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学位論文

Studies on associations between gait and cognitive function among community-
dwelling older adults in Japan

(日本地域在住高齢者における歩行と認知機能の関連に関する研究)

2024 年 9 月

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Tables of contents

List of publications and presentations.....	1
Summary	2
List of abbreviations.....	5
Introduction	6
Chapter 1: Association between comprehensive gait and cognitive function.....	10
Background.....	10
Methods	11
Results	15
Discussion.....	21
Conclusion	24
Chapter 2: Dual decline in gait speed and domain-specific cognition, and the relationship with incident dementia	26
Background.....	26
Methods	27
Results	31
Discussion.....	39
Conclusion	42
Conclusions	50
Acknowledgements	60
Disclosure of conflicts of interest	61
References	62

List of publications and presentations

Publications in this thesis:

1. Hao, Wen, Yi-Fan Shan, Takashi Kimura, Shigekazu Ukawa, Hideki Ohira, Satoe Okabayashi, Kenji Wakai, Masahiko Ando and Akiko Tamakoshi. 2024. Dual Decline in Subjective Gait Speed and Domain-Specific Cognition Is Associated with Higher Risk of Incident Dementia in Older Japanese Adults: A 15-Year Age-Specific Cohort Study. Archives of Gerontology and Geriatrics 117: 105254.
2. Hao, Wen, Wenjing Zhao, Takashi Kimura, Shigekazu Ukawa, Ken Kadoya, Katsunori Kondo and Akiko Tamakoshi. 2021. Association of gait with global cognitive function and cognitive domains detected by MoCA-J among community-dwelling older adults: a cross-sectional study. BMC Geriatrics 21(1): 523.

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2. Wen Hao, Wenjing Zhao, Takashi Kimura, Takumi Hirata, Sachiko Sasaki, Shigekazu Ukawa, Ken Kadoya, Katsunori Kondo, Akiko Tamakoshi, Association of gait with cognitive function among community-dwelling older adults: a cross-sectional study. 32nd Japanese Epidemiological conference, 2022. 18 January. (Oral presentation)
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4. Wen Hao, Yifan Shan, Takashi Kimura, Shigekazu Ukawa, Satoe Okabayashi, Kenji Wakai, Masahiko Ando, Akiko Tamakoshi. Association of dual decline in gait speed and domain-specific cognition with incident dementia in Japanese older adults: an age-specific cohort study. 2nd Public Health Conference, 16th-18th March, 2023. Singapore. (Oral Presentation)

Summary

Background and objectives: The number of older people along with prevalence of dementia is rapidly growing all over the world. By the end of 2050, 40% of the Japanese population will consist of older people and more than 25% of them are anticipated to have dementia (Nakahori et al., 2021). To help further evaluations and interventions, identifying early markers of cognitive decline and dementia is important (Verghese et al., 2007).

Gait has been proved to be strongly related with cognitive function, and the internal mechanism can be explained as some shared central nervous system deficits (Tian et al., 2021a). However, existing studies only included part of the gait characteristics and cannot capture the full picture of gait performance. In addition, redefining poor gait as direct indicator of the central nervous system problem instead of other impairments is necessary to detect deeper mechanism, yet scarcely mentioned in previous studies (Tian et al., 2023).

Meanwhile, more recent studies claimed combined characteristics of gait and cognition (such as dual decline in gait speed and memory) has an even higher risk of developing dementia than the single gait or cognitive characteristics, but the internal mechanism remains largely unknown (Montero-Odasso et al., 2020; Tian et al., 2023; Montero-Odasso et al., 2018).

What's more, similar study targets Japanese older adults at the same time with a rather long follow-up period is scarce.

Therefore, in this study, I conducted two separate sub-studies to explore the association between gait performance with cognitive function in Japanese community-dwelling older adults.

Chapter 1 aimed to find out both the cross-sectional and longitudinal associations between comprehensive gait and cognitive function in Japanese community-dwelling older adults.

Chapter 2 used the data from an on-going age-specific cohort study and aimed to find out if dual decline in gait and domain-specific cognition had higher risk of developing dementia after a 15-year follow-up in Japanese community-dwelling older adults.

Chapter 1. Association between comprehensive gait and cognitive function

Hypothesis: Several gait factors are independently associated with cognitive function, and they may provide a new insight into finding the potential mechanism of cognitive pathology.

Methodology: Data was obtained from the Cognition and Activity in Rural Environment of Hokkaido Senior Study. 236 participants lived in six towns in Hokkaido were recruited at baseline in 2018, among them, 131 participants attended the follow-up study in 2021. All the

participants underwent physical examinations, gait and cognitive assessments, and self-administered questionnaires at both baseline and follow-up. Gait was measured using two validated inertial sensors (Physilog®, GaitUp®, Switzerland) fixed on each foot and asking participants to walk a round trip of a 6-meter straight path at a self-preferred walking speed in baseline. 19 gait parameters were obtained and summarized into 4 gait domains using factor analysis. Cognitive function was evaluated using the Japanese version of the Montreal Cognitive Assessment through face-to-face interviews in follow-up by trained investigators. Cross-sectional and longitudinal associations between gait and cognitive function were evaluated using generalized linear models.

Results: Factor analysis yielded four gait factors: general cycle, initial contact, propulsion, and mid-swing. The general cycle factor was associated with both baseline MoCA-J score and score after three-year follow-up. In subtest of MoCA-J, general cycle and initial contact were related with baseline executive function, but significance disappeared in longitudinal associations.

Discussion: Poor gait is significantly associated with worse cognitive function in older adults, especially with executive function. However, simple gait indicators may be insufficient on predicting future cognition.

Chapter 2. Dual decline in gait speed and domain-specific cognition, and the relationship with incident dementia.

Hypothesis: dual decline in gait speed and cognitive function will have a higher risks of incident dementia than single or no decline in either aspect among community-dwelling older adults.

Methodology: Data was obtained from the New Integrated Suburban Seniority Investigation Project. Participants included are those who were about to reach the age of 65 years between 1997 and 2001 and finished health check-ups and self-administered questionnaires at both 65 and 70 years old. Gait speed decline was defined as subjective speed change from “fast” to “normal” or “slow”, or from “normal” to “slow” in 70-year questionnaire compares to the 65’s. Cognitive tests included the word recall and the delayed word recall from the Alzheimer’s Disease Assessment Scale, the digit span forwards and backwards from Wechsler Adult Intelligence Scale-revised, and the Stroop color and word test. Cognitive decline was defined as being in the lowest tertile of a 5-year change in each cognitive test. Dementia was diagnosed as the cognitive disability greater than Ila in the Japanese Long-

term Care Insurance system. Cox proportional hazard models were used to estimate risk of dementia adjusting for covariates, with death as competing risk.

Results: After a mean follow-up period of 12.5-years, 111 participants developed dementia. It was observed that older adults exhibiting dual decline are more likely to have conditions such as hyperlipidemia and diabetes, as well as smoking habits. The study revealed that a dual decline in gait speed and domain-specific cognition is associated with an increased risk of developing dementia compared to no decline in most cognitive tests. The greatest risk was seen when a decline in gait speed was combined with memory impairment (subdistribution hazard ratio: 3.9, 95% confidence intervals: [1.7–9.0]). However, these significant differences were only noted in male after the data was stratified by sex.

Discussion: Dual decline can predict dementia from more than a decade ago and can be an efficient target of dementia prevention with its easily recognizable features. However, subjective gait speed decline is also a good low-costing marker in predicting future incident dementia and can be considered of adding into clinical assessments.

List of abbreviations

3D	Three-dimensional
ADs	Alzheimer diseases
BMI	Body mass index
CARE-DO	Cognition and Activity in Rural Environment of HokkaiDO Senior
CI _s	Confidence intervals
CNS	Central nervous system
CVA _s	Cerebrovascular diseases
CVD _s	Cardiovascular diseases
DS	Digit span
HR _s	Hazard ratios
IADL	Instrumental activities of daily living
IR	Interference ratio
JAGES	Japan Gerontological Evaluation Study
LTCI	Long-term Care Insurance
MCI	Mild cognitive impairment
MoCA-J	Japanese version of the Montreal Cognitive Assessment
NDD _s	Neurodegenerative diseases
NISSIN	The New Integrated Suburban Seniority Investigation
sHR _s	Sub-distribution hazard ratios
WR	Word recall

Introduction

The phenomenon of population aging continues to reshape demographic structures in most areas of the world. As of recent decades, a significant increase in life expectancy coupled with declining birth rates has led to an unprecedented rise in the proportion of older individuals. In 2022, the global population aged 65 and over reached 771 million, nearly three times the from 1980, which stood at 258 million. This older demographic is projected to grow to 994 million by 2030 and further to 1.6 billion by 2050. Consequently, by 2050, the number of people aged 65 and older will more than double the number of children under 5 worldwide and will nearly equal the number of children under the age of 12 (United Nations, 2022). Among all nations, Japan presents a particularly acute case of demographic aging, with statistics indicating that 28% of its population is aged 65 or older, and over one in ten people are now aged 80 or older—the highest proportion globally. While increased longevity represents one of the key achievements of the 20th century, this demographic shift also leads to an increase in the incidence and prevalence of neurodegenerative diseases (NDDs), which are common adverse health outcomes associated with aging (Tanner, 1992).

Neurodegeneration is the slow and progressive neuronal dysfunction characterized by the progressive loss of neurons in the central nervous system (CNS) that leads to either functional loss or sensory dysfunction (Solanki et al., 2016). Research has indicated that neurodegenerative lesions are the most responsible for the gradual age-related cognitive decline that often precedes the onset of dementia in later life (Wilson et al., 2010). At the same time, as global demographics shift towards an older population, the incidence of dementia-related diseases, such as Alzheimer diseases (ADs) and Parkinson diseases, is also expected to rise sharply. Projections suggest that in the next 25 years, one in every four individuals in Japan could be living with dementia, with the prevalence potentially doubling in certain rural regions (Nakahori et al., 2021). Simultaneously, degeneration and loss of neurons, typically accompanied by pathological accumulation of different protein aggregates in the brain, could also lead to motor disorders in ageing individuals (Murthy et al., 2021). For instance, the noticeable decline in sensorimotor control and body functioning, this deterioration compromises both upper and lower limb function, critically impacting an older adult's capacity to conduct daily tasks and preserve autonomy (Seidler et al., 2010). The rapidly ageing trend might bring substantial pressure on healthcare infrastructure and the broader economy, considering NDDs tend to progress irreversibly, and currently, there are

minimal effective treatment options available (Hou et al., 2019; Kasajima et al., 2022). Given this context, identifying early markers of NDDs becomes crucial for detecting high-risk older patients, enabling timely evaluations and prompt interventions at the early stage (Verghese et al., 2007).

As two typical manifestations of functional decline associated with neurodegeneration, motor disorders and cognitive impairments have been shown to be interrelated in older adults. For example, people with mild cognitive impairment (MCI) often have impaired motor function (Aggarwal et al., 2006); low motor function, encompassing dexterity, gait, and hand strength, has been associated with accelerated declines in a range of cognitive domains, including global cognition, episodic memory, semantic memory, working memory, visuospatial abilities, and perceptual speed (Wang et al., 2023); a meta-analysis yet claimed that compare to upper limb function, poor performance in lower limb motor function, was more consistently associated with increased risk of developing dementia in older adults (Kueper et al., 2017). Pathology behind these associations could be the shared common brain regions and networks during motor regulation and cognitive processes, as indicated by neuroimaging studies (Montero-Odasso et al., 2017).

Furthermore, there is growing evidence suggesting that motor disorders could serve as a robust predictor for late-life dementia from middle age (Aggarwal et al., 2006; Verghese et al., 2007; Camargo et al., 2016; Wang et al., 2023). Cognitive decline precedes progression to dementia by several years (Wilson et al., 2011), however, motor disorders, appearing in the initial phases of aging, may precede cognitive decline by up to a decade (Skillbäck et al., 2022; Oveisgharan et al., 2024). Among all motor functions, gait disturbances, particularly slow gait in older adults, has been the most extensively studied due to its easily assessable characteristic (Figure 1). Previous study in 3,663 dementia-free old adults found that gait is slower to 7 years prior to clinical onset of dementia (Dumurgier et al., 2017), especially when considering non-ADs and vascular dementia (Beauchet et al., 2016). Gait disturbances, such as slowing and irregular stepping, are often observable before the diagnosis of MCI and can be predictive of the conversion from MCI to full-blown dementia (Montero-Odasso and Perry, 2019).

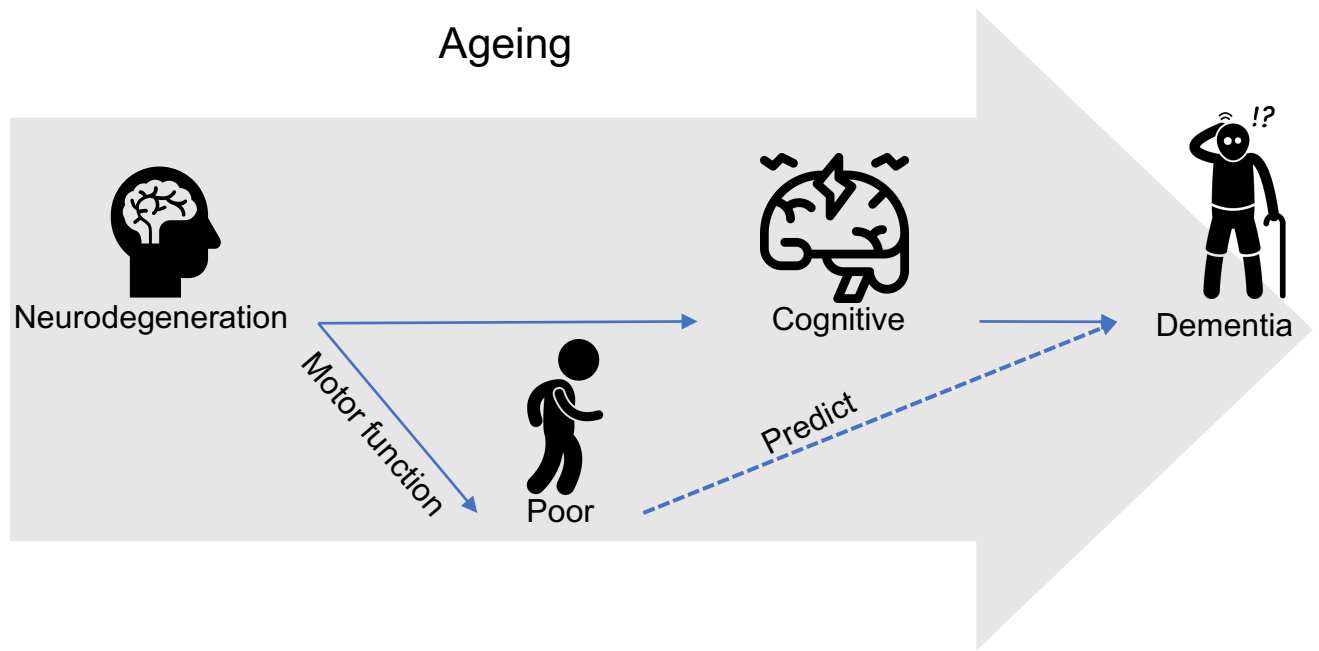


Figure 1. Conceptual model

Although poor gait is significantly related with incident dementia, the underlying pathologies have not been well addressed. Additionally, gait is multidimensional and cannot be fully encapsulated by a single characteristic. As technology has evolved, a significant breakthrough has been made with the recent invention of wearable sensors. This innovative device can measure various aspects of gait—including general, temporal, visual, and clearance factors—while allowing individuals to walk in their natural environment (Soulard et al., 2021). Therefore, in *Chapter 1*, I assessed gait using wearable sensors in a three-year cohort study. The aim was to explore both the cross-sectional and longitudinal relationships between comprehensive gait and global cognitive function, as well as six cognitive domains (Figure 2). This analysis was intended to shed light on the potential pathophysiological mechanisms underlying cognitive decline.

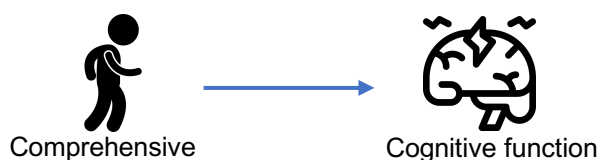


Figure 2. Conceptual model of chapter 1

Besides, also owing to the complexity of locomotion, gait regulation is associated with multiple age-related conditions. Impairments from other types of dysfunctions, such as musculoskeletal degeneration and cardiopulmonary conditions, could lead to the modest and varied predictive value of gait on future dementia, rather than being mainly attributable to CNS issues (Tian et al., 2021a). To redefine slow gait as a more accurate indicator of CNS problem, concurrent declines in gait speed and cognitive function are linked with increased risks of developing dementia in older adults (Collyer et al., 2022; Montero-Odasso et al., 2020, 2018; Tian et al., 2020). However, the internal mechanisms behind these dual declines in gait and cognitive functions are not well understood due to a limited number of studies examining their detailed characteristics. Consequently, *Chapter 2* of this study utilizes data from a well-characterized, age-specific cohort of 65-year-old Japanese community-dwelling older adults. This analysis aims to explore the association between dual declines in subjective gait speed and domain-specific cognition and the incidence of dementia (Figure 3). The hypothesis posits that identifying dual decline not only correlates with a higher risk of dementia but also provides insights into the varied underlying pathophysiologies related to personal characteristics. This understanding could facilitate targeted interventions to delay the onset of dementia.

