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Walking While Talking and Risk of Incident Dementia

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Abstract

Introduction: Walking while talking (WWT) is a performance based test of divided attention, which examines cognitive-motor interactions. The purpose of this study is to examine the predictive validity of WWT for dementia and dementia subtypes.

Methods: We prospectively studied the associations of WWT performance at baseline with risk of developing incident dementia in 1156 older adults (mean age 78.28±5.27, 60.7% female) enrolled in the Einstein Aging Study using Cox proportional hazard models. Associations were reported as hazard ratio (HR) with 95% confidence intervals (CI).

Results: Over a median follow-up of 1.90 years (IQR= 4.70), 85 participants developed incident dementia (53 Alzheimer's dementia (AD) and 26 vascular dementia (VaD). 3 gait domains were derived using principal component analysis. Only Variability, which loaded heavily for swing time SD and step time SD, was associated with an increased risk of incident dementia per 1 point increase (HR 1.24, 95% CI: 1.02-1.54)) and VaD (HR 1.50, 95% CI: 1.06-2.12)) after adjusting for demographics, disease burden, mental status and normal walking velocity. Amongst 8 individual gait variables, only swing time variability (standard deviation (SD)) was associated with increased risk for both incident dementia (HR 1.35, 95% CI: 1.03-1.77) and VaD (1.78, 95% CI: 1.12-2.83). Variability and swing time SD were not significantly associated with risk of incident AD.

Conclusion: Complex walking as assessed by the WWT task is a simple and pragmatic tool for assessing risk of developing dementia, especially VaD in older adults.

Keywords

Walking; Talking; Complex walking; Divided Attention; Older Adults; Cohort; Dementia

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Introduction

The global burden of dementia continues to grow, affecting 5 to 7% of the world's population 60 years and older. [1] While Alzheimer's disease (AD) is the most common etiology for dementia, the prevalence of non-Alzheimer's Disease (non-AD) dementias such as Vascular, Frontotemporal and Lewy Body dementias is increasing. [2] Although many clinical, biological and neuroimaging markers are available to assess the risk of AD[3, 4], there are few clinical markers that specifically predict the incidence of non-AD dementias such as Vascular dementia (VaD). While neuroimaging is helpful in identifying cerebrovascular disease, the expense, and accessibility as well as modest predictive value for dementia in non-demented individuals makes it a poor screening tool.[5]

A growing body of literature from our group as well as other investigators has identified gait dysfunction as an early feature in dementia, especially in non-AD dementias.[5–11] Gait performance during complex locomotion tasks such as the Walking while talking (WWT) test, where participants are asked to walk and recite alternate letters of the alphabet, is linked to executive function in healthy adults[12]. Conversely, impairments in WWT performance are associated with executive dysfunction, a prominent and early feature of non-AD dementias. [13] Given the clinical accessibility of the WWT test, high test-retest reliability[14], and its association with cognitive domains that are vulnerable to non-AD dementia processes[12], it is of interest to explore its role as a dementia risk predictor in clinical settings. Older adults with mild cognitive impairment syndrome (MCI) were reported to perform worse on the WWT task compared to healthy older adults.[15] Montero-Odasso and colleagues recently reported that a WWT-like task (either counting backwards from 100, subtracting serial sevens from 100, or naming animals) predicted incident all cause dementia in participants with MCI but no analysis of dementia subtypes was reported in that study.[16] However, whether WWT is a predictor of dementia and dementia subtypes in non-demented older adults (with and without MCI) has not yet been established.

We hypothesized that worse performance on WWT would predict incident all cause dementia, and in particular VaD since executive dysfunction is usually an early sign. We tested this hypothesis in 1156 initially non-demented older individuals participating in the Einstein Aging Study (EAS), a community based prospective cohort study based in Bronx County, New York USA.

