Polypharmacy and Gait Performance in Community–dwelling Older Adults

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OBJECTIVES: To examine the relationship between polypharmacy and gait performance during simple (normal walk (NW)) and complex (walking while talking (WWT)) locomotion.

DESIGN: Cross-sectional.

SETTING: Community.

PARTICIPANTS: Community-dwelling older adults (N = 482).

MEASUREMENTS: Polypharmacy, defined as use of five or more medications and a cohort-specific alternate definition of eight or more medications, was examined. Velocity (cm/s) measured quantitatively during NW and WWT conditions.

RESULTS: The 164 participants (34%) with polypharmacy of five or more medications were older (77.0 ± 6.6 vs 76.0 ± 6.4) and more likely to have hypertension, congestive heart failure, diabetes mellitus, myocardial infarction, and higher body mass index (BMI) and to have fallen within the last year than the remaining 318 without polypharmacy and walked 6 cm/s slower ($P = .004$) during NW and 4 cm/s slower during WWT ($P = .07$), adjusting for age, sex, and education. Group differences were not statistically significant after adjusting for comorbidities. Prevalence of polypharmacy of eight or more medications was 10%. This group walked 11 cm/s slower during NW ($P < .001$) and 8.6 cm/s slower during WWT ($P = .01$) than those without polypharmacy, adjusted for age, sex, and education. Participants taking eight or more medications had slower NW (8.5 cm/s; $P = .01$), and WWT (6.9 cm/s; $P = .07$), compared to those without polypharmacy, adjusting for comorbidities. Adjustments for BMI, high-risk drugs, falls, and comorbidities yielded slower NW (9.4 cm/s, $P = .005$) and WWT (7.9 cm/s, $P = .04$ among those with polypharmacy compared to those without polypharmacy).

CONCLUSION: These results suggest an association between polypharmacy and locomotion that medical comorbidities only partly explained. **J Am Geriatr Soc 2017.**

Key words: polypharmacy; physical performance; gait

Polypharmacy can be defined as the use of more medications than is clinically indicated.[1] Current data suggest that the use of five or more medications is an acceptable definition of polypharmacy and this cut point is associated with 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 people to adverse drug events (ADEs), drug interactions, medication nonadherence, and poor functional capacity.[3] The effect 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 adults. Although specific classes of medications have been linked to impaired mobility and its consequences, such as falls,[4] the effect of polypharmacy on locomotion is not well established. Human locomotion can be studied under simple or complex conditions. Simple locomotion or normal walk (NW) speed in community-dwelling older adults ranges from 0.8 to 1.2 cm/s.[5] Complex locomotion such as walking while performing a secondary cognitive activity such as reciting alternate letters of the alphabet (walking while talking (WWT)), have been helpful in revealing early age-related declines in gait and cognition,[6,7] and decline in performance on WWT has been linked to falls in community-dwelling older adults.[7,8] Norms for WWT were 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 lack of function might not be evidenced 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

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DOI: 10.1111/jgs.14957

0002-8614/17/$15.00

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 (NW) and complex (WWT) locomotion, this cross-sectional study was conducted in 482 community-dwelling older adults. Polypharmacy is modifiable, and if the results show a relationship between polypharmacy and locomotion, it might be possible to improve mobility and decrease the risk of adverse outcomes such as falls in older adults.

MATERIALS AND METHODS

Participants

A cross-sectional study was performed in 482 community-dwelling adults aged 65 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 the cognitive processes and underlying brain substrates or neuronal structures responsible for mobility in aging. The study design has been previously reported.[9] In brief, participants are initially screened by telephone using cognitive screeners (AD8 Dementia Screening interview,[10] Memory Impairment Screen[11]) to exclude individuals with dementia. Participants who pass the screen and express interest in the study are invited for further in-person testing. Inclusion criteria were age 65 and older, English speaking, ambulatory, residing in the community, and planning to be in the area for the next 3 years. Exclusion criteria for the parent study included 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 disorder, significant loss of vision or hearing, recent or planned surgical procedure that could affect mobility, and serious chronic or acute illnesses. All eligible participants provided informed consent. The Albert Einstein College of Medicine institutional review board approved the study protocol.