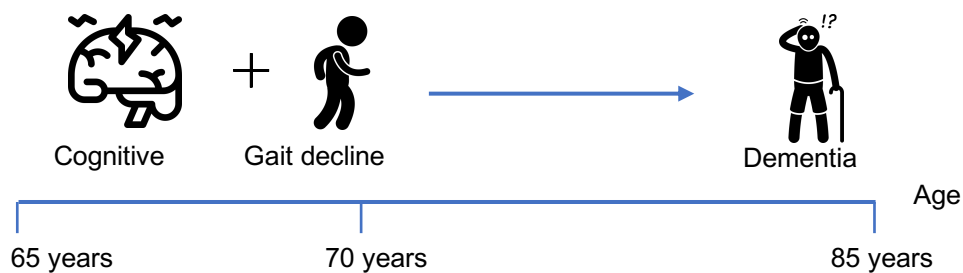


Figure 3. Conceptual model of chapter 2

Chapter 1: Association between comprehensive gait and cognitive function

Background

Dementia affects approximately 50 million individuals globally, with almost 10 million new cases emerging annually. This condition is particularly prevalent in Japan, which boasts the fastest ageing population all over the world. Projections indicate that by the year 2050, nearly 9% of Japan's population will be living with dementia (Sado et al., 2018). Dementia is typically diagnosed when acquired cognitive functional impairment has become severe enough to compromise social and occupational functioning (Hugo and Ganguli, 2014). The typical symptoms that dementia patients would possibly have are like easily forgottenness, troubling with understanding and communicating with other, difficulty finding words, and without knowing common facts (SantaCruz and Daniel L. Swagerty, 2001). Subsequently, the societal burden has been challenging a lot due to the rapid increasing number of people and the clinical features of dementia (Sado et al., 2018). However, those dilemmas can be greatly eased if we can find the way of early diagnosis so that we can help the patients live independently and using less long-term care service (Rasmussen and Langerman, 2019). So far, there are increasing evidences have been suggested that gait, the manner or style of walking, is able to be a predictive marker of dementia (Jamour et al., 2012).

Gait, the primary mode of human locomotion, is characterized by periods of loading and unloading of the limbs, facilitating movement and independence (Baker et al., 2016). Generally, gait consist of several quantifiable parameters such as speed, stride length, stride width and cadence. Several individual gait parameters have been reported to cross-sectionally and longitudinally correlate with global cognitive function in older adults, including self-preferred gait speed (Garcia-Pinillos et al., 2016), maximum gait speed (Umegaki et al., 2018), and stride length (Toots et al., 2019). Moreover, some studies demonstrated that gait also relates to domain-specific cognitive function. For instance, impaired gait velocity and reduced cadence were associated with worse executive function and immediate memory (Valkanova and Ebmeier, 2017). Mean walking speed and maximum walking speed were significantly associated with attention domain (Kaye et al., 2012).

Nevertheless, gait is multidimensional and cannot be fully encapsulated by a single characteristic. Previous applications of individual parameters failed to provide a comprehensive depiction of the association between gait and cognitive function. However, a breakthrough has been made with the recent invention of a wearable sensor, which can

measure a comprehensive gait—including general, temporal, visual, and clearance aspects—while allowing individuals to walk in their natural environment. In addition, acknowledging that quantitative gait parameters are closely interrelated and that their individual associations with cognitive function can be difficult to discern when adjusting for other gait variables (Verghese et al., 2007). Therefore, conceptual models employing techniques such as principal component analysis or factor analysis to simplify the framework for selecting grouped gait factors in gait analysis were proposed (Lord et al., 2013b). Under this circumstance, research that include gait parameters from different aspects and use conceptual model to systemically analyze gait and cognitive function is scarce.

Therefore, by employing a more advanced sensor, the goal of this study is to conduct a thorough examination of both the cross-sectional and longitudinal associations between comprehensive gait and cognitive function. This approach is aimed at establishing gait as a more credible marker for future dementia risk.

Methods

Participants

The Cognition and Activity in Rural Environment of Hokkaido Senior (CARE-DO) summer survey provided the data for this study. The CARE-DO project is a component of the 2016 Japan Gerontological Evaluation project (JAGES), a prospective cohort research. Additional papers have offered comprehensive details regarding JAGES (Kondo et al., 2018). To put it briefly, JAGES is an extensive panel study that looks at behavioral, social, and health-related issues among Japan's senior population. The 2016 wave of JAGES included over 200,000 individuals aged 65 and older who were not recipients of long-term care insurance, across 39 cities or towns in Japan. From this group, the baseline study of the CARE-DO invited residents aged 69-80 from six towns in Hokkaido to participate in the CARE-DO winter survey of 2017. This survey was designed to explore the impact of indoor temperature distribution on the health of the elderly in cold climates (Kojima et al., 2021). In 2018, all 569 participants who had responded to the 2017 winter survey were invited via postcard to partake in the CARE-DO summer survey conducted in September 2018. This survey, aimed at exploring the associations between gait and cognition in older adults, served as the baseline for the current study. The follow-up study was conducted three years later in 2021, in order to expand the sample size during Covid-19 pandemic, I still invited the participants from the CARE-DO winter survey 2017.

At baseline, 307 participants from the CARE-DO winter survey of 2017 attended, and two requested their partners to attend in their place. Given the small sample size, these substitutions were also accepted, maintaining the baseline participant count at 309. At the follow-up stage, 208 participants from the CARE-DO winter 2017 survey responded. Among these, 136 individuals who attended both the 2018 and 2021 studies were considered follow-up participants.

Both baseline and follow-up study included four parts of examination: physical examinations, gait and cognitive assessments, and a self-administered questionnaire. During the physical examination, height and weight were measured using the appropriate scale, and Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. Following completion of all assessments, participants received a self-administered questionnaire to provide information on sex, age, functional activity, and disease history, including diabetes (yes or no) and hypertension (yes or no). They were expected to return the questionnaire within two weeks. Functional activity was assessed using the Instrumental Activities of Daily Living (IADL) score, derived from a subtest of the Tokyo Metropolitan Institute of Gerontology Index of Competence. This validated 13-item self-reported index measures functional capacity, with higher scores indicating better functionality (Koyano et al., 1991a). After excluding 21 participants due to missing baseline data on cognitive and gait assessments; one due to depression; three with Parkinson's disease or ADs; five with a history of stroke; 35 with musculoskeletal pain; and eight who had experienced a fall or had a bone fracture at baseline, 236 participants were considered valid for the cross-sectional analyses. In the longitudinal analyses, an additional five participants were excluded due to missing follow-up cognitive assessment data, resulting in 131 subjects being included in the analyses (Fig.4).

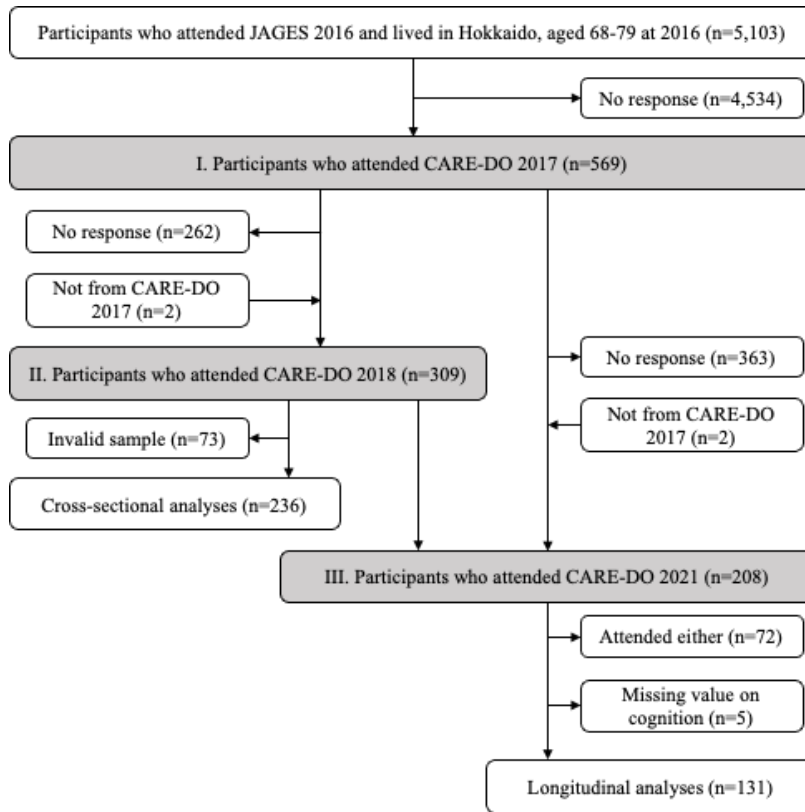


Figure 4. Population of the CARE-DO study

This study was approved by the ethics committee of the Graduate School of Medicine, Hokkaido University (no.18-025), all the experiment protocol for involving human data was in accordance with the relevant guidelines. A written informed consent was obtained from all the participants.

Baseline gait measurement

All participants were asked to walk at their self-selected speed in a round trip of a 6-meter straight path. Gait was measured using Physilog® sensors (GaitUp®, Switzerland). These devices include two small, lightweight (19 g) inertial sensors, one for each foot, attached to the dorsum of the foot with elastic straps. The Gait Analyzer software version 3.1 (GaitUp) was utilized to analyze the data on a Windows personal computer (Figure 5). The two sensors on both feet could synchronize wirelessly, and no calibration was necessary before or during the measurement (Figure 6). The placement of the



Figure 5. Gait sensors

sensor on the foot did not influence the measurements (Mariani et al., 2010). 21 kinematic gait parameters were recorded with this device, which could be divided into four categories: general (cycle duration, cadence, stride time, stride velocity, and turning angle); temporal (stance, swing, loading, foot-flat, pushing, and double support); spatial (peak angle velocity, swing speed, strike angle, lift-off angle, swing width, and three-dimensional (3D) path length); and clearance (maximum heel clearance, maximum toe clearance 1, minimum toe clearance, and max toe clearance 2). There are more publications that support the validity of this gait evaluation (Soulard et al., 2021). The gait cycle duration metric was not included in the analysis because it is simply a different way of representing cadence. The Gait Analyzer's default operation automatically removed data acquired during acceleration, deceleration, and turning. For the analysis, the means from both feet were employed. You can get more information about these settings in Additional File 1.

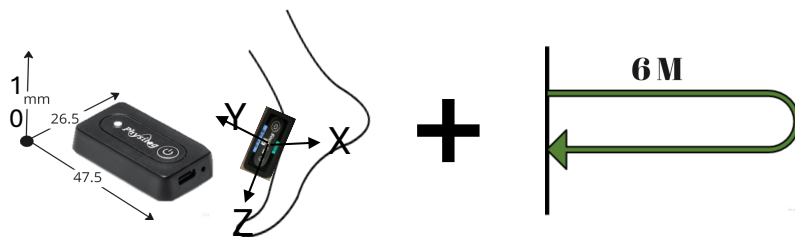


Figure 6. Gait assessment

Baseline and follow-up cognition measurement

Global cognitive function was evaluated using the Japanese version of the Montreal Cognitive Assessment (MoCA-J) through face-to-face interviews. The MoCA-J is a one-page 30-point test and has been reported to have good internal consistency reliability (Cronbach's $\alpha = 0.74$), MCI was defined as MoCA-J score less than 26 (Fujiwara et al., 2010). The total evaluation period was approximately 15 minutes, with higher scores indicating better cognitive function. To account for the effect of education, participants with less than 12 years of education added one point to their total score. Internal subtests of the MoCA-J assessed six cognitive domains: memory (five points): delayed recall; executive function (four points): letter fluency, trail making, verbal abstraction; visuospatial (four points): cube copy, clock drawing; language (five points): naming, sentence repetition; attention (six points): digit span forward and backward, letter A tapping, serial-7 subtraction; and orientation (six points): orientation to date and place (Ota and Suzuki, 2013).

Statistical analysis

Because of the various scales before analysis, all 20 baseline gait characteristics were first standardized to have a mean of zero and a standard deviation of one. In order to minimize the higher number of highly correlated variables to a smaller number of uncorrelated independent predictors, factor analysis using the principal component approach was then carried out. We performed an orthogonal quartimax rotation on the starting factors. The predominant contributions to the primary components were thought to be the gait parameters with a rotational loading of >0.5 . The original gait parameters were interpreted, and the name was tagged accordingly.

The relationship of the retained baseline gait factors with both baseline MoCA-J score and MoCA-J score after 3-year follow-up were examined using generalized linear model. Tertiles were developed for each gait element due to the low overall score of each cognitive subtest and possible bias from using the linear regression model directly. Using the least square mean value, the mean value for each group was modified for age, sex, height, and education. The linear regression model was used to evaluate the relationships and test for trends based on a variable that contained the median value for each tertile. This study considered age, sex, height, weight, educational status, presence of diabetes and hypertension, and baseline IADL scores as confounding factors. At $P<0.05$, statistical significance was established. SAS software was used for all statistical analyses (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

The baseline study included 125 male and 111 female with an average age of 75.1 years. Approximately 45% of the participants had hypertension, 14% had diabetes and 72% had MCI. The follow-up participants were 68 male and 63 female, around 45% of them had hypertension, 13% had diabetes and 66% had MCI at baseline (Table 1).

Table.1 Participants' characteristics at baseline and follow-up

		Baseline participants (N=236)		Follow-up participants (N=131)	
Age (years)	mean (SD)	75.1	2.8	75.1	2.7
Sex	n (%)	125	53.0	68	51.9
male					
female		111	47.0	63	48.1
Height (m)	mean (SD)	157.2	8.0	157.1	7.9
Weight	mean (SD)	57.9	10.0	58.1	10.1
BMI	mean (SD)	23.4	3.2	23.4	3.2
12 years of Education	n (%)	185	78.4	97	74.1
IADL score	mean (SD)	12.3	1.1	12.4	1.1
Gait measurements					
stride length(m)	mean (SD)	1.1	0.1	1.1	0.1
speed (m/s)	mean (SD)	1.0	0.2	1.0	0.2
cadence (steps/minute)	mean (SD)	114	11.0	115	10.9
stance (seconds)	mean (SD)	0.7	0.1	0.7	0.1
Medical histories					
hypertension	n (%)	107	45.3	59	45.0
diabetes	n (%)	32	13.6	17	13.0
Cognitive measurements					
MCI	n (%)	171	72.5	86	65.7
MoCA-J (points)	mean (SD)	23.4	3.2	23.8	3.0
executive (0-4)	mean (SD)	2.6	1.1	2.6	1.1
language (0-5)	mean (SD)	3.9	0.8	3.9	0.8
memory (0-5)	mean (SD)	2.4	1.9	2.4	1.9
orientation (0-6)	mean (SD)	5.7	0.6	5.7	0.6
visuospatial (0-4)	mean (SD)	3.5	0.8	3.5	0.8
attention (0-6)	mean (SD)	4.9	1.2	4.9	1.2

Note. BMI, body mass index; IADL, instrumental activities of daily living; MoCA-J, Japanese version of Montreal Cognitive Assessment; MCI, mild cognitive function.

Four orthogonal components were identified by a factor analysis using quartimax rotation, and these factors collectively explained 89.17% of the variation observed in 20 gait characteristics (Table 2). The "General Cycle" element was identified as the one that caused the greatest variance and was typified by significant loadings on stance, cadence, foot-flat, stride velocity, double support, swing, swing speed, and peak angle velocity. The second element was found to be the "Initial Contact" factor, which is a function of the striking angle, maximum toe clearance, stride length loading, and 3D path length. The third element, referred to as "Propulsion," had substantial loadings on the angle of push-off and lift-off. The "Mid-Swing" element was the last and fourth component, as shown in Fig. 7, and it placed a strong emphasis on maximal toe and heel clearance. Lower scores on the General Cycle and Propulsion factors indicate better gait performance, whereas higher scores on the Initial Contact and Mid-Swing factors are indicative of superior gait quality.

Table. 2 Factor loading of twenty gait variables on the four independent gait factors rotated and extracted by factor analysis

gait variables	General cycle	Initial contact	Propulsion	Mid-swing
stance (s)	0.97			
cadence (steps/minute)	-0.95			
foot-flat (s)	0.90			
stride velocity (m/s)	-0.82			
double support (s)	0.79			
swing (s)	0.75			
Swing speed (m/s)	-0.74			
peak angle velocity	-0.73			
strike angle (degree)		0.90		
max toe clearance 2 (m)		0.84		
stride length (m)		0.82		
loading (s)		0.79		
3d path length (meters)		0.71		
pushing (s)			0.89	
lift off angle (degree)			0.68	
max heel clearance (m)				0.85
max toe clearance 1(m)				0.82
variance explained (%)	43.27	24.56	13.31	8.03

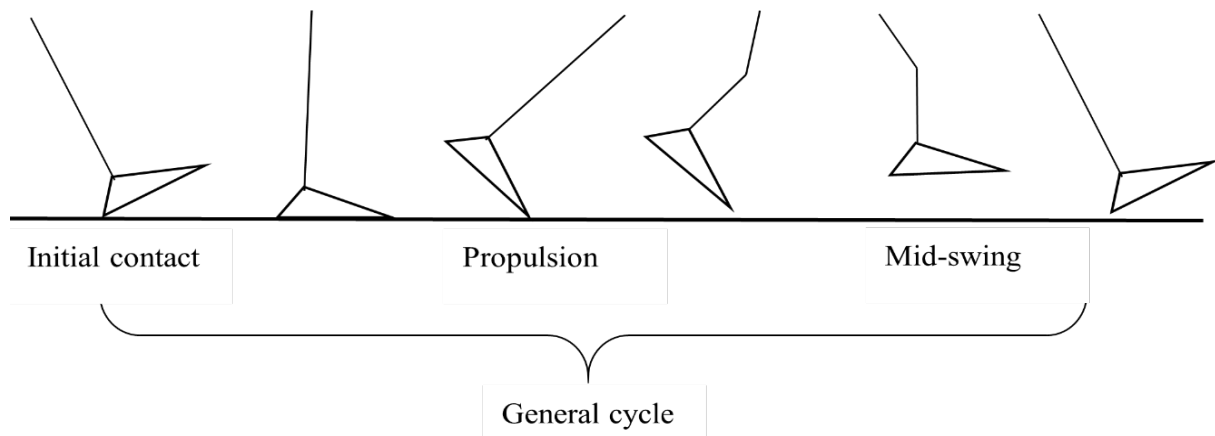


Figure 7. Illustration of the four gait factors

Cross-sectional associations

In terms of global cognitive performance, the MoCA-J score is positively correlated with initial contact and mid-swing factor, and negatively correlated with general cycle and propulsion factor. In the crude model ($\beta = -0.76$ [-1.14, -0.37]), the general cycle factor exhibited significant associations with global cognitive function; in the model adjusted for age, sex, height, and weight ($\beta = -0.58$, [-0.96, -0.21]), and in the model adjusted for diabetes, hypertension, and IADL scores ($\beta = -0.58$, [-0.95, -0.20]) (Table 3).

