failure, hypertension, angina, myocardial infarction, or stroke) was reported by the participants upon entry in the study to calculate a Global Health Score (GHS) ranging from 0–10, one point for each medical condition. Medical history was further confirmed by interviewing family members when available and any available medical records.

Global cognitive status was evaluated using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) total score. This cognitive test measures immediate a delayed memory, attention, language and visuo-spatial abilities and is reported in the form of a total index score[16]. Body Mass Index (BMI) was calculated using the participant's weight and height.

Statistical Analysis

Baseline characteristics in the participants with polypharmacy (≥5) and without polypharmacy (<5) were compared using descriptive statistics. Polypharmacy definitions vary in previous studies; both in terms of the medication count used [2] as well as whether prescription and OTC medications were included in the definition[17]. Hence, we also examined a study-specific alternate definition of polypharmacy as use of 8 or more medications (any of over the counter supplements, herbal agents, and prescription medications), which was reported by 10% in our cohort. This alternate definition also was to account for our more stringent definition of polypharmacy, which included non-prescription medications, unlike many previous studies. On average, participants in the cohort were on 1.1 ±1.3 over the counter, herbal agents, or nonprescription agents. Two standard deviations above the mean for the overall cohort equated to 3 additional medications and further justified the use of 8 more medications. Independent sample T-test was used for continuous variables and Chi Square for categorical variables. Linear regression analysis was used to determine the relationship between the presence of polypharmacy (independent variable) and gait velocity during normal walk and WWT at cross-section (dependent variable), adjusting for age (years), sex, and education (years of schooling), BMI, falls ever, the presence of high-risk drugs, and medical comorbidities in the reported models. The covariates to be included in the models were chosen if they were significant at a P value of . 05 or less in the univariate analyses (see Table 1) or based upon biological plausibility. Adjustments were made for the falls, though falls could be interpreted as an outcome. Adjustments were also not made for the use of specific classes of medications, but were made for medical comorbidities significant at a p value of ≤ .05 in bivariate analysis comparing the polypharmacy with the no polypharmacy group. Five models were created.

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Model 1 adjusted for age, sex and educational level. Medical comorbidities were added to the adjustments for model 2 in order to explore if polypharmacy was associated with gait speed irrespective of medical comorbidities. In model 3, falls ever was added to the adjustments for model 1. Model 4 adjusted for BMI, the presence of high risk drugs, falls ever, in addition to age, sex, and educational level. Finally Model 5 adjusted for age, sex, educational level, and all variables significant with a p value <0.05 with bivariate analysis of the polypharmacy compared to the no polypharmacy group. Model assumptions were examined analytically and graphically, and were adequately met. All analyses were performed on SPSS version 21, IBM.

Results

Baseline Characteristics

The prevalence of polypharmacy defined as the use of 5 or more medications was 34% (n = 164) amongst the 482 participants examined in the CCMA sample between June 2011 and February 2016, and was 10 % (n = 48) using a definition of 8 or more medications. Table 1 lists the baseline characteristics of the 164 patients with polypharmacy and the 318 without polypharmacy. The mean age was 77 ± 6.6 years in the polypharmacy group and 76.0 ± 6.4 years in the No polypharmacy group. Participants who had polypharmacy were more likely to have hypertension, congestive heart failure, diabetes, and a history of a myocardial infarction. The global health score was significantly higher at 2.2 compared to 1.4 (p<.001) in those with polypharmacy. The polypharmacy group was also more likely to have a fall within the last year (26.8% vs. 16.1%, p= 0.004), and a higher BMI (30.3 vs. 28.7; p= 0.023) than those without polypharmacy. The mean gait velocity of the cohort was 98.0 ±22.8 cm/s for normal walk and 68.7 ± 24.2 cm/s for WWT (not shown). Normal gait speed in community dwelling older adults ranges from 80 – 120 cm/s. Norms for WWT was considered to be within 1 standard deviation below group means.

Blood pressure control, educational level, knee extensor strength, total RBANS score, the presence of depression, and osteoarthritis was comparable between participants with polypharmacy and those without polypharmacy.

Table 2 shows the frequency of medication use among the cohort above 5% unless the medication was deemed to be high risk [13]. HMGCOa (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors followed by beta blockers and angiotensin converting enzyme inhibitors were more commonly used agents among participants in the sample. The prevalence of high-risk medications was 18% in our sample; antidepressants (5.6%) and alpha 1 antagonists (6%) were used with the greatest frequency. Those with polypharmacy compared to those without polypharmacy were on more medications of all listed classes; Nonsteroidal anti-inflammatory drugs and antihypertensive combinations were more frequently used in the polypharmacy group but the difference was not statistically significant. Only one participant in this ambulatory and community dwelling sample was on an antipsychotic agent. Non-prescription medications were used in 53% of the participants; 24% used 1 agent, 27% used 2 or more and 3% were on 5 or more non-prescription medications.