Medication History

The study clinician ascertained Medication use of participants using a structured questionnaire and an informal interview at the in-person visit. Medication history was further confirmed by reviewing medication bottles and any available medical records and interviewing family members when available. Over-the-counter (OTC) supplement, herbal agent, and prescription medication use was documented. Moderate to high medication adherence has previously been reported in this cohort.[12] Polypharmacy was defined as the use of five 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 an electronic walkway (GAITRite, CIR Systems, Havertown, PA). Participants walked on a 20-foot instrumented walkway that included 4 feet of nonrecording 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 previous studies and has excellent reliability.[14]

The dependent variable was velocity (cm/s) measured during steady state NW and WWT. Participants were instructed to walk at their normal pace during NW for one trial. During WWT, participants were instructed to walk while reciting alternate letters of the alphabet (e.g., A, C, E). Previous studies have shown that WWT speed predicts falls, frailty, and mortality in community-dwelling older adults.[8,15]

Clinical Evaluations

Participants underwent detailed clinical, cognitive, and mobility assessments at their baseline in-house visit and yearly follow-up visits. They were also interviewed about medical conditions and cognitive status and underwent neurological examinations with the study clinician. As previously reported,[9] participants reported presence or absence of physician-diagnosed chronic illnesses (depression, Parkinson's disease, chronic obstructive lung disease, severe arthritis) and vascular diseases (diabetes mellitus, heart failure, hypertension, angina pectoris, myocardial infarction, stroke) upon entry to the study to calculate a Global Health Score (range 0–10, 1 point for each medical condition). Medical history was further confirmed by interviewing family members when available and reviewing available medical records.

Global cognitive status was evaluated using the Repeatable Battery for Assessment of Neuropsychological Status, which measures immediate and delayed memory, attention, language, and visuospatial 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 of participants with ($\geq$5) and without ($<$5) polypharmacy were compared using descriptive statistics. Polypharmacy definitions vary in previous studies in terms of medication count used[2] and whether prescription and OTC medications were included in the definition.[17] Hence, a study-specific alternate definition of polypharmacy as use of eight or more medications (including OTC supplements, herbal agents, and prescription medications), which 10% of the cohort reported, was also examined. This alternate definition also was to account for this more-stringent definition of polypharmacy, which included nonprescription medications, unlike many previous studies. On average, participants were taking 1.1 $\pm$ 1.3 OTC, herbal, or nonprescription agents. Two standard deviations above the mean for the overall cohort equated to three additional medications, which further justified the use of eight more medications. Independent-sample *t*-tests were used for continuous variables and chi-square tests for no change categorical variables. Linear regression analysis was used to determine the

relationship between polypharmacy (independent variable) and gait velocity during NW and WWT cross sectional analysis (dependent variable), adjusting for age, sex, education (years of schooling), BMI, falls, presence of high-risk drugs, and medical comorbidities in the reported models. Covariates were chosen to be included in the models if they were significant at $P \leq .05$ in the univariate analyses (Table 1) or based upon biological plausibility. Adjustments were made for falls, although falls could be interpreted as an outcome. Adjustments were also not made for use of specific classes of medications but were made for medical comorbidities significant at $P \leq .05$ in bivariate analysis comparing the groups with and without polypharmacy. Five models were created. Model 1 adjusted for age, sex, and educational level. Medical comorbidities were added to the adjustments for Model 2 to explore whether polypharmacy was associated with gait speed irrespective of medical comorbidities. In Model 3, falls were added to the adjustments for Model 1. Model 4 adjusted for BMI, presence of high-risk drugs, and falls, in addition to age, sex, and education. Model 5 adjusted for age, sex, educational level, and all variables significant at $P < .05$ with bivariate analysis comparing the polypharmacy and no polypharmacy groups. Model assumptions were examined analytically and graphically and were adequately met. All analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY).

RESULTS

Baseline Characteristics

The prevalence of polypharmacy was 34% (n = 164) of the 482 participants examined in the CCMA sample between June 2011 and February 2016 defined as the use of five or more medications and 10% (n = 48) using a definition of eight or more medications. Table 1 shows the baseline characteristics of the 164 participants with polypharmacy and the 318 without polypharmacy. Mean age was 77.0 ± 6.6 in the polypharmacy group and 76.0 ± 6.4 in the no polypharmacy group. Participants with polypharmacy were more likely to have hypertension, congestive heart failure, diabetes mellitus, and a history of myocardial infarction. The Global Health Score of those with polypharmacy (2.2) was significantly higher than that of those without (1.4) ($P < .001$). The polypharmacy group was also more likely to have had a fall within the last year (26.8% vs 16.1%, $P = .004$) and to have a higher BMI (30.3 vs 28.7 kg/m^2; $P = .02$) than those without. The mean gait speed of the cohort was 98.0 ± 22.8 cm/s for NW and 68.7 ± 24.2 cm/s for WWT. Normal gait speed in community-dwelling older adults ranges from 80 to 120 cm/s. Norms for WWT were considered to be within 1 standard deviation below group means.