Table 3. Cross-sectional associations between grouped gait factors and global cognitive function assessed by generalized linear models (N=236)

Cross-sectional associations				
Model	β	Wald 95% Confidence Limits		P
Model 1				
General cycle	-0.76	-1.14	-0.37	<0.001
Initial contact	0.42	0.02	0.82	0.039
Propulsion	-0.06	-0.46	0.34	0.768
Mid-swing	0.24	-0.17	0.65	0.266
Model 2				
General cycle	-0.58	-0.96	-0.21	0.002
Initial contact	0.30	-0.09	0.69	0.129
Propulsion	-0.19	-0.58	0.21	0.352
Mid-swing	0.25	-0.18	0.68	0.255
Model 3				
General cycle	-0.58	-0.95	-0.20	0.003
Initial contact	0.26	-0.14	0.65	0.201
Propulsion	-0.22	-0.61	0.18	0.286
Mid-swing	0.25	-0.18	0.68	0.257

Note.

Model 1 crude model

Model 2 adjusted for age sex and height

Model 3 adjusted for age, sex, height, education, I-ADL, diabetes and hypertension

Significant differences were observed between the executive domain and the general cycle factor ($P=0.012$) and initial contact factor ($P=0.019$) with respect to the individual cognitive domains. Higher executive function scores were associated with better performance in gait speed and initial contact (Table 4).

Table 4. Cross-sectional associations of gait factors with domain-specific cognitive function in all participants

Factor		Executive	Language	Memory	Orientation	Visuospatial	Attention
General cycle	low	2.91	3.70	2.93	5.75	2.58	5.09
	moderate	2.76	3.79	2.78	5.80	2.69	4.93
	high	2.54	3.81	2.57	5.65	2.57	4.89
	<i>P</i> for trend	0.012	0.654	0.045	0.264	0.875	0.304
Initial contact	low	2.53	3.84	2.74	5.74	2.58	4.96
	moderate	2.72	3.76	2.77	5.71	2.64	4.92
	high	2.96	3.70	2.77	5.75	2.63	5.03
	<i>P</i> for trend	0.019	0.240	0.993	0.979	0.764	0.636
Propulsion	low	2.80	3.68	2.82	5.70	2.61	5.07
	moderate	2.66	3.91	2.60	5.83	2.64	4.91
	high	2.75	3.71	2.85	5.67	2.60	4.94
	<i>P</i> for trend	0.943	0.508	0.503	0.824	0.849	0.558
Mid-swing	low	2.56	3.70	2.87	5.61	2.54	4.91
	moderate	2.85	3.86	2.64	5.79	2.74	5.03
	high	2.79	3.73	2.76	5.79	2.56	4.97
	<i>P</i> for trend	0.218	0.870	0.598	0.103	0.646	0.968

Note. All scores are displayed as least-squares mean values adjusted by age, sex, education and height; linear regression models were adjusted for age, sex, education, I-ADL, height, diabetes and hypertension and test for equal medians

Longitudinal associations

In the crude model, the general cycle factor exhibited significant longitudinal associations with global cognitive function ($\beta = -0.69$ [-1.31, -0.08]). The model was further adjusted for age, sex, height, and weight ($\beta = -0.63$, [-1.24, -0.02]), and significances disappeared in the model additionally adjusted for medical histories and IADL scores ($\beta = -0.51$, [-1.07, -0.05]). Six cognitive domains and gait characteristics did not show any significant longitudinal relationships (Table 5 and Table 6).

Table 5. Longitudinal associations between grouped gait factors and global cognitive function assessed by generalized linear models (N=131)

Longitudinal associations				
Model	β	Wald 95% Confidence Limits		<i>P</i>
Model 1				
General cycle	-0.69	-1.31	-0.08	0.027
Initial contact	0.13	-0.48	0.75	0.668
Propulsion	0.59	0.00	1.19	0.051
Mid-swing	0.30	-0.43	1.03	0.419
Model 2				
General cycle	-0.63	-1.24	-0.02	0.044
Initial contact	0.20	-0.41	0.82	0.519
Propulsion	0.54	-0.07	1.14	0.083
Mid-swing	0.15	-0.59	0.89	0.696
Model 3				
General cycle	-0.51	-1.07	0.05	0.076
Initial contact	0.24	-0.30	0.79	0.381
Propulsion	0.51	-0.02	1.05	0.059
Mid-swing	0.15	-0.50	0.81	0.644
Note.				
Model 1 crude model				
Model 2 adjusted for age sex and height				
Model 3 adjusted for age, sex, height, education, I-ADL, diabetes and hypertension at baseline				

Table 6. Longitudinal associations of gait factors with domain-specific cognitive function in all participants

Factor		Executive	Language	Memory	Orientation	Visuospatial	Attention
General cycle	low	2.53	4.05	2.88	5.67	3.56	4.93
	moderate	2.86	3.86	2.18	5.66	3.48	4.86
	high	2.48	3.75	2.16	5.61	3.39	4.84
P for trend		0.794	0.136	0.683	0.879	0.597	0.906
Initial contact	low	2.40	3.86	1.84	5.60	3.44	4.70
	moderate	2.73	3.86	2.68	5.68	3.48	4.82
	high	2.75	3.93	2.68	5.66	3.50	5.11
P for trend		0.333	0.777	0.091	0.787	0.721	0.244
Propulsion	low	2.53	3.77	2.21	5.53	3.49	4.88
	moderate	2.70	3.86	1.73	5.75	3.52	4.82
	high	2.64	4.02	3.27	5.66	3.41	4.93
P for trend		0.588	0.124	0.070	0.348	0.229	0.815
Mid-swing	low	2.49	3.79	2.37	5.74	3.47	4.74
	moderate	2.68	3.93	2.59	5.57	3.39	4.91
	high	2.70	3.93	2.25	5.64	3.57	4.98
P for trend		0.967	0.316	0.870	0.457	0.458	0.679

Note. All scores are displayed as least-squares mean values adjusted by age, sex, education and height; linear regression models were adjusted for age, sex, education, height, I-ADL, diabetes and hypertension and test for equal medians

Discussion

In this 3-year cohort study, it was found that, the general cycle (speed-related gait performance) is associated with global cognitive function cross-sectionally and longitudinally among older adults aged 70–81 years; regarding on the specific cognitive domains detected by MoCA-J, better general cycle and initial contact phase related to better executive function, and significances were only found in cross-sectional study but not longitudinal study.

To the best of my knowledge, when analyzing the relationship between gait and cognitive function, this is the first research to incorporate a complete set of gait data that span almost the whole gait phase. Various methods such as stopwatches, electronic walkways, body-worn sensors, electromyography, and 3D motion analysis have been employed in gait analysis up to this point (Baker et al., 2016; Lord et al., 2013b). This study utilized an easily wearable sensor to measure 3D gait. Renowned for its accuracy, 3D motion analysis is considered the gold standard in gait assessment (Lord et al., 2013a). Additionally, the conceptual models were employed to condense different gait factor characteristics. There were several prior studies have also used a conceptual model (Darweesh et al., 2019a; Hollman et al., 2011; Lord et al., 2013b; Verghese et al., 2007; Verlinden et al., 2013), but all of the earlier research used a walkway (GAITRite, CIR System Inc.) to conduct gait evaluations. These walkways are only capable of monitoring temporal (time for swing, stance, single and double support, and turning) and general (velocity, width, cadence, and stride time) characteristics. In contrast, by assessing spatial and clearance elements, such as initial contact, propulsion, and mid-swing, the sensors employed in this study were able to give a more thorough examination of gait. As a result, our results provide a more comprehensive picture of the link between gait and cognitive performance and are more accurate than those of prior research employing less sophisticated approaches.

The current results demonstrated that general cycle factors (predominantly consist of cadence, speed, and stance time) were significantly associated with global cognitive function in both cross-sectional study and longitudinal study. Older adults who had worse performance on speed-related gait were inclined to have poor cognitive function at baseline and after a 3-year follow-up. The shared brain lesions associated with both gait and cognitive function, such as an increased percentage of periventricular and subcortical white matter hyperintensities, atrophy of the medial temporal areas, and hippocampal atrophy, can be referred to as the internal biomechanism, according to earlier research (Beauchet et al., 2019),

or small gray matter volumes based on magnetic resonance imaging in the bilateral cortex and subcortical areas might reduce the pace of walking while also affecting cognitive performance (Peel et al., 2019). Moreover, current research has started examining the biomechanism relating to several factors and cognitive function. For example, increased double support duration has been associated with higher brain amyloid- β deposition (Wennberg et al., 2018). Therefore, a stronger and more distinct link between gait and cognitive performance might be developed by adding more gait-related factors.

There was no discernible correlation between the recently discovered initial contact, propulsion, and mid-swing parameters and overall cognitive performance. While prior research has shown a link between cognitive function and stride length, which is a component of the first contact factor, our results did not support this hypothesis (Savica et al., 2017), nonetheless, their association was likely impacted by the substantial correlation with gait speed. Furthermore, electrocortical activity gradually drops throughout the pre-swing and acceleration phases, according to research on the dynamics of the brain while walking (Pauw et al., 2019). Furthermore, this result would suggest that the general cycle factor—which encompasses postural control traits like foot-flat and double support—has a stronger correlation with overall cognitive performance than the preceding phases.

Studies on gait factors and cognitive domains showed varied results from previous studies. For example, the current study found significant association of baseline general cycle and initial contact with baseline executive function. The recently found initial contact, propulsion, and mid-swing factors did not show any significant relationship with total cognitive function. Although previous studies have shown a connection between stride length, a first contact factor, and cognitive performance, our findings did not corroborate this theory (Diamond, 2013) nonetheless, their relationship was probably influenced by the strong correlation with gait speed. Additionally, studies on the dynamics of the brain while walking have shown that electrocortical activity gradually decreases during the pre-swing and acceleration phases (Yogev et al., 2008). Furthermore, compared to the earlier phases, this finding would indicate a larger association between the general cycle component and overall cognitive performance. This factor includes postural control qualities like foot-flat and double support (Nadkarni et al., 2012). However, the associations disappeared in longitudinal study, which is different from the previous ones (Callisaya et al., 2015; Cohen et al., 2016). In addition, some individual gait parameters were also reported to have a significant relationship with language,

memory and attention (Montero-Odasso et al., 2012). After being detained by the factor analysis, combined gait characteristics did not show any relationship with those domains. Besides, , no significance were found regarding on the other rarely studied two domains: orientation and visuospatial in this study (Duff et al., 2008). The limited sample size may have contributed to the variability observed in the data, potentially obscuring significant relationships that might be apparent in a larger sample. Future research included a larger and more diverse sample to enhance the robustness and generalizability of the findings is warranted.

Even though this study's advanced equipment and conceptual models enable more thorough and accurate gait evaluations, the following study-related issues still demand discussion: First, because the gait characteristics were being measured across a short walking distance, the first and last two cycles were not omitted. Despite the fact that several studies have shown that the beginning and end of a gait are occasionally thought to be unstable and erroneous (Ferreira et al., 2019). It was also claimed by other studies, that older adults need to walk at least four cycles to reach a steady-state walking speed (Lindemann et al., 2008). Secondly, there was no thorough cognitive battery included during the cognitive exam; just the MoCA-J questionnaire was used. While the MoCA was shown to be a useful tool for assessing global cognition, there are still some worries that the internal subtests for some domains are not sensitive or specific enough to detect deficits in language or attention (Hendershott et al., 2017; Julayanont et al., 2014). Therefore, to ensure the accuracy of cognitive function assessments, especially when exploring different cognitive domains, future research should include extensive neuropsychological batteries. Additionally, it is important to note that the participants in this study were older than 70 years, with more than 70% having MCI. This is higher than the typical prevalence of MCI among older adults, which usually ranges between 3% and 42% (Tricco et al., 2012). The atypical MCI prevalence observed in this study may be associated with potential physical functional impairments and the disease history of the participants, which were not excluded prior to analysis. This limitation may affect the generalizability of the results to a broader population.

Conclusion

This study included a wide variety of gait characteristics and employed modern gait assessment techniques, however only the general cycle and global cognitive performance showed significant relationships. Furthermore, this study demonstrated the robust cross-sectional relationships between gait and executive function; however, no meaningful longitudinal relationships were discovered between gait and any of the cognitive domains. To identify the causal relationship between gait and cognitive performance, more comprehensive neuropsychological testing and a larger sample size will be required in future studies.

Additional file 1. Definition of each gait parameter

One cycle's duration is expressed in cycle duration (seconds).

The number of cycles in a minute is known as cadence (step/minute).

The distance, measured in meters, between the heels of two consecutive footsteps on the ground, one cycle apart, is called the stride length.

Miles per second, or stride velocity, is the forward speed of one cycle.

The angle on a horizontal plane between two successive foot-flat phases of the same foot is called the turning angle (degree).

The moment a foot touches the ground is known as the stance (second).

The moment a foot is in the air and not in contact with the ground is called a swing (second).

The moment between the heel strike and the foot landing flat on the ground is known as loading (second).

Foot-flat(second): the moment a foot touches the ground completely flat

The moment the toe lifts off the ground and the foot is flat on the ground during takeoff is known as pushing (second).

At double support (second), both feet must contact the ground.

The maximal angular velocity during the swing phase, between the maximum heel clearance and the minimum toe clearance, is known as the peak angle velocity (degree/s).

The greatest forward speed of the foot during a swing is known as the swing speed (meters/s).

The angle formed on a vertical plane during heel strike between the foot and the ground is known as the striking angle (degree).

The angle of the foot near the conclusion of the push phase, right before takeoff, is known as the lift-off angle (degree).

The maximal lateral excursion of the foot during swing is measured in swing width (meters).

The length of the foot's actual route in three dimensions, including swing breadth and stride length, is measured in meters and is called 3D path length.

The highest point the heel may reach above the ground in a cycle is called the maximum heel clearance (meters).

Maximum Toe Clearance The highest point that the toes may reach above the ground after heel max clearance is 1 (meters).

The lowest height of the toes during the swing phase is known as Min. Toe Clearance (in meters).

The highest point the toes may reach above the ground just before to heel impact is called Max. Toe Clearance 2 (meters).

Chapter 2: Dual decline in gait speed and domain-specific cognition, and the relationship with incident dementia

Background

The number of older adults got dementia is increasing rapidly in most areas of the world. It is projected that by 2050, older adults will constitute 40% of the Japanese population, with over 25% of these individuals expected to be affected by dementia (Nakahori et al., 2021). It is therefore suggested that seeking early markers of cognitive dysfunction and dementia is crucial for the prevention and intervention.

Poor gait, as the sign of increased age, is proved to be a strong predictor of various adverse health outcomes, including MCI and dementia-related diseases (Darweesh et al., 2019b; Rasmussen et al., 2019; Verghese et al., 2008). Recent studies have shown that a decline in gait may precede cognitive deterioration and has been associated with ADs for multiple years (Skillbäck et al., 2022). However, the predictive value of gait measurements can be subtle and change across studies. This variation is due to its association with multiple conditions that related with age, such as CNS deficits, musculo-skeletal degradation, and cardio-pulmonary conditions (Tian et al., 2021a).

In order to better categorize slow gait as a more accurate sign related with CNS issues, researchers demonstrated that the combined features of slow gait and cognitive impairments, such as the simultaneous presence of cognitive complaints and slow gait, known as motoric cognitive risk syndrome (Verghese et al., 2014), or the combination of slow gait with low activity fragmentation—an indicator of reduced higher-order cognition—has shown a stronger association with dementia risk than either characteristic alone (Verghese et al., 2013). Furthermore, recent papers indicates that instead of one time-point event, dynamic decline in walk speed and cognition, such as simultaneous declines in memory and walk speed, are related with higher risks of developing dementia in senior adults. These longitudinal observations have demonstrated better goodness-of-fit in predicting outcomes compared to assessments at a single time point (Collyer et al., 2022; Montero-Odasso et al., 2020, 2018; Tian et al., 2020).

However, the number of studies investigating the internal mechanisms behind dual declines in gait and cognitive functions is limited, with only four published studies to date (Montero-Odasso et al., 2020; Tian et al., 2020; Verghese, 2022; Collyer et al., 2022). Further research

is needed to explore the pathophysiological profiles and personal characteristics of individuals experiencing such declines. This additional insight is essential to understand the underlying mechanisms potentially involved (Tian et al., 2023). Furthermore, research on these findings within Asian populations is scarce, highlighting the need for studies that examine potential similarities and differences across ethnic groups. Additionally, the path of decline in gait and cognitive function vary significantly across different age groups (Murman, 2015; Lee et al., 2019). Previous studies suggest that motor and cognitive declines begin after midlife, initially progressing at a slow pace and then accelerating after the age of 70 (Aartsen et al., 2002; Zaninotto et al., 2018; van der Willik et al., 2020). Given these variations, current studies that recruit participants across a wide age range, from 60 to 97 years, may face challenges in identifying common characteristics and potential causes for dual declines.