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Gait Performance

Gait performance is presented in Table 3. Participants with polypharmacy walked 6 cm/s slower(p=0.004) during the normal walk condition and 4 cm/s slower during WWT (p=.068) than participants without polypharmacy after adjusting for age, sex, and educational level (Model 1). When additionally adjusted for medical comorbidities (hypertension, diabetes, congestive heart failure and myocardial infarction (Model 2), the group differences were not statistically significant for polypharmacy defined as the use of 5 or more medications; suggesting that polypharmacy may be reflecting disease effect on the walking tasks. Adjusting for history of falls did effect the effects of polypharmacy on gait for NW or WWT. After adjusting for age, sex, educational level, BMI, high risk drugs, and falls in model 4, normal walk velocity (estimate: −5.7 cm/s, p=0.007) and WWT velocity (estimate: −5.0 cm/s, p=0.034) was slower in the polypharmacy group compared to the no polypharmacy group. A final model (5) adjusted for all covariates including medical comorbidities and neither NW or WWT velocity was significant when polypharmacy was defined as the use of 5 or more medications.

In a separate analysis, using the CCMA specific definition of polypharmacy as 8 or more medications, both normal walk velocity −11cm/s, p=0.001 and WWT velocity −8.6 cm/s p=0.015 were significantly decreased in those with polypharmacy compared to the no polypharmacy group when adjustments were made for age, sex, educational level (Table 3, Model 1). When adjusting for age, sex, educational level and medical comorbidities in Model 2, normal walk velocity was slower in polypharmacy participants (−8.5 cm/s p=0.010), but the association of polypharmacy with WWT velocity was borderline significant (estimate: −6.9 p=0.072). Both normal walk (−9.4cm/s p=.005) and WWT velocity (−7.9 p=0.037) was slower when adjustments were made for age, sex, educational level, BMI, falls, high risk drugs, and medical comorbidities (Model 5).

Discussion

Our results show a strong association between gait velocity during simple locomotion and the presence of polypharmacy (≥5 medications) in community dwelling older adults. The strongest explanation for the association between polypharmacy and gait appears to be that the presence of polypharmacy is a surrogate for the presence of an increasing number of chronic medical illnesses. However, the stronger association of the study specific polypharmacy definition (≥8) with normal pace walking and walking while talking suggests that this relationship is partly but not completely explained by multi-morbidity. The association of locomotion with polypharmacy persisted when adjusting for the use high risk drugs. This suggests that the association between polypharmacy and slower gait speed cannot be attributed to the use of high risk drugs alone.

A major difference between our definition of polypharmacy and those used in many previous studies is that we included both nonprescription (OTC and herbal agents) in addition to prescription drugs in our medication count. While this could have led to an over estimation of the prevalence of polypharmacy in this sample and a bias towards the null when polypharmacy was defined as 5 or more medications, we felt strongly that OTC and herbal agents may carry similar risks as prescription drugs; and disentangling this would require a

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subjective decision on the part of the study clinician to determine which medications were important enough to be documented.

Our study is one of the first to explore the role polypharmacy on gait performance as measured by quantitative assessments of simple and complex locomotion in community dwelling older adults who are free of major cognitive and functional limitations. Our findings are supported by previous studies, but with notable differences. In hospitalized older adults, Sganga and colleagues[18], noted that poor physical performance as measured by grip strength and walking speed was associated with polypharmacy defined as 8 or more medications. In community dwelling older adults, several prospective studies[19,20] have revealed that polypharmacy predicted a decline in lower extremity strength[19] and functional decline as measured performance of activities of daily living (ADLs),[20] independent of comorbidities.

With a polypharmacy cutoff of 5 or more medications, WWT gait velocity (complex locomotion) did not decline to a statistically significant degree in all models examined. While those on more medications may walk slower, their ability to prioritize during cognitive motor tasks does not appear to be affected by the number of medications alone. One explanation is that our sample represents a subset of high functioning community dwelling older adults who are more robust and less likely to have significant cognitive effects due to polypharmacy. When we adjusted the definition of polypharmacy to include participants on 8 or more medications, both simple and complex gait velocities were significantly decreased while adjusting for age, sex, educational Level, BMI, medical comorbidities, falls and high risk drugs. Our results suggest an association between more extreme definitions of polypharmacy (8 or more) and a decline in complex locomotion. Given the link between WWT velocity and falls [7,8] in high functioning older adults, the presence of polypharmacy (8 or medications) is a useful marker for those who may be at risk.