Blood pressure control, educational level, knee extensor strength, total Repeatable Battery for Assessment of Neuropsychological Status score, depression, and osteoarthritis were comparable in participants with and without polypharmacy.

Table 2 shows the frequency of medication use in the cohort above 5% unless the medication was deemed to be high risk.[13] 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors were the most commonly used agents of participants in the sample, followed by beta-blockers and angiotensin-converting enzyme inhibitors. Eighteen percent of participants were taking high-risk medications; antidepressants (5.6%) and alpha 1 antagonists (6%) were

Table 1. Baseline Characteristics of Participants with and without Polypharmacy

Variable	Total, N = 483	Polypharmacy, n = 164	No Polypharmacy, n = 318	*P*-Value
Baseline Characteristic				
Age, years, mean ± SD	74.4 ± 6.5	77.1 ± 6.6	76.0 ± 6.4	.08
Female, n (%)	274 (56.8)	90 (54.9)	184 (57.9)	.56
Education, years, mean ± SD	14.5 ± 3.1	14.5 ± 3.0	14.6 ± 3.1	.86
Global Health Score, mean ± SD	1.7 ± 1.1	2.2 ± 1.1	1.4 ± 1.0	<.001
Medical conditions, n (%)				
Hypertension	295 (61.2)	136 (83.0)	159 (50.0)	<.001
Congestive heart failure	8 (1.7)	6 (3.7)	2 (1.0)	.02
Diabetes mellitus	92 (19.1)	48 (28.4)	48 (1.3)	<.001
Myocardial infarction	32 (6.6)	18 (11.0)	14 (4.4)	.01
Chronic obstructive pulmonary disease	35 (7.3)	16 (10.0)	19 (5.2)	.14
Stroke	29 (6.0)	14 (8.6)	15 (2.3)	.11
Depression	50 (10.4)	20 (12.2)	30 (9.4)	.35
Osteoarthritis	229 (87.4)	82 (50.0)	147 (46.2)	.85
Measures				
Systolic blood pressure, mmHg, mean ± SD	130.4 ± 13.4	129.6 ± 14.0	130.8 ± 13.0	.33
Diastolic blood pressure, mmHg, mean ± SD	77.8 ± 7.6	77.4 ± 8.1	78.0 ± 7.4	.43
Knee extensor strength, kg, mean ± SD	34.7 ± 66.6	30.1 ± 13.1	37.0 ± 81.1	.32
Falls within last year, n (%)	1.2 ± 0.39	44 (26.9)	48 (15.1)	.004
Falls, n (%)	1.6 ± 0.50	111 (65.7)	187 (51.6)	.04
Body mass index (kg/m^2), mean ± SD	29.3 ± 6.8	30.3 ± 7.9	28.7 ± 6.2	.02
Grip strength, mean ± SD	24.0 ± 8.9	23.6 ± 8.6	24.2 ± 9.1	.51
Repeatable Battery for Assessment of Neuropsychological Status score, mean ± SD (range 0–100)	91.2 ± 12.1	91.7 ± 12.1	91.0 ± 12.1	.53

SD = standard deviation.

Table 2. Medication Use Frequency of Participants with and without Polypharmacy

Medication	All, N = 482	Polypharmacy, n = 164	No Polypharmacy, n = 318	*P*-Value
Nonprescription drug	259 (53.5)	133 (81.1)	30 (9.4)	<.001
3-hydroxy-3-methyl-glutaryl-coenzyme A inhibitor	239 (49.6)	112 (68.3)	127 (39.9)	<.001
Beta-blocker	123 (25.5)	72 (44.2)	51 (16.0)	<.001
Angiotensin-converting enzyme inhibitor	99 (20.5)	51 (31.3)	48 (15.0)	<.001
Antiplatelet agent	92 (19.1)	55 (33.7)	37 (11.6)	<.001
Angiotensin receptor blocker	80 (16.8)	43 (26.4)	38 (11.9)	<.001
Vitamin and mineral combination	66 (13.7)	38 (23.3)	28 (8.8)	<.001
Oral hypoglycemic agent	65 (13.5)	37 (22.7)	28 (8.8)	<.001
Thyroid hormone replacement	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 inhibitor	36 (7.5)	25 (15.3)	11 (3.4)	<.001
Antihypertensive combination	32 (6.6)	13 (8.0)	19 (6.0)	.44
Ophthalmic agent	39 (6.0)	17 (10.4)	12 (3.8)	.007
Anticoagulant	29 (6.0)	20 (12.3)	9 (2.8)	<.001
Agent for gout	28 (5.8)	22 (13.5)	6 (1.9)	<.001
Nonsteroidal antiinflammatory drug	28 (5.8)	12 (7.4)	16 (5.0)	.31
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 drug	87 (18)	51 (31.3)	36 (11.3)	<.001
Antidepressant	27 (5.6)	15 (9.2)	11 (3.4)	.01
Alpha 1 antagonist	29 (6.0)	19 (11.7)	10 (3.1)	<.001
Benzodiazepine, anxiolytic	19 (3.9)	12 (7.4)	7 (2.2)	.01
Antihistamine	10 (2.1)	6 (3.7)	4 (1.3)	.09
Opioid	5 (1.0)	5 (3.1)	0 (0.0)	.004
Anticholinergic	3 (0.6)	3 (1.8)	0 (0.0)	.04
Muscle relaxant	2 (0.4)	2 (1.2)	0 (0.0)	.11
Antipsychotic	1 (0.2)	0 (0.0)	1 (0.3)	>.99