Therefore, this study utilized data from a well-characterized, age-specific cohort of 65-year-old Japanese community-dwelling older adults, with all participants provide detailed information on demographic characteristics, life habits, and four cognitive batteries, by which I decided to explore the association of dual decline in gait speed and specific cognitive domains with the incidence of dementia in this population. It was hypothesized: 1) older adults with dual decline might presented unique characteristics at baseline, and this could offer insights into the diverse underlying pathophysiologies associated with gait and dementia onset; 2) the dual decline group would have a higher risk of incident dementia than single decline and no decline group. Those understandings together could enable targeted preventative measures to delay the dementia onset.

Methods

Participants

Data obtained in this study were from The New Integrated Suburban Seniority Investigation (NISSIN) Project, which is an ongoing, age-specific, prospective cohort study conducted in Nisshin City, Aichi Prefecture, Japan. From 1996 to 2005, researchers invited individuals approaching the age of 65 to undergo a health check-up and to complete a self-administered questionnaire. When participants reached the ages of 70, researcher asked them to come again to attend the follow-up health check-ups and additional questionnaire surveys. If the participants were still in the city but did not go to attend the follow-up sessions, municipal public health nurses would go to a home visit and conduct the face-to-face interview to finish the questionnaires. After 2000, all of the participants were monitored, and incidence of

disability were traced under the Japanese Long-term Care Insurance (LTCI) system. Further details on the NISSIN Project have been published in prior studies (Kitamura et al., 2009). Finally, 3,073 older adults provided us with their informed consent and take the initial investigation at ages 64 or 65. However, as cognitive evaluations were conducted only during the 1997-2001 health check-ups, the data of 1,530 recruited in 1996 and after 2001 were ignored. Additionally, 698 participants who did not respond the follow-up investigations were excluded. I further excluded the data of seven individuals who were considered being dementia, moved out, or died before reaching the age of 70. Also, 192 of them who declined to take the cognitive assessments at baseline and another 153 who declined at follow-up were excluded. Lastly, I excluded 11 subjects with any incomplete values in any cognitive or gait speed tests in either survey. Ultimately, 482 participants were finally included and put into the analyses (Figure 8).

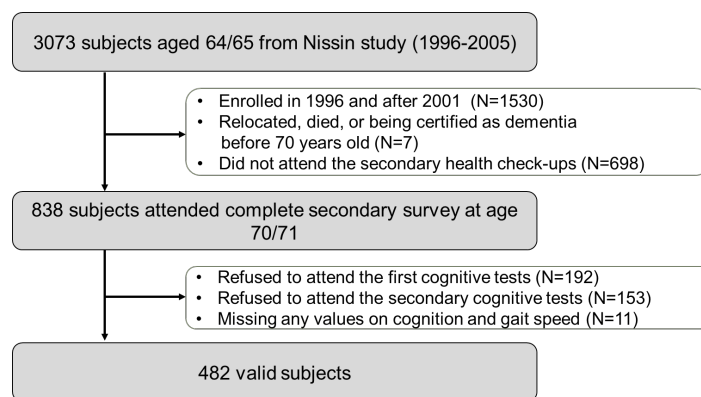


Figure 8. Flow diagram of study enrollments

This study was approved by the ethics committees of the Nagoya University Graduate School of Medicine, the National Center for Geriatrics and Gerontology of Japan, the Aichi Medical University School of Medicine, and the Hokkaido University Graduate School of Medicine in accordance with the Helsinki Declaration of 1975. All the participants provided informed consent, with oral informed consent until 2001 after which written consent was provided through an opt-out approach.

Subjective gait speed

Subjective gait speed was measure by asking the question: “How do you feel about your walking speed during the past year?” during the self-administered questionnaire conducted at baseline and follow-up. Participants could select from these three answers: “Fast”, “Normal”, and “Slow”. Decline in gait speed was defined as the answers changed from “Fast” to

“Normal” or “Slow”, or from “Normal” to “Slow”, based on the responses in the questionnaire conducted at follow-up compared to the initial survey at baseline.

Domain-specific cognition

In this study, measurements were made across four cognitive areas. The Alzheimer's Disease Assessment Scale (Homma et al., 1992)) was used to assess memory (word recall [WR]); the Wechsler Adult Intelligence Scale-revised (Shinagawa et al., 1990) was used to assess verbal memory and working memory (forward digit span [forward-DS] and backward digit span [backward-DS]); and the Stroop color and word test (Sisco et al., 2016) was used to measure processing speed (interference ratio [IR]). Every assessment was carried out by knowledgeable investigators. Cognitive decline was defined as falling into the lowest tertile of each cognitive test's 5-year change.

Follow-up outcomes

Dementia was diagnosed using the disability standard under the LTCI system in Japan by standardized physicians. The LTCI is an obligatory program for all adults aged 40 years or older in Japan (Iwagami and Tamiya, 2019). The system categorizes dementia-related symptoms and care needs into eight levels: 0, I, IIa, IIb, IIIa, IIIb, IV, and M. Level 0 indicates the absence of dementia-related symptoms and the absence of need for disability care, while level M indicates serious mental and behavioral impairments or a physical condition that needs specialized medical support. If a person was certified as grade greater than IIa, then he/she shall be considered as having dementia. A previous study validated this dementia criterion with a sensitivity of 73% and specificity of 96% (Noda et al., 2018). Participants' deaths and evictions were under surveillance by the city's Basic Resident Register.

Dementia status, deaths cases and relocation situation are collected annually. Follow-up period was calculated at the second day of the second survey and continues till the end in the year in which the participant reaches age 85. For example, follow-up for attendants in 2001 will continue until December 31, 2021.³ The follow-up period for participants recruited in 2001 will continue until December 31, 2021.

Baseline personal information

Baseline lifestyle data and socio-demographic were collected through a self-administered questionnaire, including sex, weight, height, educational background (junior high school or below, high school, college, or college or above), year of participation (1997-2001), marital status (married or other), living arrangement (living alone or other), alcohol consumption (current alcohol consumption, other), smoking (never smoked, former smoker, current smoker), depressive symptoms (Japanese version of the Geriatric Depression Scale 15), social activities and regular exercise habits (yes or no), and medical history (yes or no). BMI was calculated by dividing weight in kilograms by the square of height in meters. A score greater than 6 on the Geriatric Depression Scale 15 Japanese version is considered an indicator of depressive symptoms (Sugishita et al., 2017). Using a subtest of the Tokyo Metropolitan Institute of Gerontology Index of Competence in health check-ups, functional activity was assessed as a I-ADL score (Koyano et al., 1991b). A scores greater than 11 is considered as self-independent (Okabayashi et al., 2019). Medical histories were recorded by asking the participants whether they have or once had hypertension, hyperlipidemia, diabetes, cardiovascular diseases (CVDs), cerebrovascular diseases (CVAs), arthritis. If the participants have or once had the history of both CVDs and CVAs, he/she will be considered as having morbidities. Social activity was asked in a 20-question scale while doing the self-administered questionnaire, it included the aspects of work status, socially relevant activities, learning activities, and personal activities. A total measure of social activity was calculated regarding on guidelines published in a published paper, and it is specified that a score of ≥ 8 was a high level of social activity (Aoki et al., 1996).

Statistical methods

Regarding on declines in subjective gait speed and cognitive performance across each test (WR, IR, forward-DS, and backward-DS), participants were classified into four groups. Taken WR group as an example, the "dual decline" group includes individuals who experienced a change in subjective gait speed from baseline to follow-up and were in the lowest third for cognitive decline in WR tests. Likewise, the "pure gait decline" group consists of those with a subjective gait speed change during the same period but who fell within the highest two-thirds in WR test changes. The "pure cognitive decline" group comprises individuals did not have changes in gait speed but at the same time in the lowest third of WR test changes. Lastly, the "no decline" group includes those without changes in subjective gait speed and who are in the highest two-thirds of WR test changes.

Differences across the dual decline group and the no decline group were compared using Chi-square tests. To explore the survival data and validate the assumptions underlying the Cox proportional hazards model, the non-parametric cumulative incidence curves were plotted. Then, cox proportional hazards regression models with "no decline" group as the reference were performed to calculate hazard ratios (HRs) as well as confidence intervals (CIs) for dementia onset. Additionally, death was modeled as a competing risk using Fine and Gray's sub-distribution hazards model (Austin and Fine, 2017). Subdistribution hazard ratio (sHR) were calculated in competing risk models. I also performed linear contrasts of relevant coefficients in all tests to determine if dual decline has significantly higher risks of dementia than pure gait as well as cognitive decline. Adjustments for confounders included sex, year of participation, educational background, smoking status, living arrangements, medical histories, total social activity measures (≥ 8 ; < 8), and regular exercise habits. To verify the robustness of the model results, I conducted survival risk analyses up to the ages of 80 (I did not perform the analyses in 5-year follow-up due to the extreme small incident dementia cases: only 8). Statistical significance was defined as a two-sided *P* value of less than 0.05. I used SAS Enterprise Guide (version 7.15; SAS Institute Inc., Cary, NC, USA) to perform the statistical analyses.

Results

The current study analyzed 482 65-year-old older adults. Over an average 12.5-year follow-up, 34 participants moved out, 64 died, and 111 were identified as dementia. Socio-demographic and lifestyle information at baseline are detailed in Tables 7 to 9, segmented by decline status in all four cognitive tests. It was observed that male was more likely to have drinking and smoking habits, being currently engaged in marriage, and living with someone at recruitment compared to female. Male also more frequently had diabetes, CVDs or CVAs, and lower self-independence (Table 7).

Among all participants, those with dual decline were more like being hyperlipidemia (found in the WR, IR, and backward-DS), to be currently smoking (observed in the WR, IR, and forward-DS), as well as to have diabetes mellitus (found in the WR) compared with people without any decline (Table 8-9)

Table 7. Participants characteristics at 65 years stratified according to sex

Characteristics	Total (N=482)	Male (N=231)	Female (N=251)	P
Participation year				
1997	84 (17.4)	40 (17.3)	44 (17.5)	
1998	95 (19.7)	44 (19.1)	51 (20.3)	
1999	90 (18.7)	38 (16.5)	52 (20.7)	
2000	91 (18.9)	41 (17.8)	50 (19.9)	
2001	122 (25.3)	68 (29.4)	54 (21.5)	0.335
BMI				
<18.5	24 (5.0)	8 (3.5)	16 (6.4)	
18.5-25	353 (73.2)	171 (74.0)	182 (72.5)	
≥25	105 (21.8)	52 (22.5)	53 (21.1)	0.334
Educational background				
Junior high or lower	155 (32.2)	58 (25.1)	97 (38.7)	
High school	215 (44.6)	95 (41.1)	120 (47.8)	
College or higher	112 (23.2)	78 (33.8)	34 (13.6)	<0.001
Never smoker	279 (57.9)	46 (19.9)	233 (92.8)	<0.001
Current drinker	210 (43.6)	156 (67.5)	54 (21.5)	<0.001
Current married	441 (91.5)	225 (97.4)	216 (86.1)	<0.001
Living alone	17 (3.5)	3 (1.3)	14 (5.6)	0.010
Medical histories				
Depressive symptoms	106 (22.0)	50 (21.7)	56 (22.3)	0.805
Morbidities	38 (7.9)	26 (11.3)	12(4.8)	0.008
Hypertension	111 (23.0)	53 (22.9)	58(23.1)	0.966
Hyperlipidemia	68 (14.1)	22 (9.5)	46(18.3)	0.006
Diabetes	35 (7.3)	30 (13.0)	5(2.0)	<0.001
Arthritis	26 (5.4)	10 (4.3)	16(6.4)	0.321
I-ADL score<11	47 (9.8)	29 (12.6)	18(7.2)	0.048
Total social activity measure≥8	234 (48.6)	113 (48.9)	121(48.2)	0.876
Regular exercise habits	249 (51.7)	132 (57.1)	117(46.6)	0.018
Death cases	64 (13.3)	40 (17.3)	24(9.6)	0.031
Incident dementia	111 (23.0)	53 (22.9)	58(23.1)	0.966

Note, N=Number, BMI=Body Mass Index; Morbidities: cardiovascular diseases and cerebrovascular diseases; I-ADL, instrumental activities of daily living

Table 8. Participants characteristics for memory and processing speed in all participants at 65 years (N=482)

	Memory				Processing Speed				All
	No decline	Dual decline	Pure gait decline	Pure cognitive decline	No decline	Dual decline	Pure gait decline	Pure cognitive decline	
Female	140(53.4)	14(51.9)	34(64.2)	63(45.0)	123(49.0)	20(66.7)	28(56.0)	80(53.0)	251(52.1)
Participation Year									
1997	42(16)	6(22.2)	11(20.8)	25(17.9)	43(17.1)	6(20.0)	11(22.0)	24(15.9)	84(17.4)
1998	53(20.2)	4(14.8)	9(17.0)	29(20.7)	63(25.1)	3(10.0)	10(20.0)	19(12.6)	95(19.7)
1999	52(19.9)	3(11.1)	11(20.8)	24(17.1)	49(19.5)	5(16.7)	9(18.0)	27(17.9)	90(18.7)
2000	49(18.7)	7(25.9)	11(20.8)	24(17.1)	38(15.1)	6(20.0)	12(24.0)	35(23.2)	91(18.9)
2001	66(25.2)	7(25.9)	11(20.8)	38(27.1)	58(23.1)	10(33.3)	8(16.0)	46(30.5)	122(25.3)
BMI									
<18.5	14(5.3)	3(11.1)	1(1.9)	6(4.3)	10(4.0)	2(6.7)	2(4.0)	10(6.6)	24(5.0)
18.5-25	190(72.5)	18(66.7)	38(71.7)	107(76.4)	187(74.5)	19(63.3)	37(74.0)	110(72.9)	353(73.2)
≥25	58(22.1)	6(22.2)	14(26.4)	27(19.3)	54(21.5)	9(30.0)	11(22.0)	31(20.5)	105(21.8)
Educational Background									
Junior or lower	79(30.2)	3(11.1)	18(34.0)	55(39.3)	70(27.9)	8(26.7)	13(26.0)	64(42.4)	155(32.2)
High school	127(48.5)	12(44.4)	23(43.4)	53(37.9)	126(50.2)	15(50.0)	20(40.0)	54(35.8)	215(44.6)
College or higher	56(21.4)	12(44.4) *	12(22.6)	32(22.9)	55(21.9)	7(23.3)	17(34.0)	33(21.9)	112(23.2)
Never smoker	156(59.5)	14(51.9) *	37(69.8)	72(51.4)	136(54.2)	20(66.7) *	31(62.0)	92(60.9)	279(57.9)
Current drinker	106(40.5)	15(55.6) *	24(45.3)	65(46.4)	106(42.2)	15(50.0)	24(48.0)	65(43.1)	210(43.6)
Current married	241(92.0)	25(92.6)	42(79.3)	133(95.0)	234(93.2)	25(83.3)	42(84.0)	140(92.7)	441(91.5)
Living alone	8(3.1)	2(7.4)	4(7.6)	3(2.1)	8(3.2)	3(10.0)	3(6.0)	3(2.0)	17(3.5)
Medical histories									
Depressive symptoms	60(22.9)	6(22.2)	12(22.6)	28(20.0)	51(20.3)	8(26.7)	10(20.0)	37(24.5)	106(22.0)
Morbidities	23(8.8)	1(3.7)	6(11.3)	8(5.7)	17(6.8)	4(13.3)	3(6.0)	14(9.3)	38(7.9)
Hypertension	64(24.4)	6(22.2)	10(18.9)	31(22.1)	55(21.9)	7(23.3)	9(18.0)	40(26.5)	111(23.0)
Hyperlipidemia	27(10.3)	7(25.9) *	11(20.8)	23(16.4)	31(12.4)	8(26.7) *	10(20.0)	19(12.6)	68(14.1)
Diabetes	17(6.5)	5(18.5) *	3(5.7)	10(7.1)	15(6.0)	3(10.0)	5(10.0)	12(8.0)	35(7.3)
Arthritis	17(6.5)	1(3.7)	4(7.6)	4(2.9)	14(5.6)	2(6.7)	3(6.0)	7(4.6)	26(5.4)
I-ADL score≥11	231(88.2)	25(92.6)	48(90.6)	124(88.6)	228(90.8)	27(90.0)	46(92.0)	127(84.1)	428(88.8)
Social activity measure≥8	133(50.8)	12(44.4)	35(66.0)	54(38.6)	121(48.2)	20(66.7)	27(54.0)	66(43.7)	234(48.6)
Regular exercise habits	129(49.2)	14(51.9)	34(64.2)	72(51.4)	126(50.2)	17(56.7)	31(62.0)	75(49.7)	249(51.7)
Death case	37(14.1)	3(11.1)	6(11.3)	18(12.9)	42(16.7)	1(3.3)	8(16.0)	13(8.6)	64(13.3)
Incident dementia	49(18.7)	10(37.0) *	15(28.3)	37(26.4)	50(19.9)	11(36.7) *	14(28)	36(23.8)	111(23.0)

Note, BMI, body mass index; Morbidities; cardiovascular diseases and cerebrovascular diseases; I-ADL, instrumental activities of daily living. * Indicates significant *P*-value (<0.05) in chi-square tests between dual decline and no decline.