Methods

Study Sample

Data for this study were gathered from the EAS. The primary aim of the EAS was to identify risk factors for dementia. [17] Potential participants (age 70 and over) identified from population lists of Bronx County were contacted first by letter, then by telephone explaining the purpose and nature of the study. Telephone interviews included verbal consent, medical history and cognitive screeners. The exclusion criteria included severe auditory or visual loss, inability to ambulate, and institutionalization. At entry and during annual visits, participants received clinical evaluations to determine presence of neurological or non-neurological gait abnormalities. Participants return annually for clinical, cognitive, and

mobility assessments. Informed consent was obtained at enrollment according to protocols approved by the Einstein Institutional Review Board.

Gait Assessment

The EAS implemented gait assessments as part of its study protocol beginning in 2002.[18, 19] Participants enrolled with gait assessments from 2002 to 2015 were included in the study. Quantitative gait assessment was conducted at baseline using the GAITRite system (CIR Systems, PA), a computerized walkway (dimensions 180×35.5×0.25 inches) with embedded pressure sensors, in a quiet well-lit room. Participants walked on the mat at their normal pace while computer software recorded gait variables as the mean of two trials. To account for initial acceleration and terminal deceleration, data capture begins and ends three feet from either end of the walkway. The GAITRite system is widely used and has excellent reliability. [20–22]

Walking While Talking

WWT is conducted by having participants walk on the GAITRite walkway, while reciting alternate letters of the alphabet aloud for one trial. They were instructed to pay equal attention to walking and talking to avoid task prioritization.[12] To reduce learning effects, subjects were randomly assigned to start the WWT task with either the letter “A” or “B.”[12] Testers intervened only if subject safety was an issue. Based on our previous work on gait in community dwelling older adults,[20, 23, 24] we selected the following eight gait variables: velocity (cm/s), cadence (step/min), step length (cm), swing (percent), stance (percent), double support (percent), step time variability (standard deviation (SD)), and swing time variability (SD). Velocity (cm/sec) is the distance traveled divided by the ambulation time. Cadence is the rate at which the participant walks as measured by steps per minute.[25] Step length is the distance covered in an average step, from one heel to the other heel.[25] Swing time is the percentage of time that the foot spends in the air from toe up to heel strike on the same foot.[25] Swing time variability is the standard deviation of the time the foot spends up in the air during a single walk. Stance is the percentage of time the foot is on the ground, from heel strike to toe up on the same foot.[24] Double support is the percentage of time that both are on the ground during two periods of a gait cycle.[24] Step time variability is the standard deviation in the time elapsed from the first contact of the one foot to the first contact of the other foot during a single walk.[24]

Dementia diagnosis

As part of the EAS protocol, participants return for a follow-up clinic visit every 12 to 18 months at which they complete a neuropsychological battery. They are asked medical, epidemiological, social, and behavioral questions as well as undergo a complete neurological assessment by the study clinician and neuropsychological assessment supervised by a licensed neuropsychologist.[17] The full clinical and neuropsychological battery includes verbal IQ estimates from the short form Weschsler Adult Intelligence Scale-Revised (WAIS-R), vocabulary from the Mill Hill Vocabulary Scale, and the Free and Cued Selective Reminding Test (FCSRT).[26] In the EAS, subjects are identified as at high risk for dementia based on performance on the Blessed Information-Memory-Concentration test (BIMC), the FCSRT, or if cognitive changes were identified by the participant, a significant

other, or a study staff member.[3, 27] Dementia was diagnosed at consensus case conferences attended by study clinician and neuropsychologist after reviewing all available clinical and neuropsychological data. Dementia diagnosis was based on Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and a diagnosis of probable or possible AD, VaD and Lewy Body dementia (LBD) is determined based on established criteria.[10] Once a dementia diagnosis is made, participants undergo neuroimaging and other laboratory tests as indicated to subtype the dementia. We have reported good clinicopathological agreement for dementia subtype diagnoses in our cohort.[10, 28, 29] Diagnosticians were blinded to quantitative gait and WWT information at the conferences.