used with the greatest frequency. Those with polypharmacy were taking more medications in all listed classes than those without polyphamacy; nonsteroidal antiinflammatory 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, community-dwelling sample was taking an antipsychotic. Fifty-three percent of the participants were taking nonprescription medications; 24% were using one agent, 27% were using two or more, and 3% were taking five or more.

Gait Performance

Gait performance is presented in Table 3. Participants with polypharmacy walked 6 cm/s slower ($P = .004$) during NW and 4 cm/s slower during WWT ($P = .07$) than participants without polypharmacy after adjusting for age, sex, and educational level (Model 1). When additionally adjusting for medical comorbidities (hypertension, diabetes mellitus, congestive heart failure, myocardial infarction (Model 2), the group differences were not statistically significant for polypharmacy defined as the use of five or

Table 3. Linear Regression of Gait Performance during simple and complex locomotion

	cm/s (95% Confidence Interval), *P*-Value			
	Polypharmacy (≥5)		Polypharmacy (≥8)	
Model	NW	WWT	NW	WWT
1	−6.0 (−1.0 to −2.0), .004	−4.1 (−8.6 to 0.30), .07	−11.0 (−17.2 to −4.7), <.001	−8.59 (−15.5 to −1.7), .01
2	−4.1 (−8.4 to −0.15), .06	−2.4 (−7.2 to 2.4), .32	− 8.5 (−15.0 to −2.0), .01	−6.89 (−14.1 to 0.3), .07
3	−5.7 (−9.7 to −1.7), .005	−4.6 (−9.0 to −0.19), .04	−10.8 (−17.0 to −4.6), .001	−8.7 (−15.6 to −1.9), .01
4	−5.7 (−9.8 to −1.5), .007	−5.0 (−9.6 to −0.37), .03	−13.3 (−17.8 to −5.0), <.001	−9.3 (16.5 to −2.2), .01
5	−4.6 (−9.0 to −0.16), .04	−3.7 (−8.7 to 1.20), .14	−9.4 (−16.0 to −2.8), .005	−7.9 (−15.3 to −0.47), .04

NW = Normal walk; WWT = Walking While Talking.

Model 1 adjusted for age, sex, educational level.

Model 2 adjusted for age, sex, educational level, comorbidities (diabetes mellitus, hypertension, heart failure, myocardial infarction).

Model 3 adjusted for age, sex, educational level, falls.

Model 4 adjusted for age, sex, educational level, body mass index, high risk drugs, falls.

Model 5 adjusted for age, sex, educational level, body mass index, high risk drugs, falls, comorbidities.

more medications; suggesting that polypharmacy may be reflecting disease effect on the walking tasks. Adjusting for history of falls did not moderate 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, NW speed (estimate: −5.7 cm/s, $P = .007$) and WWT speed (estimate: −5.0 cm/s, $P = .03$) were slower in the polypharmacy group than the no polypharmacy group. In Model 5, adjusted for all covariates including medical comorbidities, only NW speed was statistically significantly lower among those with polypharmacy when polypharmacy was defined as the use of five or more medications. WWT speed was when polypharmacy was defined as the use of five or more medications.

In a separate analysis, using the CCMA-specific definition of polypharmacy as eight or more medications, NW (−11 cm/s, $P = .001$) and WWT (−8.6 cm/s, $P = .01$) speed were significantly slower in those with polypharmacy than in those without when adjustments were made for age, sex, and educational level (Table 3, Model 1). When adjusting for age, sex, educational level, and medical comorbidities in Model 2, NW speed was slower in participants with polypharmacy (−8.5 cm/s, $P = .01$), but the association between polypharmacy and WWT speed was not significant (estimate: −6.9 cm/s, $P = .07$). NW slower normal walk velocity in those with polypharmacy compared to those without polypharmacy (−9.4 cm/s, $P = .005$) and WWT (−7.9 cm/s, $P = .04$) speed were slower when adjustments were made for age, sex, educational level, BMI, falls, high-risk drugs, and medical comorbidities (Model 5).