Strengths and limitations

The strengths of this study includes the use of a community dwelling cohort of older adults without functional or cognitive impairments and the use of systematic gait assessment. The cross-sectional design limits establishment of causation, but we are continuing follow-up and plan to report longitudinal associations. It is likely that the results will be more exaggerated in a hospitalized or institutionalized population, but additional confounders would have to be considered. While drug interactions may play a role in gait impairment, it was not possible to account for all possible drug-drug, drug-food, or drug-disease interactions given our sample size. While we controlled for several potential confounders in our analyses, residual or unmeasured confounding may still be present. The influence of dose and duration of use of medications in gait performance was not examined; however, these variables may be confounded by disease duration and severity; those taking higher doses for longer might have more severe comorbidities or could be more stable than those who have been newly started on a regimen or newly diagnosed. We did not explore the effects of ethnicity and socioeconomic status on the relationship between polypharmacy and gait, but the study population is rather homogeneous from one area of the Bronx, NY. The

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cohort is 79% white, 16% African American, and 5 % self-identified as Hispanic white (1.7%), Hispanic black(0.2%), Asian (1.2%), or other(0.2%). Hence, there are insufficient numbers to compare polypharmacy effects by race. Further study is needed to determine the role of specific classes of medication on complex locomotion and explore the interplay between polypharmacy, specific classes of medication, and medical comorbidities.

Conclusion

Our results suggest an association between polypharmacy and locomotion in aging, which was only partly explained by multi-morbidity. Longitudinal studies are needed to follow up on our findings. Polypharmacy including non-prescription medication use should be ascertained in all older adults regardless of their level of function. In clinical practice, physicians should consider measuring walking speed during normal walk and WWT in patients on polypharmacy to assess and identify a potentially modifiable mobility risk.

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Conflict of Interest Checklist:

Elements of Financial/Personal Conflicts	*Author 1 C. George		Author 2 J. Verghese		Author 3		Etc.	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		x		x				
Grants/Funds	x		x					
Honoraria		x		x				
Speaker Forum		x		x				
Consultant		x		x				
Stocks		x		x				
Royalties		x		x				
Expert Testimony		x		x				
Board Member		x		x				
Patents		x		x				
Personal Relationship		x		x				

For “yes”, provide a brief explanation:

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Table 1

Baseline Characteristics of participants with and without polypharmacy

Baseline Characteristic	Total N=483	Polypharmacy N=164	No Polypharmacy N= 318	P-value
Age (years) mean, SD	74.4±6.5	77.1 ± 6.6	76.0 ± 6.4	0.077
Female, n (%)	274, (56.8)	90 (54.9)	184 (57.9)	0.561
Educational level (years), mean, SD	14.5 ± 3.1	14.5 ± 3.0	14.6 ± 3.1	0.857
Global Health Score, mean, SD	1.7,±1.1	2.2 ± 1.1	1.4 ± 1.0	<.000
Medical Conditions				
Hypertension	295 (61.2)	136 (83.0)	159 (50)	<.000
Congestive Heart Failure, n (%)	8(1.7)	6 (3.7)	2 (1.0)	.021
Diabetes, n (%)	92(19.1)	48 (28.4)	48 (1.3)	<.000
Myocardial Infarction, n (%)	32(6.6)	18 (11.0)	14 (4.4)	.011
Chronic Obstructive Pulmonary Disease, n (%)	35(7.3)	16 (10.0)	19 (5.2)	.142
Stroke, n (%)	29(6)	14 (8.6)	15 (2.3)	.107
Depression, n (%)	50(10.4)	20 (12.2)	30 (9.4)	.347
Osteoarthritis, n(%)	229(87.4)	82 (50)	147 (46.2)	.848
Measures				
Systolic Blood pressure (mm Hg), SD	130.4±13.4	129.6 ± 14.0	130.8 ± 13.0	.327
Diastolic Blood pressure (mm Hg), SD	77.8±7.6	77.4 ± 8.1	78.0 ± 7.4	.430
Knee Extensor Strength (KG), mean, SD	34.7±66.6	30.1 ± 13.1	37.0 ±81.1	.319
Falls within the last year, n (%)	1.2±0.39	44 (26.9)	48 (15.1)	.004
Falls Ever, n (%)	1.6± 0.50	111 (65.7)	187 (51.6)	.038
Body Mass Index (kg/m^2), mean, SD	29.3±6.8	30.3 ± 7.9	28.7 ± 6.2	.023
Grip strength, mean, SD	24.0±8.9	23.6 ± 8.6	24.2 ± 9.1	.512
Total RBANS[a] score (0–100), SD	91.2± 12.1	91.7 ±12.1	91.0 ± 12.1	.534