Covariates

Covariates included in the analyses were gender, years of education, and age. General cognitive status was assessed by the BIMC test. [26, 27] Self-reported comorbidities such as depression, diabetes, heart failure, hypertension, angina, myocardial infarction, strokes, Parkinson's disease, chronic obstructive lung disease, and arthritis were used to calculate a summary illness index (range 0 to 10).[20] Clinical gait abnormalities were diagnosed by visual inspection of walking patterns by study clinicians. [10, 19] Gait velocity (cm/sec) during normal pace walking , recorded using the GAITRite system was also included in the model. [30]

Statistical Analysis

Baseline characteristics of participants who did and did not develop dementia (of any etiology) were examined with bivariate analyses. Continuous variables were assessed using the independent sample t-test. Dichotomous variables, gender and death, were assessed using a Pearson's chi square test. Race/ethnicity category was assessed using Fisher's exact test as 33% of cells had less than 5 expected count. Cox proportional hazards models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI) to predict incident dementia, VaD and AD, based on the selected baseline WWT gait variables. In this analysis, VaD included Possible Vascular Dementia, Probable Vascular Dementia and Mixed Dementia.[31] Quantitative gait variables are highly correlated. To address the problem of collinearity, a principal component analysis of the eight quantitative gait variables (described above) was conducted to derive statistically independent gait domains, which facilitates simultaneous analysis.[20,23,24] The eigenvalue is calculated for each factor that is extracted. If the eigenvalue drops below 1 it means that the factor explains less variance in the model than any of the individual gait variables. Only factors that explain more of the variance than any individual variable are extracted. After extracting the factors, the Varimax orthogonal rotational method minimizes the number of variables that load highly to each factor and produces uncorrelated factors. Gait domains of normal pace walking derived using a principal component analysis have been reported to predict dementia and decline in specific cognitive domains including executive function, letter fluency and episodic memory in the EAS cohort.[25] While, WWT gait domains were reported to predict falls in EAS,[30] WWT gait domains have not been previously examined as predictors of incident dementia in this cohort. As a secondary approach to facilitate clinical comparisons with previous studies we also examined the eight individual WWT gait variables in individual models adjusted for all covariates included in the primary model. The time scale included in the Cox proportional

hazard model was follow-up time (days) to incident dementia or final contact. All models were adjusted to include age, gender, education, illness index, BIMC score, and normal pace walking velocity, given the previously reported association of gait dysfunction and these other covariates with dementia and cognitive decline[25]. Models were checked for the proportional hazards assumption graphically and with statistical tests. Cox regression analyses were conducted including a time-dependent covariate in the models. All analyses were conducted using SPSS version 24 (SPSS Inc. Chicago, IL).

Results

Study Sample

1156 participants were followed from 2002 to 2015. The median follow-up time from baseline WWT gait assessment to diagnosis of dementia or final contact date was 1.90 years (interquartile range= 4.70). Over the study follow-up, there were 85 (7%) incident dementia cases, 53 possible or probable AD and 26 mixed dementia (AD and VaD) or VaD. Table 1 compares participants that developed dementia with those who did not. Participants who developed dementia were significantly older and performed significantly worse on the BIMC. After excluding participants who died, 895 participants remained. 64.5% (522) of participants who did not develop dementia and 92% (46) participants who developed dementia dropped out (Pearson chi-square p <.001). The mean follow up time differed significantly as well with participants who did not develop dementia having a mean follow up time of 2.9 years (±3.16) and participants who did develop dementia with a mean follow up time of 5.0 years (±3.12) (independent t-test p<.001).

WWT Gait Domains

Principal component analysis of eight WWT gait variables resulted in three independent factors accounting for 84.7% of the variance in WWT performance (Table 2). The WWT factors extracted each explain more of the variance than any individual WWT gait variable. This WWT factor structure replicated that which was presented in previous EAS reports.[30] Swing (%), Stance (%), and Double Support (%) variables loaded heavily in the first factor termed “Rhythm” and accounted for the largest variance (33.5%). Swing time SD and step time SD loaded heavily in the second factor termed “Variability” and accounted for 28.1% of variance. Velocity and cadence loaded heavily in the third factor termed “Pace” and accounted for 23.1% of the variance. The factors can be conceptualized as summary risk score with higher scores indicating worse performance. The units are standardized with a mean =0 and SD =1.