Table 9. Participants characteristics for verbal memory and working memory in all participants at 65 years (N=482)

	Verbal memory				Working memory				All
	No decline	Dual decline	Pure gait decline	Pure cognitive decline	No decline	Dual decline	Pure gait decline	Pure cognitive decline	
Female	153(48.6)	6(40)	42(64.6)	50(57.5)	137(50.7)	12(52.2)	36(63.2)	66(50.0)	251(52.1)
Participation Year									
1997	45(14.3)	4(26.7)	13(20)	22(25.3)	44(16.3)	5(21.7)	12(21.1)	23(17.4)	84(17.4)
1998	67(21.3)	3(20.0)	10(15.4)	15(17.2)	57(21.1)	3(13.0)	10(17.5)	25(18.9)	95(19.7)
1999	56(17.8)	3(20.0)	11(16.9)	20(23.0)	47(17.4)	5(21.7)	9(15.8)	29(22.0)	90(18.7)
2000	65(20.6)	3(20.0)	15(23.1)	8(9.2)	52(19.3)	4(17.4)	14(24.6)	21(15.9)	91(18.9)
2001	82(26.0)	2(13.3)	16(24.6)	22(25.3)	70(25.9)	6(26.1)	12(21.1)	34(25.8)	122(25.3)
BMI									
<18.5	17(5.4)	1(6.7)	3(4.6)	3(3.5)	15(5.6)	0(0.0)	4(7.0)	5(3.8)	24(5.0)
18.5-25	231(73.3)	10(66.7)	46(70.8)	66(75.9)	196(72.6)	19(82.6)	37(64.9)	101(76.5)	353(73.2)
≥25	67(21.3)	4(26.7)	16(24.6)	18(20.7)	59(21.9)	4(17.4)	16(28.1)	26(19.7)	105(21.8)
Educational Background									
Junior high or lower	108(34.3)	4(26.7)	17(26.2)	26(29.9)	87(32.2)	10(43.5)	11(19.3)	47(35.6)	155(32.2)
High school	134(42.5)	6(40.0)	29(44.6)	46(52.9)	117(43.3)	5(21.7)	30(52.6)	63(47.7)	215(44.6)
College or higher	73(23.2)	5(33.3)	19(29.2)	15(17.2)	66(24.4)	8(34.8)	16(28.1)	22(16.7)	112(23.2)
Never smoker	173(54.9)	4(26.7) *	47(72.3)	55(63.2)	154(57.0)	12(52.2)	39(68.4)	74(56.1)	279(57.9)
Current drinker	142(45.1)	11(73.3) *	28(43.1)	29(33.3)	118(43.7)	12(52.2)	27(47.4)	53(40.2)	210(43.6)
Current married	291(92.4)	12(80.0)	55(84.6)	83(95.4)	254(94.1)	20(87.0)	47(82.5)	120(90.9)	441(91.5)
Living alone	11(3.5)	1(6.7)	5(7.7)	0(0.0)	5(1.9)	2(8.7)	4(7.0)	6(4.6)	17(3.5)
Medical histories									
Depressive symptoms	72(22.9)	3(20.0)	15(23.1)	16(18.4)	52(19.3)	5(21.7)	13(22.8)	36(27.3)	106(22.0)
Morbidities	26(8.3)	2(13.3)	5(7.7)	5(5.8)	19(7.0)	3(13.0)	4(7.0)	12(9.1)	38(7.9)
Hypertension	76(24.1)	4(26.7)	12(18.5)	19(21.8)	62(23.0)	3(13.0)	13(22.8)	33(25.0)	111(23.0)
Hyperlipidemia	42(13.3)	2(13.3)	16(24.6)	8(9.2)	32(11.9)	8(34.8) *	10(17.5)	18(13.6)	68(14.1)
Diabetes	24(7.6)	2(13.3)	6(9.2)	3(3.5)	23(8.5)	2(8.7)	6(10.5)	4(3.0)	35(7.3)
Arthritis	15(4.8)	0(0.0)	5(7.7)	6(6.9)	12(4.4)	2(8.7)	3(5.3)	9(6.8)	26(5.4)
I-ADL score≥11	279(88.6)	13(86.7)	60(92.3)	76(87.4)	241(89.3)	22(95.7)	51(89.5)	114(86.4)	428(88.8)
Social activity measure ≥8	145(46.0)	9(60.0)	38(58.5)	42(48.3)	136(50.4)	11(47.8)	36(63.2)	51(38.6)	234(48.6)
Regular exercise habits	163(51.8)	8(53.3)	40(61.5)	38(43.7)	135(50.0)	14(60.9)	34(59.7)	66(50.0)	249(51.7)
Death case	46(14.6)	4(26.7)	5(7.7)	9(10.3)	34(12.6)	3(13.0)	6(10.5)	21(15.9)	64(13.3)
Incident dementia	65(20.6)	5(33.3)	20(30.8)	21(24.1)	58(21.5)	9(39.1) *	16(28.1)	28(21.2)	111(23.0)

Note. BMI, body mass index; Morbidities; cardiovascular diseases and cerebrovascular diseases; I-ADL, instrumental activities of daily living. * Indicates significant *P*-value (<0.05) in chi-square tests between dual decline group and no decline group.

The non-parametric curves indicated that dual decline in WR and IR had a noticeably higher cumulative incidence, especially in male (Supplementary figure 1-8). In adjusted models, dual decline was significantly associated with the onset of dementia, with increased sHRs in the WR (sHRs: 3.8, 95% CI: [1.6-8.8]), IR (2.5, 1.1-5.6), and forward-DS tests (2.8, 1.2-6.6), as compared with no decline. sHRs were elevated in the WR test, IR, and forward-DS tests (2.8, 1.2-6.6). SHRs were highest in the WR test. sHRs were higher in the WR test (1.8, 1.2-5.6), and in the forward-DS test (2.8, 1.2-6.6), as compared with the no-decline test. Pure cognitive decline in the WR test (1.8, 1.1-3.1) and pure gait decline in the forward-DS test (2.0, 1.11-3.8) were also significantly associated with the onset of dementia. No significant correlation was found in the linear comparison results (Table 10). The results in 10-year follow-up period also showed a higher risk in dual decline of gait speed and WR test (4.1, 1.1-14.8) as well as IRS test (3.8, 1.2-11.9), indicating the robustness of the results (Supplementary table 1).

Table 10. Association of decline group with incident disabling dementia in different models (mean follow-up period: 12.5 years)

Cognitive measures	N	Dementia Cases	Model ^a		Model ^b		Model ^c	
			HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	sHR (95% CI)	<i>P</i>
Memory (WR)								
No decline	262	49	1		1		1	
Dual decline	27	19	4.2 (1.9,9.3)	<0.001	3.9 (1.8,8.8)	0.001	3.8 (1.6,8.8)	0.002
Pure gait decline	53	15	1.8 (0.9,3.3)	0.080	1.7 (0.9,3.2)	0.127	1.7 (0.9,3.1)	0.119
Pure cognitive decline	140	37	1.7 (1.1,2.7)	0.020	1.8 (1.1,2.9)	0.018	1.8 (1.1,3.1)	0.022
Processing speed (IR)								
No decline	251	50	1		1		1	
Dual decline	30	11	2.3 (1.0,4.8)	0.024	2.2 (1.0,4.7)	0.044	2.5 (1.1,5.6)	0.030
Pure gait decline	50	14	1.9 (0.9,3.5)	0.062	1.9 (0.9,3.7)	0.077	1.8 (0.9,3.5)	0.069
Pure cognitive decline	151	36	1.1 (0.7,1.8)	0.642	1.1(0.7,1.8)	0.672	1.2 (0.8,1.9)	0.410
Verbal memory (forward-DS)								
No decline	315	35	1		1		1	
Dual decline	15	12	2.4 (0.9,6.2)	0.078	2.1(0.8,5.8)	0.132	2.1 (0.8,5.3)	0.113
Pure gait decline	65	13	2.0 (1.2,3.5)	0.015	2.0 (1.1,3.6)	0.019	2.0 (1.1,3.8)	0.022
Pure cognitive decline	87	51	1.3 (0.8,2.2)	0.319	1.3(0.8,2.1)	0.407	1.3 (0.7,2.2)	0.399
Working memory (backward-DS)								
No decline	270	22	1		1		1	
Dual decline	23	16	3.2 (1.5,7.1)	0.004	2.9 (1.2,6.6)	0.014	2.8 (1.2,6.6)	0.018
Pure gait decline	57	9	1.7 (0.9,3.2)	0.076	1.7 (0.9,3.3)	0.099	1.7 (0.9,3.2)	0.121
Pure cognitive decline	132	64	1.3 (0.8,2.2)	0.230	1.2 (0.7,2.0)	0.432	1.2 (0.7,2.0)	0.550

Note: N, number; PY, person year; HR, hazard ratio; sHR, sub-distributional hazard ratio; CI, confidence interval; WR, word recall; IR, interference ratio; DS, digit span.

^a adjusted for baseline gait and according to cognitive performance.

^b further adjusted for sex, participation year, smoking status, educational background, living arrangement, presence of medical histories, regular exercise habits, and total social activity measure.

^c adjusted for covariates in model ^b with death as a competing risk using Fine and Grays sub-distribution hazards mode

Fifty-three male and fifty-eight female has proceeded to dementia after follow-up. Their baseline characteristics by decline group were presented in Supplementary table 2-5. No common characteristics were found for individual who had dual decline in gait speed and cognitive domains. However, it might be due to the small sample size of dual decliners in this study.

When classified the participants into different sex, it was found that compare with no decline male participants, dual decline in all tests, except for forward-DS, was significantly associated with incident dementia. For linear contrast test, dual declines on the WR, IR, and backward-DS tests were observed to be associated with significantly higher risk of dementia onset compared with cognitive decline alone, but not with gait decline alone. In contrast, all these significances were absent in female (Table 11, Figure 10-11). I also presented the hazard ratios of each covariate in fully-adjust model to better explain the sex differences in Supplementary table 6-7. Slow gait speed and living alone were the risk factors for male participants but not for female. WR was related to dementia in female and Backward-DS was related to dementia in male. No potential covariates seemed to be able to explain the sex difference in the associations.

Table 11. Association of decline group with incident disabling dementia in competing risk models according to sex

Cognitive measures	Male (N=231)				Female (N=251)			
	N	N of cases	Competing risk model sHRs (95% CI)	P	N	N of cases	Competing risk model sHRs (95% CI)	P
Memory (WR)								
No decline	122	23	1		140	25	1	
Dual decline	13	5	7.6 (2.0,28.8)	<0.001	14	3	1.9 (0.5,6.9)	0.351
Pure gait decline	19	8	2.4 (0.9,6.4)	0.077	34	9	1.3 (0.5,3.3)	0.556
Pure cognitive decline	77	16	1.6 (0.7,3.5) *	0.255	63	21	2.7 (1.3,5.5)	0.010
Processing speed (IR)								
No decline	128	22	1		123	30	1	
Dual decline	10	6	7.4 (2.5,22.6)	<0.001	20	4	1.6 (0.5,5.5)	0.434
Pure gait decline	22	7	2.3 (0.9,6.0)	0.081	28	8	1.1 (0.5,2.5)	0.787
Pure cognitive decline	71	18	1.2 (0.5,2.6) *	0.688	80	12	1.1 (0.6,2.0)	0.814
Verbal memory (forward-DS)								
No decline	162	29	1		153	31	1	
Dual decline	9	3	2.6 (0.7,9.1)	0.139	6	2	1.0 (0.2,4.2)	0.991
Pure gait decline	23	10	3.9 (1.5,10.0)	0.004	42	10	1.2 (0.6,2.7)	0.601
Pure cognitive decline	37	10	1.7 (0.7,4.0)	0.219	50	11	0.9 (0.4,1.9)	0.671
Working memory (backward-DS)								
No decline	133	23	1		137	31	1	
Dual decline	11	5	7.1 (1.9,26.9)	0.004	12	4	1.8 (0.5,6.8)	0.403
Pure gait decline	21	8	3.3 (1.2,8.9)	0.017	36	8	1.0 (0.4,2.2)	0.895
Pure cognitive decline	66	16	2.2 (1.0,5.0) *	0.056	66	11	0.8 (0.4,1.9)	0.610

Note: N, number; PY, person year; sHR, sub-distributional hazard ratio; CI, confidence interval; WR, word recall; IR, interference ratio; DS, digit span. Covariates included baseline gait and cognitive performance, sex, participation year, smoking status, educational background, living arrangement, presence of medical histories, regular exercise habits, and total social activity measure, and death was treated as a competing risk using Fine and Grays subdistribution hazards model. * Indicates significant *P*-value (<0.05) in linear contrast review (see results for details).

Discussion

Following an average follow-up of 12.5 years, it was discovered that older adults experiencing a dual decline in subjective gait speed and domain-specific cognition (WR, IR, and backward-DS) between the ages of 65 and 70 faced a higher risk of developing dementia before turning 85 compared to those with single or without such declines. Notably, the greatest risk was associated with a dual decline in subjective gait speed and WR test performance. Additionally, the study highlighted significant sex differences in these associations, with male participants exhibiting markedly higher risks.

Studies in some other countries have consistently shown that if an older adults experienced a simultaneous decline in both gait speed and cognitive domains (dual decline), their risks of having later dementia onset would be increased compare to those who did not have such conditions (Collyer et al., 2022; Montero-Odasso et al., 2020; Tian et al., 2020; Verghese, 2022). The results of this study also proved this finds, moreover, it is the first study confirmed this association in Asian populations. More important, this study utilized data from an age-specific cohort so that age-related bias in cognitive-related studies could be eliminated. In addition, I focused on a 5-year period of dual decline from age 65 to age 70 rather than until the age of 85. The current study is similar to one previous study conducted by Collyer et al (Collyer et al., 2022), and we both found that the dual decline in gait speed and memory domain had the highest risk of dementia onset. However, what my study is different from his is that I did not find the significance in single cognitive declines with dementia (such as single memory decline), which I speculated, possibly due to the relatively younger age of participants in my study, and in other perspective, suggesting that dual decline may represent a prodromal phase of dementia, which even earlier than common motor and cognition deterioration. Although exact reason why dual decline had a higher risk of being dementia remained largely unaddressed, Tian et al. (Tian et al., 2023) in earlier study presented a hypothesis regarding this issues. It was proposed that a higher total burden caused by CNS causes, consist of impaired sensory-motor integration or movement, as well as their combination with a number of non-CNS causes like mitochondrial dysfunction, or vascular burden, metabolic dysfunction, lead to both cognitive and mobility impairments. These finding together, address the significance of thinking adding symptoms of dual decline in future dementia risk screening and highlight the potential necessity of dual decline on early screening and follow-up in the potential targeted population.

Given that sex plays an important role in dementia and dementia-related diseases, stratification analyses were performed (Mazure and Swendsen, 2016). By doing so I found that the dual decline had significantly higher risk in only male participants. Although I did not observe a notable difference between male and female who experienced dual decline and proceeded dementia, these sex differences in the associations might be explained on the basis of the possible speculation that summarized by the previous findings. First, I assumed that dual decline in different sex does not reflect the same underlying pathophysiology as dementia. Although dual decline can sometimes be viewed as a clinical reflection of structural brain abnormalities (Tian et al., 2023), this may be the result of cumulative risk for gait and cognitive function. For example, dual decline is associated with initial brain damage in specific frontal, parietal, and temporal lobe regions (Tian et al., 2021b). It is indicated that in this aspect, male would have an earlier and greater damage on brain volume and neurons of most brain regions than woman while getting old (Armstrong et al., 2019; Buchpiguel et al., 2020). Second, non-pathological dual decline caused by external risks, such as sociocultural or female-specific factors, may be more frequent in female (Nebel et al., 2018). In such cases, female would be affected much greatly by some sociocultural and female-only factors at the late life, at the same time, they tend to have a lower educational background (which was also observed in current study) as well as a poor occupational attainment (Albert, 2015). Due to less physical activity while young, they also experienced a quicker muscle loss after getting older (The Lancet Public Health, 2019). Besides, they would be affected by some female-only exposures such as menopause and hormone therapy in special age (Shumaker et al., 2003). Overall, these making the reasons of being dual decline in younger-old woman varied more greatly in different situations. Dual decline that caused by internal brain pathology would possibly expedite the future onset of dementia; however, dual decline that attributed to some external factors (such as socio-environment background) might not be able to serve as an effective predictor of dementia at an early stage. Nevertheless, it is also noted that this study only contained a relatively small sample size and so far, it has been the first study to explore sex differences in this context, therefore, more research is needed to improve the generalizability of this study.

In this study, I found that older adults who had dual decline in gait speed and cognition were more likely to have dyslipidemia, which was also reported in a previous study (Montero-Odasso et al., 2020). Additionally, it was shown that baseline alcohol use, smoking, and a history of diabetes are among the vascular risk factors that are more common in individuals

with dual decline. The internal vascular pathology that links dementia with dual decline is strengthened by these findings (Montero-Odasso et al., 2020; Tian et al., 2023). Midlife vascular risk factors can cause amyloid deposition, white matter hyperintensities, and damage to neural networks. These variables can all impact gait and cognition concurrently and ultimately cause dementia. Future research on possible vascular load control preventative strategies, such as encouraging quitting smoking and regulating alcohol intake, may thus be able to postpone the onset of dementia when dual decline signs was detected to appear.

This study is subject to a number of limitations that should be acknowledged. First, not all participants underwent comprehensive cognitive testing throughout the study period, which hindered the ability to monitor cognitive decline accurately. As a result, only a limited subset of the original NISSIN participants was included, making the results being hardly generalized into a broad population, especially for results of sex-stratified analyses. Second, the study relied on self-reported gait speeds rather than those measured by devices. While subjective gait speed has been used for risk stratification in heart failure and CVDs, this method may compromise the precision and reliability of the data (Ohno et al., 2023; Ueno et al., 2022). Moreover, a previous study has already proved the validity of subjective gait speed in the NISSIN database (Zhao et al., 2015). In other perspective, self-reported gait speed could be anticipated as a more convenient and low-cost indicator when considering integrate gait into routine clinical assessments in the future. However, its association with cognitive-related diseases has rarely been examined. This gap may lead to misinterpretations of personal gait speed, especially among individuals experiencing cognitive decline. Third, the diagnosis of dementia was evaluated under the standards in the LTCI system. Being accredited with LTCI certificate based on the individuals' or families' needs of day care services. Therefore, even some patients can be certified as dementia, they would prefer not to use the certificate, and which may potentially lead to underestimation of dementia rate. Fourth, this study did not capture information on the phenotypes of dementia, which could have been beneficial for predicting different types of dementia and understanding underlying mechanisms. Finally, this study did not evaluate genetic information such as the apolipoprotein E gene. Male and female have various manifestations of apolipoprotein, a major dementia risk factor (Farrer et al., 1997), which may potentially account for sex disparities in the results.