[a] RBANS: Repeatable Battery for Assessment of Neuropsychological Status

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Table 2

Medication Use Frequency for participants with and without Polypharmacy

Medication	All N=482 n (%)	Polypharm N=164 n (%)	No Polypharm N= 318 n (%)	P value
Non-Prescription Drug	259(53.5)	133(81.1)	30(9.4)	<.001
HMGCoA Inhibitors[a]	239(49.6)	112(68.3)	127(39.9)	<.001
Beta Blockers	123(25.5)	72(44.2)	51(16.0)	<.001
Ace Inhibitors	99(20.5)	51(31.3)	48(15.0)	<.001
Antiplatelet Agents	92 (19.1)	55(33.7)	37(11.6)	<.001
Angiotensin Receptor Blockers	80(16.8)	43(26.4)	38(11.9)	<.001
Vitamin and Mineral Combinations	66(13.7)	38(23.3)	28(8.8)	<.001
Oral hypoglycemic Agents	65 (13.5)	37(22.7)	28(8.8)	<.001
Thyroid Hormone Replacements	56 (11.3)	33(20.2)	23(7.2)	<.001
Calcium	50(10.4)	29(17.8)	31(6.6)	<.001
Vitamin D	37 (7.7)	26(16)	11(3.4)	<.001
Proton Pump Inhibitors	36 (7.5)	25(15.3)	11(3.4)	<.001
Antihypertensive Combination	32(6.6)	13(8.0)	19(6.0)	0.441
Ophthalmic Agents	39 (6.0)	17(10.4)	12(3.8)	0.007
Anticoagulants	29(6.0)	20(12.3)	9(2.8)	<.001
Agents for Gout	28(5.8)	22(13.5)	6(1.9)	<.001
NSAID analgesic	28(5.8)	12(7.4)	16(5.0)	0.308
Loop Diuretic	25(5.2)	19(11.7)	6(1.9)	<.001
Thiazide diuretic	25(5.2)	18(11.0)	7(2.2)	<.001
High Risk Drugs	87(18)	51(31.3)	36(11.3)	<.001
Antidepressants	27(5.6)	15(9.2)	11(3.4)	0.011
Alpha 1 antagonists	29(6.0)	19(11.7)	10(3.1)	<.001
Benzodiazepines/anxiolytics	19(3.9)	12(7.4)	7(2.2)	0.011
Antihistamines	10(2.1)	6(3.7)	4(1.3)	0.095
Opioids	5(1.0)	5(3.1)	0 (0)	0.004
Anticholinergics	3(0.6)	3(1.8)	0(0)	0.038
Muscle relaxants	2(0.4)	2(1.2)	0(0)	0.114
Antipsychotics	1(0.2)	0 (0)	1(0.3)	1.000

[a]HMGCoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A

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Table 3

Linear Regression of Gait Performance during simple and complex locomotion

	Polypharmacy (≥5)		Polypharmacy (≥8)	
	NW[a] (cm/s) Estimate (95% CI), p-value	**WWT[b] (cm/s) Estimate (95% CI), p-value**	**NW (cm/s) Estimate 95% CI), p-value**	**WWT (cm/s) Estimate (95%CI), p-value**
Model 1[c]	−6.0 (−1.0, −2.0) .004	−4.1 (−8.6, 0.30).068	−11.0 (−17.2, −4.7) <.001	−8.59 (−15.5, −1.7) .015
Model 2[d]	−4.1 (−8.4, −.15) .059	−2.4 (−7.2, 2.4) .321	− 8.5 (−15.0, −2.0) .010	−6.89 (−14.1, 0.29) .072
Model 3[e]	−5.7 (−9.7, −1.7) .005	−4.6(−9.0, −0.19).041	−10.8 (−17.0, −4.6) .001	−8.7 (−15.6, −1.9) .013
Model 4[f]	−5.7(−9.8, −1.5).007	−5.0(−9.6, −0.37).034	−13.3(−17.8, −5.0) <.001	−9.3(16.5, −2.2).011
Model5[g]	−4.6(−9.0, −.16).042	−3.7(−8.7, 1.20) .137	−9.4(−16.0, −2.8) .005	−7.9 (−15.3 −0.47).037

[a] NW: Normal walk

[b] WWT: Walking While Talking

[c] **Model 1:** Adjusted for age, sex educational level

[d] **Model 2:** Adjusted for age, sex educational level, comorbiditities (diabetes, hypertension, heart failure, myocardial infarction)

[e] Model 3: Adjusted for age, sex, educational level, falls ever

[f] **Model 4:** Adjusted for age, sex, educational level, body mass index, high risk drugs, falls ever,

[g] Model 5. Adjusted for age, sex, educational level, body mass index, high risk drugs, falls ever, comorbidities