The three gait domains: Rhythm, Variability and Pace were analyzed simultaneously in the fully adjusted Cox regression model (see Table 3). The overall test of significance for the models for all cause dementia, VaD and AD outcomes was significant; indicating that all three fully adjusted models were significant. The 1 point increase in the Variability domain was significantly associated with a 24% increased risk of incident all-cause dementia as well as a 50% increased risk of VaD, but not an increased risk of incident AD.

Individual Gait Variables

Swing time SD was the only individual WWT gait variable that was associated with increased risk for both incident dementia (HR per 1 SD: 1.35, 95% CI: 1.03-1.77, Wald test p=.03) and VaD (HR per 1 SD: 1.78, 95% CI: 1.12-2.83, Wald test p=.02). In the fully adjusted models, none of the WWT individual variables were significantly associated with incident AD.

Discussion

In this prospective cohort study of community dwelling older adults, a complex walking condition (WWT) predicted risk of developing incident all-cause dementia and incident VaD after adjusting for age, gender and education, baseline cognitive performance, disease burden and normal pace walking velocity as covariates. When WWT gait performance was evaluated as 3 gait domains (Rhythm, Variability and Pace), only the WWT Variability domain was associated with a 24% increased risk of developing incident dementia and a 50% increased risk of VaD, but not AD after adjusting for demographics including age, BIMC and normal pace velocity. Similarly, amongst 8 individual gait variables, only swing time SD, a measure of variability, was associated with a 35% increased risk of incident dementia and a 78% increased risk of VaD over the study follow-up, but not an increased risk of AD. Based on these findings, increased variability during WWT appeared to be a more specific predictor for VaD then AD, suggesting variability in gait during WWT may be a particularly good marker of executive dysfunction. Recent studies conducted in patients with dementia[32], depressed patients[33] and community dwelling adults[34] without dementia support the association between gait variability and executive dysfunction. In contrast, previous work from our group using the EAS cohort found that the WWT Pace domain was associated with falls[30], suggesting specificity of gait domains in terms of disease prediction. Neither WWT individual gait variables nor gait domains were significantly associated with AD.

WWT has been well established as a predictor of incident and recurrent falls.[18, 30, 35, 36] Our group has also found that poor performance on WWT is a predictor of disability, frailty and mortality in older adults.[37] In this study, our findings extend the role of WWT to a predictor of dementia. The association between complex walking swing time variability and VaD but not AD, is consistent with the literature that executive dysfunction (assessed by WWT) is a hallmark of early clinical stages of VaD and other non-AD dementias.[7, 38] Cross sectional studies have shown that adults with cognitive impairment due to a variety of neurologic disorders perform worse on complex (dual task) walking.[15, 39–45] Older adults with MCI were reported to decrease gait speed during dual task walking compared to cognitively intact participants.[15] A systematic review of the literature found that complex walking conditions discriminated those with MCI from cognitively intact older adults better than simple walking.[46] Our findings are supported by Montero-Odasso and colleagues who followed 112 community dwelling adults with MCI for up to 6 years and found that WWT predicted incident all cause dementia. [16] However, in contrast to this study which found WWT velocity to be a predictor of incident dementia, our fully adjusted model did not show a statistically significant association between WWT velocity and incident all-cause dementia,

VaD and AD. The difference may be due to the study sample which included participants with MCI as opposed to cognitively intact participants included in our study. In addition Montero-Odasso and colleagues reported only one case of incident VaD in their cohort, and consequently analysis of subtypes of dementia could not be completed. While other studies have investigated normal walking condition (without talking) gait variables as predictors of incident dementia or WWT gait variables in patients with baseline cognitive impairment, ours is the first study to suggest the predictive value of WWT for incident VaD in cognitively intact community dwelling older adults.