Conclusion

Dual decline in subjective gait speed and cognition reflects underlying brain pathology and can significantly predict dementia over a decade before its onset, especially in male.

Screening for dual decline should be included in future clinical assessments, and forthcoming studies should investigate early preventative strategies targeting vascular risk factors as potential methods to delay dementia in individuals showing signs of dual decline. Further evaluation and research are essential to better understand the sex differences and underlying mechanisms of dual decline and its link to dementia risk.

Supplement table 1. Association of decline group with incident dementia in different models (up to 80-year-old, number of depressive cases: 40)

	N of cases	Baseline performance adjusted model ^a			Baseline performance plus demographics adjusted model ^b			Competing risk model ^c		
		HR	95% CI	P	HR	95% CI	P	sHR	95% CI	P
Memory (WR)										
No decline	20	1			1			1		
Dual decline	4	5.2	(1.5,17.4)	0.007	5.0	(1.1,14.2)	0.031	4.1	(1.1,14.8)	0.030
Pure gait decline	3	1.2	(0.3,4.4)	0.814	1.3	(0.3,4.7)	0.683	1.2	(0.4,6.9)	0.587
Pure cognitive decline	13	1.5	(0.7,3.1)	0.258	1.4	(0.7,3.0)	0.387	1.2	(0.5,2.2)	0.963
Processing speed (IR)										
No decline	20	1			1			1		
Dual decline	4	3.1	(1.1,8.4)	0.032	2.7	(1.0,8.1)	0.073	3.8	(1.2,11.9)	0.027
Pure gait decline	3	0.7	(0.2,2.8)	0.539	0.8	(0.2,3.4)	0.738	1.3	(0.3,5.9)	0.780
Pure cognitive decline	13	1.5	(0.7,3.0)	0.354	1.3	(0.6,2.8)	0.533	1.1	(0.5,2.6)	0.836
Verbal memory (forward-DS)										
No decline	11	1			1			1		
Dual decline	3	1.1	(0.3,3.8)	0.967	1.30	(0.4,4.7)	0.749	2.0	(0.5-8.3)	0.342
Pure gait decline	4	1.9	(0.6,5.8)	0.302	1.8	(0.6,5.9)	0.375	2.8	(0.8-10.2)	0.109
Pure cognitive decline	22	1.2	(0.6,2.4)	0.732	1.1	(0.6,2.4)	0.830	1.0	(0.4-2.4)	0.994
Working memory (backward-DS)										
No decline	9	1			1			1		
Dual decline	4	1.3	(0.4,4.3)	0.732	1.50	(0.5,5.4)	0.543	2.8	(0.7,11.1)	0.150
Pure gait decline	3	3.8	(1,14.7)	0.062	3.2	(0.8,13.5)	0.126	4.1	(0.9,18.2)	0.068
Pure cognitive decline	24	1.6	(0.7,3.6)	0.326	1.6	(0.7,3.7)	0.344	1.9	(0.7,4.9)	0.206

Note: WR, word recall; IR, interference ratio; DS, digit span.

^a adjusted for baseline gait and according to cognitive performance; ^b further adjusted for sex, participation year, smoking status, educational background, living arrangement, presences of medical histories, regular exercise habits, and total social activity measure; ^c adjusted for covariates in model ^b with death as a competing risk using Fine and Grays sub distribution hazards model.

sTable 2. Participants characteristics for WR and IR tests in male proceeded dementia (N=53)

	WR				IR			
	No decline	Dual decline	Pure gait decline	Pure cognitive decline	No decline	Dual decline	Pure gait decline	Pure cognitive decline
N	24	7	6	16	22	6	7	18
Participation year								
1997	5(20.8)	0(0)	1(16.7)	4(25)	4(18.2)	1(16.7)	0(0)	5(27.8)
1998	5(20.8)	1(14.3)	2(33.3)	5(31.3)	8(36.4)	1(16.7)	2(28.6)	2(11.1)
1999	2(8.3)	1(14.3)	1(16.7)	0(0)	2(9.1)	1(16.7)	1(14.3)	0(0)
2000	3(12.5)	2(28.6)	0(0)	3(18.8)	4(18.2)	1(16.7)	1(14.3)	2(11.1)
2001	9(37.5)	3(42.9)	2(33.3)	4(25)	4(18.2)	2(33.3)	3(42.9)	9(50)
BMI								
<18.5	1(4.2)	1(14.3)	0(0)	1(6.3)	2(9.1)	1(16.7)	0(0)	0(0)
18.5-25	16(66.7)	3(42.9)	5(83.3)	12(75)	17(77.3)	4(66.7)	4(57.1)	11(61.1)
≥25	7(29.2)	3(42.9)	1(16.7)	3(18.8)	3(13.6)	1(16.7)	3(42.9)	7(38.9)
Educational background								
Junior high or lower	8(33.3)	1(14.3)	3(50)	4(25)	5(22.7)	2(33.3)	2(28.6)	7(38.9)
High school	8(33.3)	1(14.3)	3(50)	7(43.8)	10(45.5)	2(33.3)	2(28.6)	5(27.8)
College or higher	8(33.3)	5(71.4)	0(0)	5(31.3)	7(31.8)	2(33.3)	3(42.9)	6(33.3)
Never smoker	5(20.8)	1(14.3)	1(16.7)	4(25)	7(31.8)	1(16.7)	1(14.3)	2(11.1)
Current drinker	14(58.3)	6(85.7)	5(83.3)	11(68.8)	11(50)	6(100)	5(71.4)	14(77.8)
Current married	23(95.8)	6(85.7)	6(100)	15(93.8)	21(95.5)	5(83.3)	7(100)	17(94.4)
Living with others	1(4.2)	1(14.3)	0(0)	1(6.3)	1(4.6)	1(16.7)	0(0)	1(5.6)
Medical histories								
Depressive symptoms	8(33.3)	1(14.3)	0(0)	6(37.5)	8(36.4)	1(16.7)	0(0)	6(33.3)
Morbidity	3(12.5)	0(0)	3(50)	2(12.5)	4(18.2)	2(33.3)	1(14.3)	1(5.6)
Hypertension	6(25)	2(28.6)	3(50)	4(25)	3(13.6)	2(33.3)	3(42.9)	7(38.9)
Hyperlipidemia	3(12.5)	2(28.6)	0(0)	0(0)	1(4.6)	2(33.3)	0(0)	2(11.1)
Diabetes	3(12.5)	3(42.9)	1(16.7)	2(12.5)	2(9.1)	2(33.3)	2(28.6)	3(16.7)
Arthritis	1(4.2)	1(14.3)	0(0)	0(0)	1(4.6)	1(16.7)	0(0)	0(0)
I-ADL score≥11	20(83.3)	6(85.7)	6(100)	10(62.5)	17(77.3)	5(83.3)	7(100)	13(72.2)
Social activity measure≥8	15(62.5)	3(42.9)	5(83.3)	6(37.5)	13(59.1)	3(50)	5(71.4)	8(44.4)
Regular exercise habits	14(58.3)	3(42.9)	4(66.7)	6(37.5)	10(45.5)	2(33.3)	5(71.4)	10(55.6)

Note, data were presented in number and percentage, BMI, body mass index; Morbidity; cardiovascular diseases and cerebrovascular diseases; I-ADL, instrumental activities of daily living

sTable 3. Participants characteristics for Backward-DS and Forward-DS tests in male proceeded dementia (N=53)

	Forward-DS				Backward-DS			
	No decline	Dual decline	Pure gait decline	Pure cognitive decline	No decline	Dual decline	Pure gait decline	Pure cognitive decline
N of cases	30	3	10	10	24	5	8	16
Participation year								
1997	7(23.3)	1(33.3)	0(0)	2(20)	5(20.8)	1(20)	0(0)	4(25)
1998	10(33.3)	2(66.7)	1(10)	0(0)	7(29.2)	1(20)	2(25)	3(18.8)
1999	1(3.3)	0(0)	2(20)	1(10)	2(8.3)	1(20)	1(12.5)	0(0)
2000	5(16.7)	0(0)	2(20)	1(10)	4(16.7)	0(0)	2(25)	2(12.5)
2001	7(23.3)	0(0)	5(50)	6(60)	6(25)	2(40)	3(37.5)	7(43.8)
BMI								
<18.5	2(6.7)	0(0)	1(10)	0(0)	1(4.2)	0(0)	1(12.5)	1(6.3)
18.5-25	21(70)	3(100)	5(50)	7(70)	16(66.7)	5(100)	3(37.5)	12(75)
≥25	7(23.3)	0(0)	4(40)	3(30)	7(29.2)	0(0)	4(50)	3(18.8)
Educational background								
Junior high or lower	6(20)	2(66.7)	2(20)	6(60)	5(20.8)	4(80)	0(0)	7(43.8)
High school	12(40)	1(33.3)	3(30)	3(30)	12(50)	0(0)	4(50)	3(18.8)
College or higher	12(40)	0(0)	5(50)	1(10)	7(29.2)	1(20)	4(50)	6(37.5)
Never smoker	6(20)	0(0)	2(20)	3(30)	7(29.2)	0(0)	2(25)	2(12.5)
Current drinker	17(56.7)	2(66.7)	9(90)	8(80)	14(58.3)	4(80)	7(87.5)	11(68.8)
Current married	28(93.3)	3(100)	9(90)	10(100)	23(95.8)	4(80)	8(100)	15(93.8)
Living with others	2(6.7)	0(0)	1(10)	0(0)	1(4.2)	1(20)	0(0)	1(6.3)
Medical histories								
Depressive symptoms	11(36.7)	0(0)	1(10)	3(30)	6(25)	0(0)	1(12.5)	8(50)
Morbidities	4(13.3)	1(33.3)	2(20)	1(10)	3(12.5)	2(40)	1(12.5)	2(12.5)
Hypertension	9(30)	1(33.3)	4(40)	1(10)	5(20.8)	1(20)	4(50)	5(31.3)
Hyperlipidemia	3(10)	0(0)	2(20)	0(0)	1(4.2)	1(20)	1(12.5)	2(12.5)
Diabetes	5(16.7)	2(66.7)	2(20)	0(0)	5(20.8)	1(20)	3(37.5)	0(0)
Arthritis	1(3.3)	0(0)	1(10)	0(0)	0(0)	1(20)	0(0)	1(6.3)
I-ADL score≥11	24(80)	3(100)	9(90)	6(60)	21(87.5)	5(100)	7(87.5)	9(56.3)
Social activity measure≥8	14(46.7)	1(33.3)	7(70)	7(70)	13(54.2)	2(40)	6(75)	8(50)
Regular exercise habits	16(53.3)	1(33.3)	6(60)	4(40)	10(41.7)	2(40)	5(62.5)	10(62.5)

Note, data were presented in number and percentage, BMI, body mass index; Morbidities; cardiovascular diseases and cerebrovascular diseases; I-ADL, instrumental activities of daily living

sTable 4. Participants characteristics for WR and IR tests in female proceeded dementia (N=58)

	WR				IR			
	No decline	Dual decline	Pure gait decline	Pure cognitive decline	No decline	Dual decline	Pure gait decline	Pure cognitive decline
N of cases	25	3	9	21	28	5	7	18
Participation year								
1997	5(20)	2(66.7)	1(11.1)	2(9.5)	6(21.4)	1(20)	2(28.6)	1(5.6)
1998	6(24)	0(0)	0(0)	5(23.8)	10(35.7)	0(0)	0(0)	1(5.6)
1999	8(32)	1(33.3)	3(33.3)	5(23.8)	6(21.4)	1(20)	3(42.9)	7(38.9)
2000	3(12)	0(0)	1(11.1)	3(14.3)	2(7.1)	0(0)	1(14.3)	4(22.2)
2001	3(12)	0(0)	4(44.4)	6(28.6)	4(14.3)	3(60)	1(14.3)	5(27.8)
BMI								
<18.5	0(0)	0(0)	0(0)	1(4.8)	1(3.6)	0(0)	0(0)	0(0)
18.5-25	18(72)	3(100)	6(66.7)	17(81)	21(75)	3(60)	6(85.7)	14(77.8)
≥25	7(28)	0(0)	3(33.3)	3(14.3)	6(21.4)	2(40)	1(14.3)	4(22.2)
Educational background								
Junior high or lower	10(40)	1(33.3)	4(44.4)	12(57.1)	10(35.7)	2(40)	3(42.9)	12(66.7)
High school	12(48)	1(33.3)	4(44.4)	7(33.3)	14(50)	2(40)	3(42.9)	5(27.8)
College or higher	3(12)	1(33.3)	1(11.1)	2(9.5)	4(14.3)	1(20)	1(14.3)	1(5.6)
Never smoker	19(76)	3(100)	8(88.9)	21(100)	25(89.3)	5(100)	6(85.7)	15(83.3)
Current drinker	7(28)	2(66.7)	1(11.1)	4(19.1)	6(21.4)	0(0)	3(42.9)	5(27.8)
Current married	20(80)	2(66.7)	6(66.7)	19(90.5)	24(85.7)	4(80)	4(57.1)	15(83.3)
Living with others	2(8)	0(0)	1(11.1)	2(9.5)	3(10.7)	0(0)	1(14.3)	1(5.6)
Medical histories								
Depressive symptoms	6(24)	1(33.3)	2(22.2)	4(19.1)	5(17.9)	1(20)	2(28.6)	5(27.8)
Morbidity	1(4)	0(0)	2(22.2)	2(9.5)	2(7.1)	1(20)	1(14.3)	1(5.6)
Hypertension	5(20)	1(33.3)	0(0)	5(23.8)	5(17.9)	1(20)	0(0)	5(27.8)
Hyperlipidemia	5(20)	1(33.3)	3(33.3)	5(23.8)	7(25)	4(80)	0(0)	3(16.7)
Diabetes	0(0)	0(0)	0(0)	1(4.8)	1(3.6)	0(0)	0(0)	0(0)
Arthritis	1(4)	0(0)	2(22.2)	0(0)	1(3.6)	1(20)	1(14.3)	0(0)
I-ADL score≥11	20(80)	3(100)	7(77.8)	19(90.5)	25(89.3)	5(100)	5(71.4)	14(77.8)
Social activity measure≥8	10(40)	3(100)	6(66.7)	8(38.1)	13(46.4)	5(100)	4(57.1)	5(27.8)
Regular exercise habits	12(48)	1(33.3)	2(22.2)	7(33.3)	10(35.7)	1(20)	2(28.6)	9(50)

Note, data were presented in number and percentage, BMI, body mass index; Morbidity; cardiovascular diseases and cerebrovascular diseases; I-ADL, instrumental activities of daily living

sTable 5. Participants characteristics for Backward-DS and Forward-DS tests in female proceeded dementia (N=58)

	Forward-DS				Backward-DS			
	No decline	Dual decline	Pure gait decline	Pure cognitive decline	No decline	Dual decline	Pure gait decline	Pure cognitive decline
N of cases	35	2	10	11	34	4	8	12
Participation year								
1997	4(11.4)	1(50)	2(20)	3(27.3)	5(14.7)	0(0)	3(37.5)	2(16.7)
1998	8(22.9)	0(0)	0(0)	3(27.3)	11(32.4)	0(0)	0(0)	0(0)
1999	9(25.7)	1(50)	3(30)	4(36.4)	9(26.5)	2(50)	2(25)	4(33.3)
2000	5(14.3)	0(0)	1(10)	1(9.1)	2(5.9)	0(0)	1(12.5)	4(33.3)
2001	9(25.7)	0(0)	4(40)	0(0)	7(20.6)	2(50)	2(25)	2(16.7)
BMI								
<18.5	1(2.9)	0(0)	0(0)	0(0)	1(2.9)	0(0)	0(0)	0(0)
18.5-25	26(74.3)	2(100)	7(70)	9(81.8)	24(70.6)	2(50)	7(87.5)	11(91.7)
≥25	8(22.9)	0(0)	3(30)	2(18.2)	9(26.5)	2(50)	1(12.5)	1(8.3)
Educational background								
Junior high or lower	17(48.6)	0(0)	5(50)	5(45.5)	16(47.1)	3(75)	2(25)	6(50)
High school	13(37.1)	2(100)	3(30)	6(54.6)	15(44.1)	1(25)	4(50)	4(33.3)
College or higher	5(14.3)	0(0)	2(20)	0(0)	3(8.8)	0(0)	2(25)	2(16.7)
Never smoker	31(88.6)	1(50)	10(100)	9(81.8)	28(82.4)	4(100)	7(87.5)	12(100)
Current drinker	10(28.6)	1(50)	2(20)	1(9.1)	8(23.5)	1(25)	2(25)	3(25)
Current married	30(85.7)	0(0)	8(80)	9(81.8)	28(82.4)	3(75)	5(62.5)	11(91.7)
Living with others	4(11.4)	1(50)	0(0)	0(0)	3(8.8)	0(0)	1(12.5)	1(8.3)
Medical histories								
Depressive symptoms	8(22.9)	0(0)	3(30)	2(18.2)	8(23.5)	2(50)	1(12.5)	2(16.7)
Morbidities	3(8.6)	0(0)	2(20)	0(0)	1(2.9)	1(25)	1(12.5)	2(16.7)
Hypertension	7(20)	0(0)	1(10)	3(27.3)	8(23.5)	1(25)	0(0)	2(16.7)
Hyperlipidemia	9(25.7)	0(0)	4(40)	1(9.1)	6(17.7)	1(25)	3(37.5)	4(33.3)
Diabetes	1(2.9)	0(0)	0(0)	0(0)	1(2.9)	0(0)	0(0)	0(0)
Arthritis	1(2.9)	0(0)	2(20)	0(0)	1(2.9)	1(25)	1(12.5)	0(0)
I-ADL score≥11	29(82.9)	2(100)	8(80)	10(90.9)	28(82.4)	4(100)	6(75)	11(91.7)
Social activity measure≥8	15(42.9)	2(100)	7(70)	3(27.3)	14(41.2)	2(50)	7(87.5)	4(33.3)
Regular exercise habits	13(37.1)	1(50)	2(20)	6(54.6)	14(41.2)	2(50)	1(12.5)	5(41.7)