DISCUSSION

These results show a strong association between gait speed during simple locomotion and polypharmacy (≥5 medications) in community-dwelling older adults. The strongest explanation for the association between polypharmacy and gait speed appears to be that polypharmacy is a surrogate for having multiple chronic medical illnesses, although the stronger association between the study-specific polypharmacy definition (≥8) and NW and WWT suggests that multimorbidity partly but not completely explains this relationship. The association between locomotion and polypharmacy persisted after adjustment for the use high-risk drugs, which 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 the current study definition of polypharmacy and those used in many previous studies is that the current included nonprescription (OTC and herbal agents) and prescription drugs in the medication count. Although this could have led to an overestimation of the prevalence of polypharmacy in this sample and a bias toward the null when polypharmacy was defined as five or more medications, the authors felt strongly that OTC and herbal agents may have risks similar to those of prescription drugs and that disentangling this would require a subjective decision on the part of the study authors to determine which medications were important enough to be documented.

This study is one of the first to explore the effect polypharmacy on gait performance as measured according to quantitative assessments of simple and complex locomotion in community-dwelling older adults free of major cognitive and functional limitations. Previous studies support the findings but with notable differences. In hospitalized older adults, a previous study[18] noted that poor physical performance measured according to grip strength and walking speed was associated with polypharmacy defined as eight 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 measured as performance of activities of daily living (ADLs)[20] independent of comorbidities.

With a polypharmacy definition of five or more medications, WWT gait speed (complex locomotion) did not decline to a statistically significant degree in all models examined. Although participants taking more medications may walk more slowly than those taking fewer, number of medications alone does not appear to affect their ability to prioritize during cognitive motor tasks. One explanation is that the sample represents a subset of high-functioning community-dwelling older adults who are more robust and less likely to have significant cognitive effects because of polypharmacy. When the definition of polypharmacy was adjusted to include participants taking eight or more medications, gait speeds with simple and complex tasks were significantly slower, adjusting for age, sex, educational level, BMI, medical comorbidities, falls, and high-risk drugs. The results suggest an association between more-extreme definitions of polypharmacy (≥8) and decline in complex locomotion. Given the link between WWT speed and falls[7,8] in high-functioning older adults, polypharmacy (≥8 medications) is a useful marker for those who may be at risk.

Strengths and Limitations

The strengths of this study include the use of a cohort of community-dwelling older adults without functional or cognitive impairments and the use of systematic gait assessment. The cross-sectional design limits establishment of causation, but follow-up is continuing, and there are plans to report longitudinal associations. It is likely that the results would be more exaggerated in a hospitalized or institutionalized population, but additional confounders would have to be considered. Although 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 the sample size. Although several potential confounders were controlled for in the 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, although disease duration and severity may confound these variables; 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. The effects of ethnicity and socioeconomic status on the relationship between polypharmacy and gait were not explored, but the study population was rather homogeneous, being from one area of the Bronx, New York. The cohort was 79% white and 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 according to race. Further study is needed to determine the effect of specific classes of medication on complex locomotion and explore the interplay between polypharmacy, specific classes of medication, and medical comorbidities.

CONCLUSION

These results suggest an association between polypharmacy and locomotion in aging that multimorbidity only partly explained. Longitudinal studies are needed to follow up on these findings. Polypharmacy including nonprescription 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 NW and WWT in individuals taking multiple medications to assess and identify a potentially modifiable mobility risk.

ACKNOWLEDGMENTS

Conflict of Interest: This study was supported by grants from the National Institute on Aging (R01AG036921–01A1: PI R. Holtzer; R01AG044007–01A1: PI J. Verghese). C. George is supported by the National Institutes of Health, National Center for Advancing Translational Science Einstein-Montefiore Clinical and Translational Science Award KL2TR001071. J. Verghese receives funding support from National Institute on Aging Grants R01 AG039330, RO1AGO44007, RO1 AGO44829, R01AG036921, and PO1 AGO3949.

Author Contributions: George, Verghese: Design, acquisition of subjects, analysis and interpretation of data, preparation of manuscript.

Sponsor's Role: The funding sources had no role in study design; collection, analysis, or interpretation of data; writing of the report; or decision to submit the article for publication.

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