The WWT paradigm assesses divided attention.[12] The relationship between divided attention and cerebrovascular lesions has been demonstrated in several animal models. [47–49] For instance Deziel and colleagues induced vasoconstriction in the medial prefrontal cortex in male rats, which resulted in poor performance on set shifting during a maze task. [49] Cordova and colleagues recreated the presence of lacunar infarcts in male rats by injecting bilateral endothelin-1 in the mediodorsal nucleus of the thalamus or the medial prefrontal cortex, which resulted in impaired ability to shift attention once food was paired with new stimuli based on odor or texture.[48] In human studies, young adults performing simple walking and then a complex walking task (counting backwards by 7s from 10,000 while walking) demonstrated changes in middle cerebral artery blood flow velocity measured by trans-cranial Doppler.[50] Taken together, these animal and human studies highlight the role of cerebrovascular lesions in impaired executive function.

The relationship between WWT tasks and executive function suggests possible preventative and therapeutic interventions. For instance, several studies have evaluated the role of gait training programs in cognitive rehabilitation.[51–53] A multicenter randomized controlled trial, compared strength and balance training to strength-balance-cognitive training (computerized divided attention training) in older adults and found positive effects on WWT tasks (walking at a self-selected speed while subtracting sevens or threes from a randomly assigned number or naming animals or flowers).[53] Schoene and colleagues demonstrated that cognitive motor step training improved executive function.[51] In the MINDVital trial, participants with early dementia received rehabilitation combining cognitive stimulation and physical exercise; improvements in cognitive performance over time was a significant determinant of improvement in dual-task gait speed in this study.[52] Future studies should investigate whether improved WWT performance reduces dementia risk.

Our study was conducted in a well-established longitudinal cohort of community dwelling older adults, which allowed us to evaluate the predictive value of WWT for incident dementia. Gait was assessed objectively utilizing the GAITRite walkway (CIR Systems, PA) rather than a subjective clinical assessment. In addition we utilized a principal component analysis, to assess this association between WWT and dementia allowing for all three gait domains to be assessed simultaneously in one model; providing a more comprehensive coverage of gait performance during WWT. Utilizing domains may be more conceptually relevant as different domains may be associated with different outcomes such as Pace and falls versus Variability and executive dysfunction. Still, our study had several limitations. Firstly, there was a relatively low incidence of dementia in this cohort consistent with a community volunteer sample compared to clinical or institutionalized samples. It is likely

that longer follow-up time would have resulted in more incident dementia cases, and possibly strengthened our reported associations. Second, our primary finding was the association between the WWT Variability domain and all cause dementia and VaD; but the variability metrics may be sample specific. While other community based studies support the association between gait intraindividual variability and executive dysfunction[34], replication of this in other distinct samples would confirm this association. Third, our findings do not provide information on mechanisms that mediate the relationship between WWT and dementia. Given the observational nature of the study, causality cannot be established though our findings indicate that WWT performance worsens before the clinical diagnosis of dementia. Lastly, while we adjusted for several potential confounders known be associated with dementia, we do not discount the possibility of residual or unmeasured confounding.

Conclusions

In sum, complex walking as assessed by the WWT task is a simple and pragmatic tool for assessing risk of developing dementia, especially VaD in older adults.

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Highlights:

- Walking while talking (WWT) is a performance based test of divided attention, which examines cognitive-motor interactions.
- The purpose of this study is to examine the predictive validity of WWT for dementia, especially non-Alzheimer's dementia.
- In this study of community dwelling older adults, a complex walking condition (WWT) predicted risk of developing incident all cause dementia and incident Vascular dementia (VaD), but not incident AD.
- This is the first study to report the predictive value of WWT for incident VaD.
- WWT is a simple clinical tool, which can help identify older patient populations at risk of developing dementia, especially VaD.