Note, data were presented in number and percentage, BMI, body mass index; Morbidities; cardiovascular diseases and cerebrovascular diseases; I-ADL, instrumental activities of daily living

sTable 6 sHRs of covariates in fully adjusted Fine-Gray model in male (N=231)

		N of cases	Percentage	WR			IRS			Backward-DS		
				SHRs	95%CI		SHRs	95%CI		SHRs	95%CI	
Cognitive test				0.8	0.6	1.0	2.4	0.5	12.2	0.7	0.5	1.0
Gait speed	Slow	8	33.3	4.9	1.2	20.9	4.7	1.2	17.9	4.6	1.2	18.2
	Normal	37	21.4	2.0	0.6	6.8	1.9	0.6	5.9	1.8	0.6	5.1
	Fast	8	23.5	1			1			1		
Educational background	Junior or lower	16	27.6	1			1			1		
	High school	19	20.0	0.7	0.3	1.5	0.7	0.3	1.4	0.7	0.3	1.5
	College or higher	18	23.1	0.9	0.4	1.9	0.9	0.4	1.7	0.7	0.3	1.6
Smoking status	Never smoker	11	23.9	1			1			1		
	Current smoker	30	24.6	0.8	0.4	1.7	0.8	0.4	1.8	0.8	0.4	1.7
	Past smoker	12	19.4	0.7	0.3	1.7	0.8	0.3	1.9	1.1	0.5	2.2
living alone	Yes	3	100.0	9.3	2.7	32.3	7.8	2.1	28.4	8.8	3.0	26.1
	Other	50	21.9	1			1			1		
Presence of medical histories	Yes	19	27.1	1.7	0.9	3.1	1.5	0.8	2.7	1.5	0.8	2.8
	No	34	21.1	1			1			1		
Total social activity measure ≥ 8	Yes	24	20.3	0.6	0.3	1.0	0.7	0.4	1.2	0.6	0.4	1.1
	No	29	25.7	1			1			1		
Regular exercise habits	Yes	27	20.5	0.8	0.5	1.5	0.8	0.5	1.4	0.9	0.5	1.6
	No	25	25.8	1			1			1		

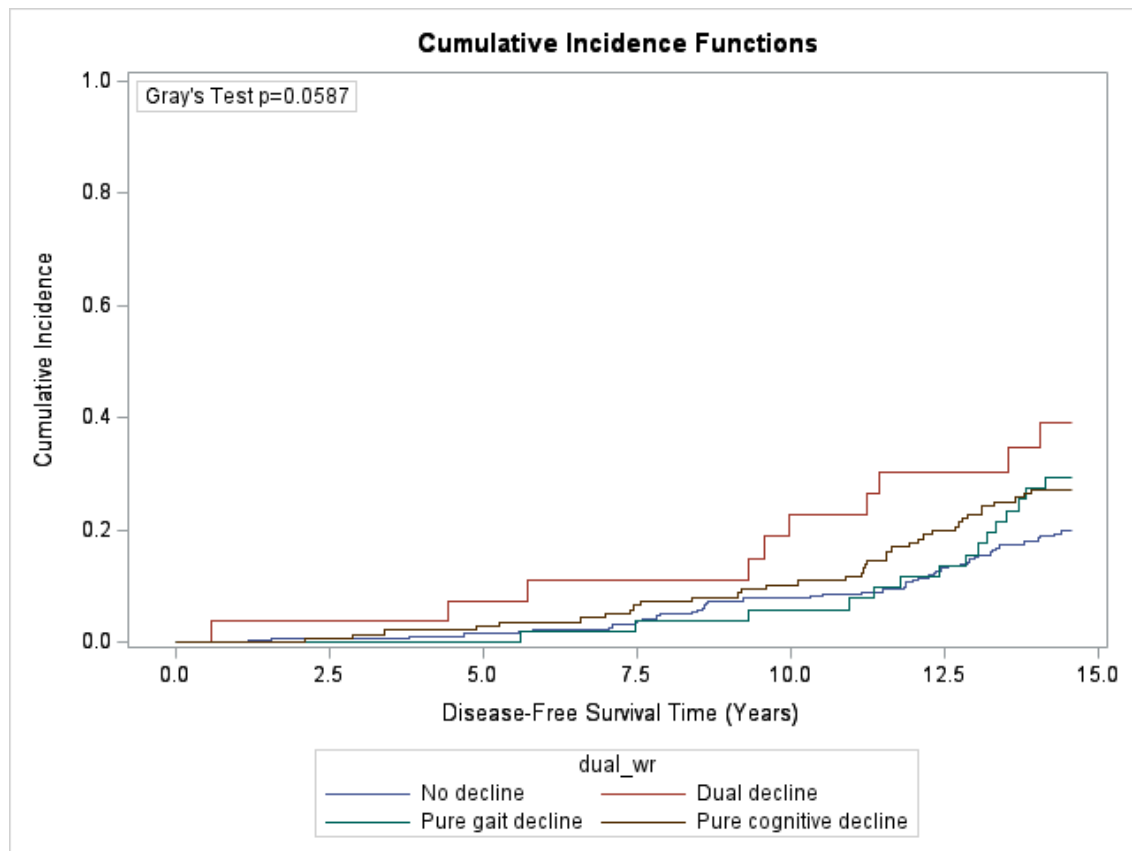
Note, sHRs of dual decline group were presented in Table 11, Forward-DS were eliminated due to finding no sex difference.

sTable 7 sHRs of covariates in fully adjusted Fine-Gray model in female (N=251)

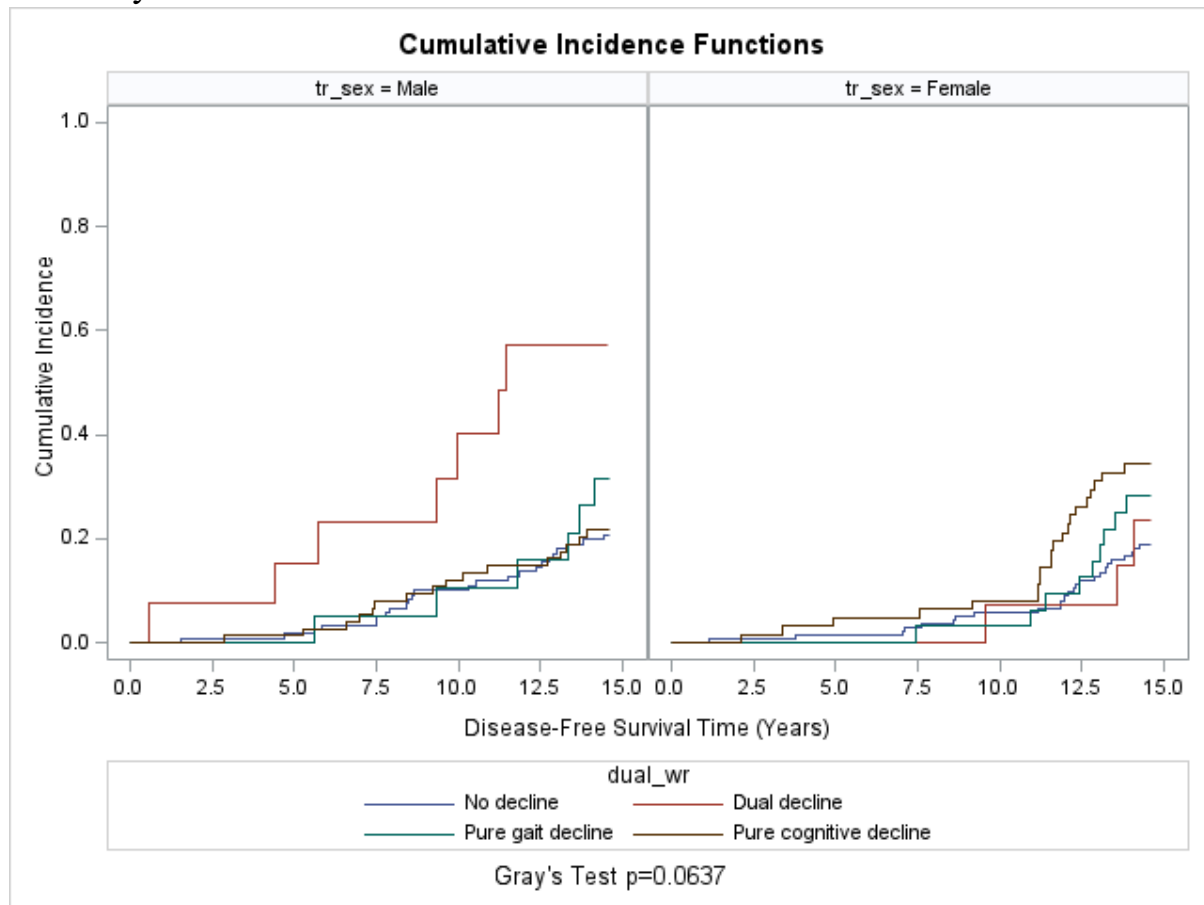
		N of cases	Percentage	WR			IRS			Backward-DS		
				SHRs	95%CI		SHRs	95%CI		SHRs	95%CI	
Cognitive test				0.8	0.6	1.0	0.6	0.1	2.1	1.9	0.6	5.6
Gait speed	Slow	9	31.0	1.7	0.5	5.2	1.9	0.7	5.5	1.4	0.6	3.0
	Normal	42	22.58	1.2	0.6	2.8	1.4	0.6	2.9	0.9	0.7	1.2
	Fast	7	22.6	1			1			1		
Educational background	Junior or lower	27	19.4	1			1			1		
	High school	24	20.0	0.9	0.5	1.9	0.8	0.4	1.5	0.9	0.5	1.8
	College or higher	7	20.6	0.8	0.3	2.3	0.6	0.2	1.6	0.6	0.2	1.8
Smoking status	Never smoker	51	21.9	1			1			1		
	Current smoker	4	40.0	2.2	0.6	8.5	2.7	0.8	9.9	2.8	0.8	9.5
	Past smoker	3	37.5	1.6	0.5	4.9	1.3	0.4	4.6	1.1	0.3	4.4
living alone	Yes	5	35.7	1.7	0.7	4.3	1.4	0.5	4.1	1.5	0.5	4.3
	Other	53	22.6	1			1			1		
Presence of medical histories	Yes	13	20.6	0.8	0.4	1.5	0.8	0.4	1.5	0.8	0.4	1.5
	No	45	23.9	1			1			1		
Total social activity measure ≥ 8	Yes	27	22.3	0.9	0.5	1.5	1.0	0.6	1.8	1.1	0.6	1.9
	No	31	23.9	1			1			1		
Regular exercise habits	Yes	22	18.8	0.7	0.4	1.3	0.7	0.4	1.3	0.7	0.4	1.4
	No	36	27.1	1			1			1		

Note, sHRs of dual decline group were presented in Table 11, Forward-DS were eliminated due to finding no sex difference.

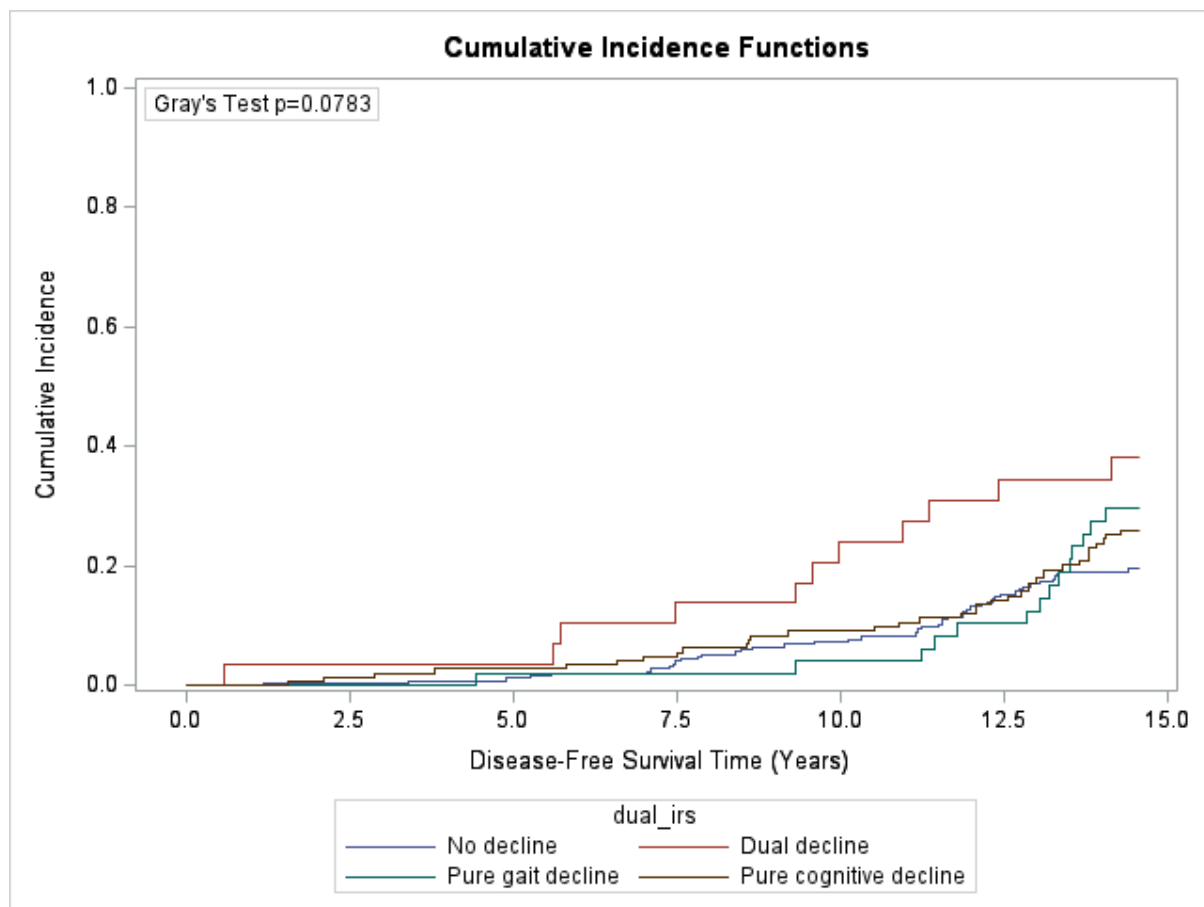
Supplementary figure 1 non-parametric cumulative incidence curve of Word Recall



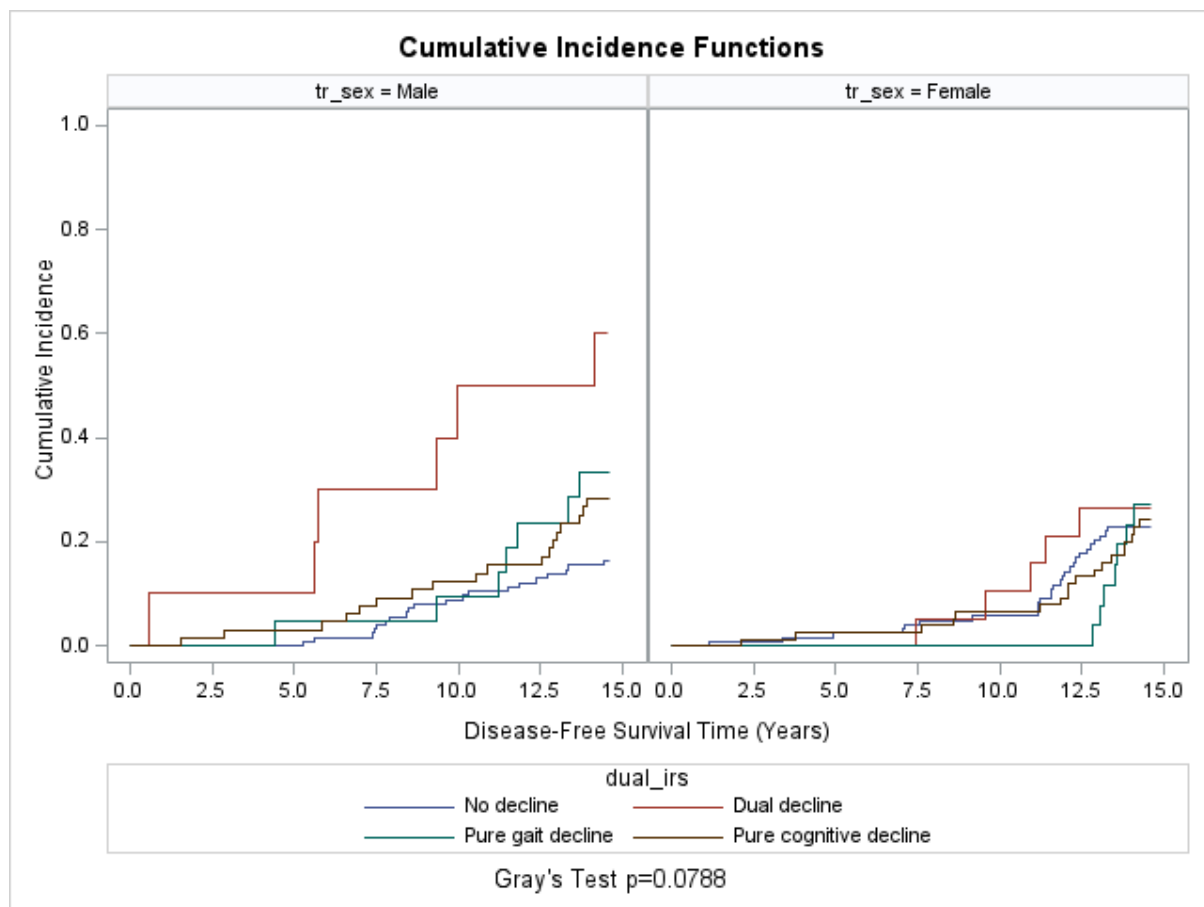
Supplementary figure 2 non-parametric cumulative incidence curve of Word Recall by sex