Table 1:

Comparison of Baseline Characteristics of Einstein Aging Study Participants Based on Development of Incident Dementia

Variable	All Subjects N=1156 Mean(±SD)[a]	No Dementia N=1071 Mean(±SD)[a]	Dementia N=85 Mean(±SD)[a]	Statistics	P-value
Age, years	78.28±5.27	78.02 (±5.18)	81.76 (± 5.30)	t=−6.30	<.001
Female % (N)	60.7 (702)	60.7 (652)	61.0 (50)	X^2=.002[d]	.96
Race Ethnicity %(N)				Fisher's Exact=2.305	.73
White	64.4 (763)	66.1 (710)	64.6 (53)		
Black	26.9 (318)	27.4 (294)	29.3 (24)		
Hispanic White	3.4 (40)	3.4 (37)	3.7 (3)		
Hispanic Black	1.0 (12)	1 (11)	1.2 (1)		
Asian	.6 (7)	.6 (6)	.5 (1)		
Other	1.4 (16)	1.5 (16)	0 (0)		
Education years	14.12± 3.43	14.16 (± 3.43)	13.70 (± 3.45)	t=1.18	.24
Illness Index[b] (0-10)	1.27±1.06	1.28 (±1.08)	1.09 (± 0.79)	t=1.62	.11
Blessed Score (0-32)	2.16±2.14	2.01 (± 1.95)	4.11 (±3.27)	t=.8.84	<.001
Normal Walking Velocity (cm/s)	94.12±22.89	94.42 (±23.07)	90.19 (±20.11)	t=1.60	.11
WWT variables					
Velocity (cm/s)	69.01 ±25.62	69.31 (±25.57)	65.38 (±26.17)	t=1.34	.18
Cadence (step/min)	80.02±20.97	80.05 (±.20.89)	79.55 (±22.16)	t=.21	.84
Step Length(cm)	51.29±11.92	51.45 (±11.97)	49.13 (±11.06)	t=1.71	.09
Swing %	34.49±5.41	34.43 (±5.45)	35.16 (±4.70)	t=−1.17	.24
Stance %	65.52±5.32	65.57 (±5.37)	64.84 (±4.70)	t=1.21	.23
Double Support %	31,33±9.34	31.40 (±9.43)	30.35 (±7.99)	t=.98	.33
Swing Time SD	.15±.72	.15 (±.74)	.16 (±.33)	t=−.14	.89
Step Time SD	.16 (±.8)	.16 (±.78)	.15 (±.30)	t=.11	.92

[a] Unless otherwise indicated

[b] Illness index includes self-report of depression, diabetes, heart failure, hypertension, angina, myocardial infarction, strokes, Parkinson's disease, chronic obstructive lung disease, and arthritis

[c] df=1

Table 2:

Principal Component Analysis of WWT Gait Variables

Gait Domain*	Rhythm	Variability	Pace
Velocity	.430	−.109	**.865**
Cadence	.133	−.040	**.944**
Step Length	.624	−.175	.323
Swing %	**.841**	.424	.184
Stance %	**−.850**	−.398	−.184
Double Support %	**−.813**	.220	−.146
Swing Time SD	.028	**.956**	−.080
Step Time SD	.028	**.950**	−.087

Extraction Method: Principal Component Analysis

Rotation Method: Varimax with Kaiser Normalization

*All gait variables contribute to each domain.

Table 3:

Model of Risk of Incident Dementia, Vascular Dementia and Alzheimer's Dementia * N=1156
Hazard ratios (HR) with 95 % confidence intervals (CI) adjusted for age, gender, years of education, illness index, BMIC [a] score and normal velocity

	All Dementia N=85	P-value [b]	Vascular Dementia N=26	P-value [b]	Alzheimer's Dementia N=53	P-value [b]
WWT Gait Domains	**HR (95% CI)**		**HR (95% CI)**		**HR (95% CI)**	
Rhythm	.96 (.73-1.25)	.74	1.40 (.84-2.33)	.20	.80 (.56-1.14)	
Variability	1.24 (1.02-1.54) *	.04 *	1.50 (1.06-2.12) *	.02 *	.85 (.65-1.12)	
Pace	.90 (.72-1.14)	.39	1.02 (.63-1.66)	.94	1.26 (.95-1.69)	
Overall model p-value [c]	<.001 *		<.001 *		<.001 *	

[a] BIMC (Blessed Information-Memory-Concentration)

* P value <0.05

[b] Wald test for significance, df=1

[c] Overall test of significance of model coefficients (−2 Log Likelihood chi-square, df=7)