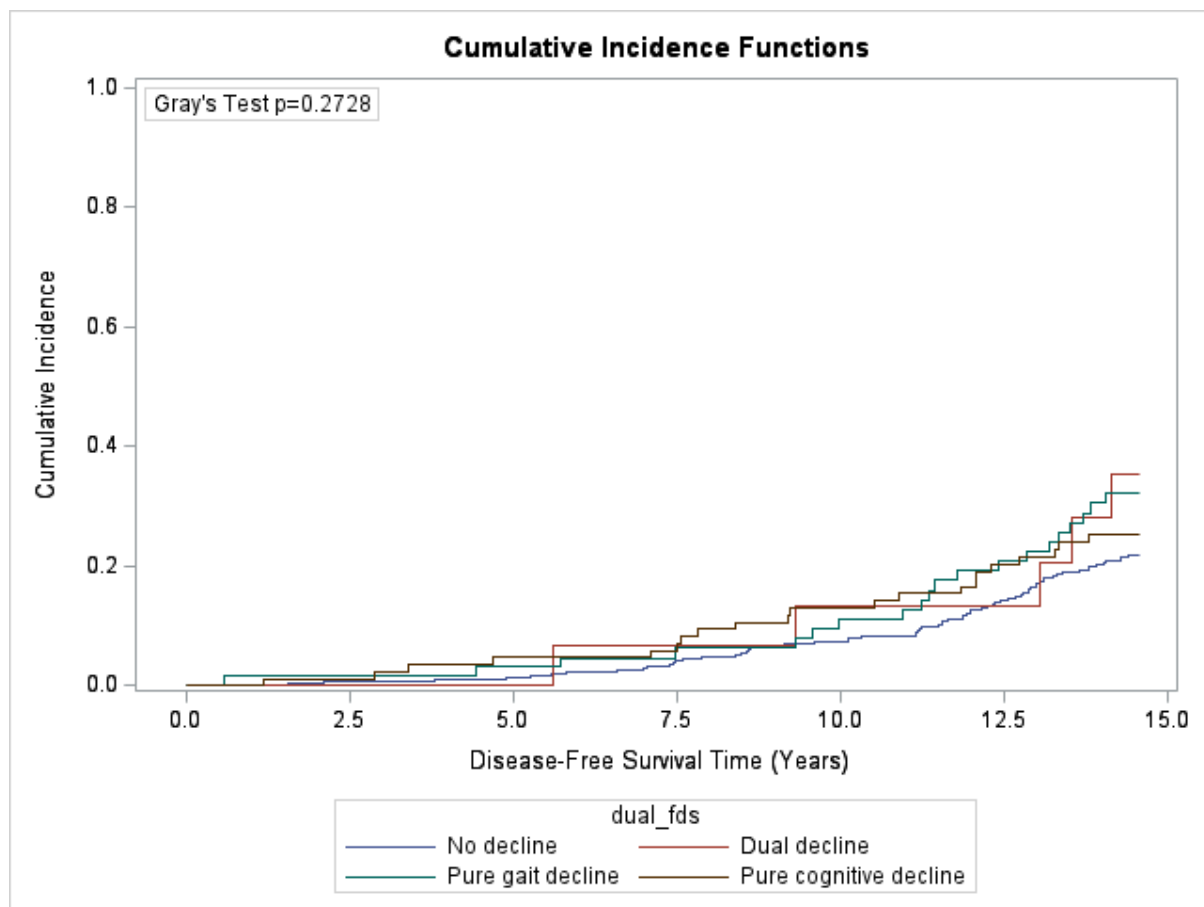
Supplementary figure 3 non-parametric cumulative incidence curve of Inference Ratio



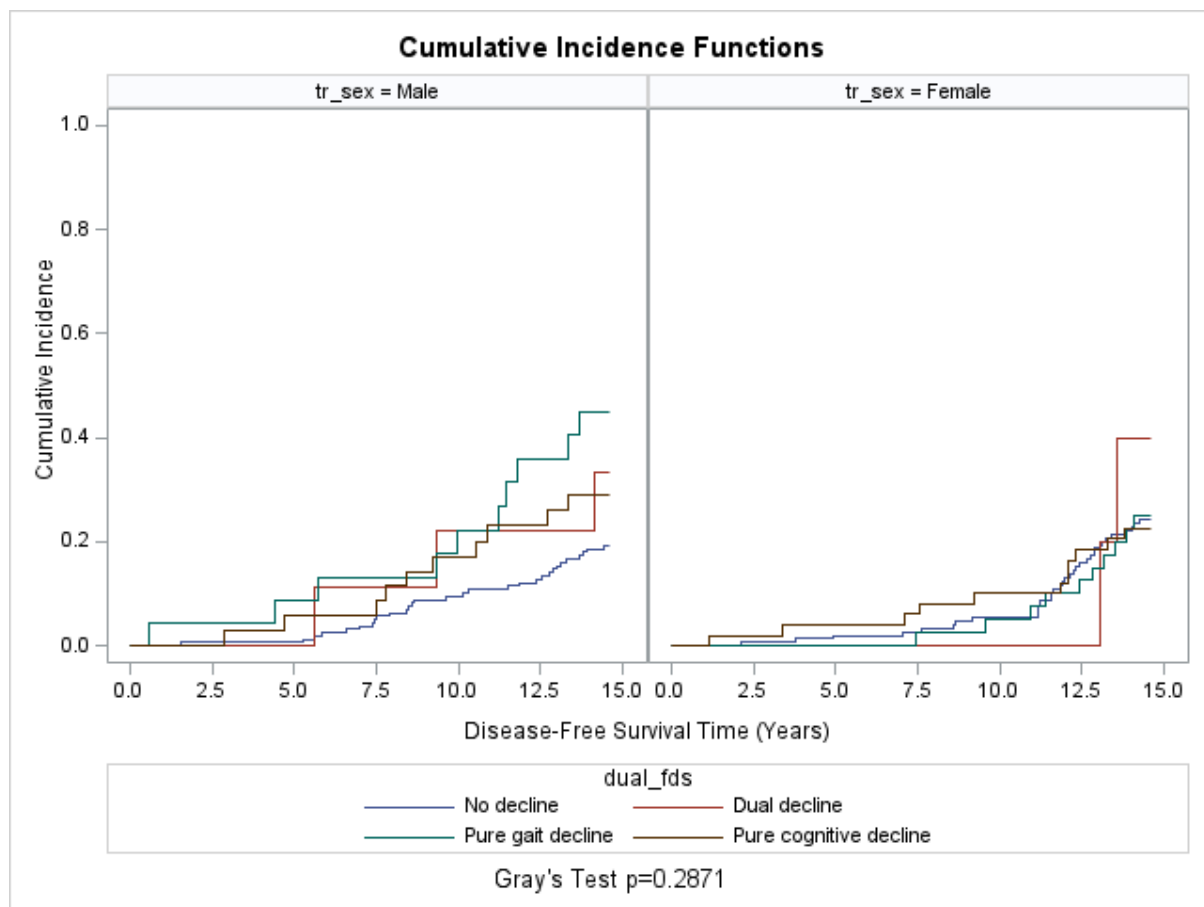
Supplementary figure 4 non-parametric cumulative incidence curve of Inference Ratio by sex



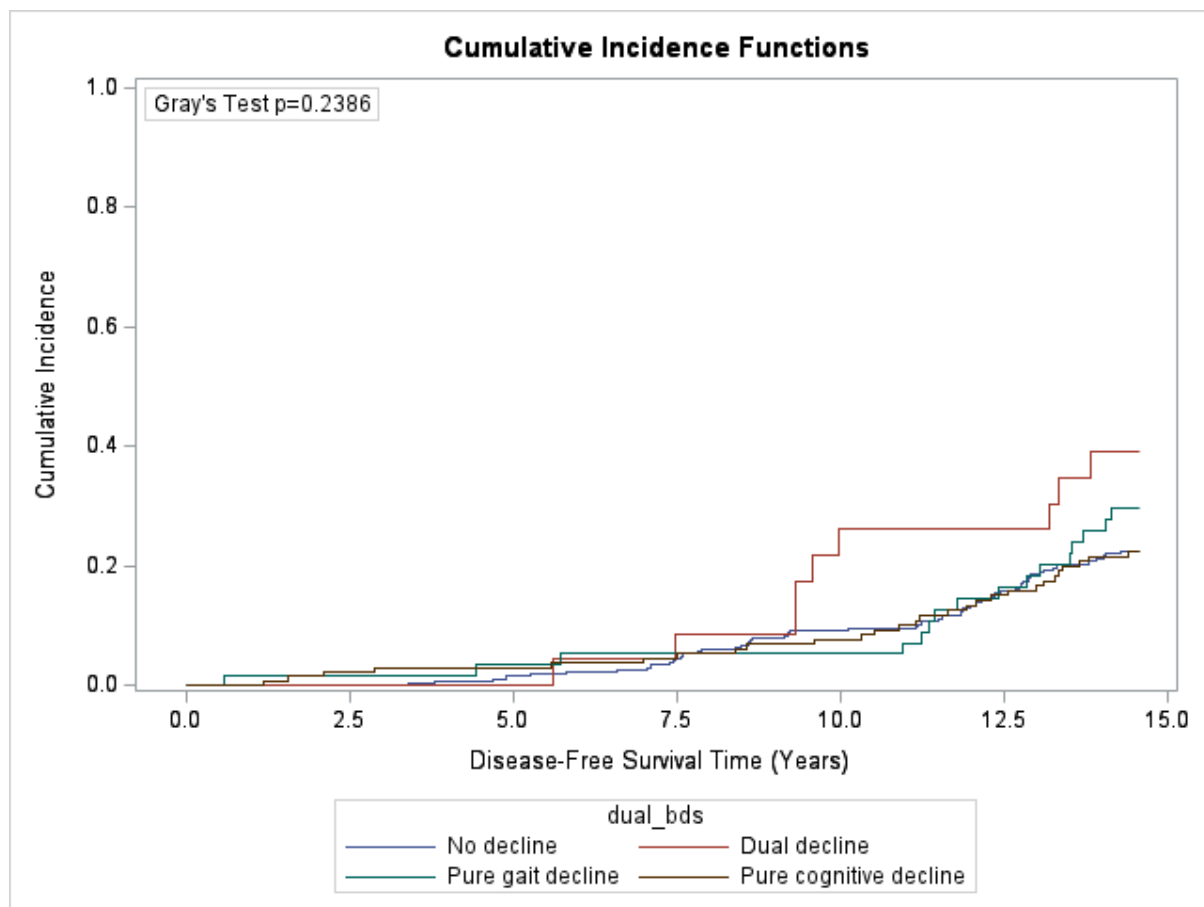
Supplementary figure 5 non-parametric cumulative incidence curve of Forward-Digit span



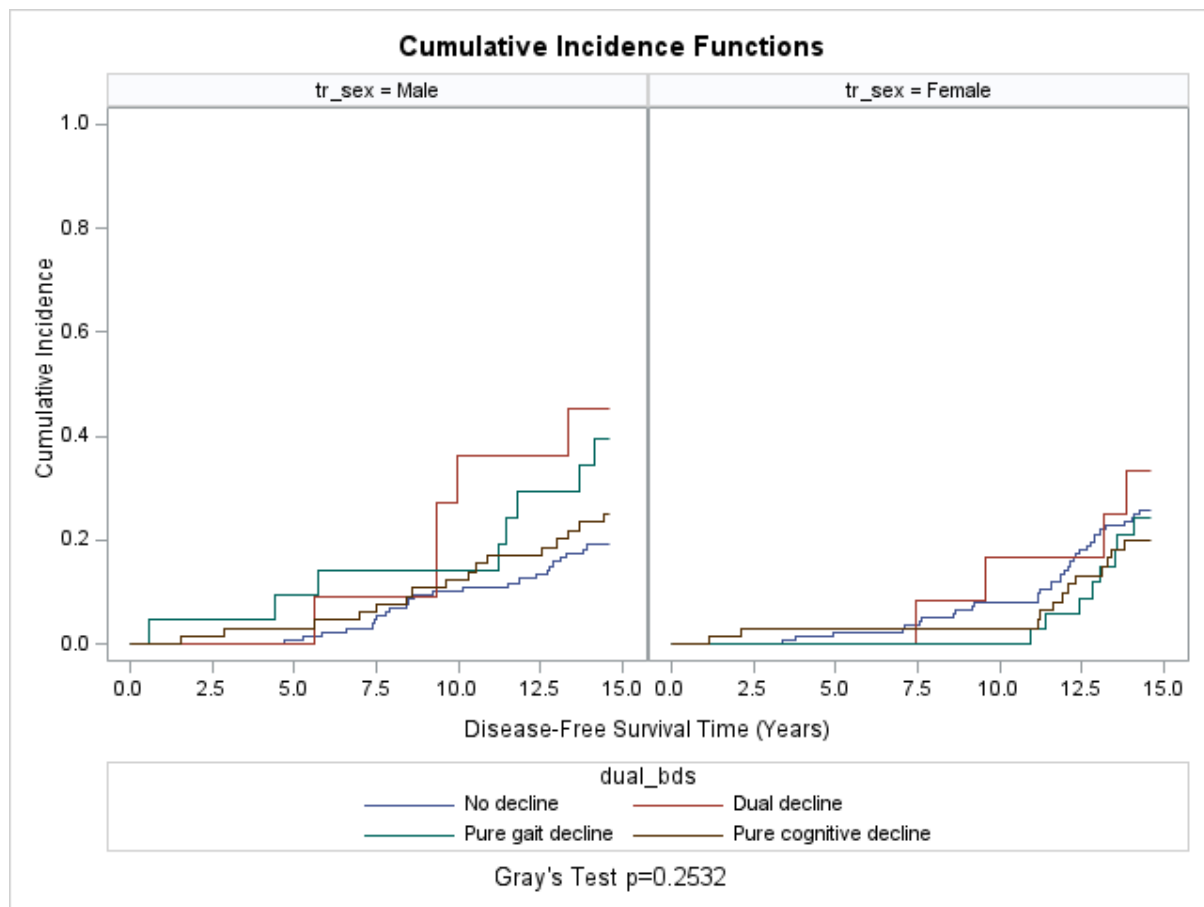
Supplementary figure 6 non-parametric cumulative incidence curve of Forward-Digit span by sex



Supplementary figure 7 non-parametric cumulative incidence curve of Backward-Digit span



Supplementary figure 8 non-parametric cumulative incidence curve of Backward-Digit span by sex



Conclusions

The global aging trend has led to a dramatic increase in the older population, this demographic change is increasing the prevalence of NDDs worldwide, particular in Japan. The relationship between gait and cognitive function in older adults has been growingly recognized as a significant area of research due to its potential implications for early diagnosis and intervention strategies for conditions like dementia. Under this background, the studies summarized here provide additional valuable insights into how gait is associated with cognitive function and the risk of dementia.

Chapter 1 investigated the associations between various gait parameters and cognitive functions in a cohort of older adults aged 70–81 years. The study utilized advanced gait sensors to analyze the comprehensive gait and its relation to cognitive function both cross-sectionally and longitudinally. Key findings from this study include:

- Significant associations between the general gait cycle and global cognitive function were observed in both cross-sectional and longitudinal studies.
- The general cycle and initial contact phase of the gait cycle was related to better executive function in cross-sectional assessments but did not show a consistent relationship in longitudinal data.
- Despite the inclusion of various gait parameters, significant associations were only found between the general gait cycle and cognitive function, suggesting that basic gait metrics may be insufficient indicators of cognitive health.

Chapter 2 focused on a long-term cohort with an average follow-up of 12.5 years, tracking changes in gait and cognitive function among older individuals from the youngest-old age (65-70 years) to before the age of 85. This study's findings include:

- Older individuals exhibiting a dual decline in subjective gait speed and specific cognitive domains were at a higher risk of developing dementia by age 85 compared to whom with single or no decline in either gait or cognition.
- The greatest risk was found in people with a combined decline in subjective gait speed and Memory.
- Sex differences were noted, with male participants showing significantly higher risks of dementia while female participants are not.
- The study suggests that dual decline is indicative of underlying brain pathology and serves as a strong early predictor of dementia, especially in male.

The converging findings from these studies underline the critical interplay between gait and cognitive health. It is suggested that gait, particularly its speed, could serve as an early clinical marker for cognitive decline and dementia risk. This is especially pertinent given the differential impacts observed between sexes and across specific cognitive domains.

Implications for Future Research

- Both studies highlight the need for larger sample sizes and more personal characteristics and comprehensive neuropsychological assessments to further elucidate the causal relationships between gait and cognitive functions.
- Future research should also explore the potential of routine gait and cognitive decline screening as part of clinical assessments to identify individuals at high risk of dementia.
- Additionally, examining the role of vascular risk factors and other modifiable elements in slowing the progression of NDDs through early preventative measures could be crucial.

Overall, these studies contribute to the growing body of evidence suggesting that monitoring gait could be an effective non-invasive way to predict and potentially mitigate the progression of dementia, highlighting the need for integrated approaches in geriatric care and research.

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Disclosure of conflicts of interest

The author declares no conflict of interest.

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