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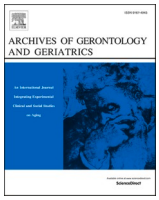

Association of gait speed with regional brain volumes and risk of dementia in older Japanese: The Hisayama study

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ABSTRACT

Background: To investigate the association of gait speed with regional brain volumes and the risk of incident dementia.

Methods: A total of 1112 dementia-free Japanese residents aged ≥65 years who underwent brain magnetic resonance imaging were followed for 5.0 years (median). The participants were classified into the age- and sex-specific quartile levels of maximum gait speed. Regional gray matter volumes (GMV) and white matter hyperintensities volumes (WMHV) were measured by applying voxel-based morphometry methods. The cross-sectional association of maximum gait speed with regional GMV was examined using an analysis of covariance. We also estimated the association between maximum gait speed level and the risk of developing dementia using a Cox proportional hazards model. Mediation analyses were conducted to determine the contribution of regional brain volumes to the association between maximum gait speed and dementia.

Results: Lower maximum gait speed was significantly associated with lower GMV of the total brain, frontal lobe, temporal lobe, cingulate gyrus, insula, hippocampus, amygdala, basal ganglia, thalamus, and cerebellum, and increased WMHV at baseline. During the follow-up, 108 participants developed dementia. The incidence rate of all dementias increased significantly with decreasing maximum gait speed after adjusting for potential confounders (P for trend = 0.03). The mediating effects of the GMV of the hippocampus, GMV of the insula, and WMHV were significant.

Conclusions: Lower maximum gait speed was significantly associated with an increased risk of dementia. Reduced GMV of the hippocampus or insula, and an increase in WMHV was likely to be involved in this association.

1. Introduction

The rapidly increasing number of people with dementia has become a major medical and social problem worldwide (World Alzheimer Report, 2015). Although the causes of dementia are gradually being revealed, they are still incompletely understood. Therefore, there is an urgent need to identify possible risk factors for dementia (Norton et al., 2014).

Gait speed is one of the most widely used measures of physical function in clinical practice (Middleton et al., 2015; Peel et al., 2013). Recent epidemiological studies have shown that lower gait speed is associated with an increased risk of future nursing care needs, fractures, hospitalization, and death (Perera et al., 2016; Studenski et al., 2011) Additionally, it has been reported that lower gait speed is associated with cognitive decline and the risk of dementia (Beauchet et al., 2016; Kuate-Tegueu et al., 2017; Peel et al., 2019; Quan et al., 2017)

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Decrements of gait speed are multifactorial (Ferrucci et al., 2000; Rosso et al., 2015): not only aging, musculoskeletal diseases, and cardiorespiratory diseases, but also neurodegenerative cerebral diseases and cerebral microvascular diseases can affect gait speed (Stijntjes et al., 2016). Several clinical studies of gait speed and brain magnetic resonance imaging (MRI) have reported that lower gait speed is associated with decreased volume of cerebral gray matter (Allali et al., 2019; Callisaya et al., 2014; Dumurgier et al., 2012) and increased volume of cerebral white matter hyperintensities (Zheng et al., 2011). Since significant associations of gray matter atrophy or white matter hyperintensities enlargement with the increased risk of dementia have been reported (Nakazawa et al., 2022; Prins & Scheltens, 2015; Wu et al., 2019), it is assumed that there are shared neural substrate changes between reduced gait speed and cognitive decline (Montero-Odasso & Hachinski, 2014; Rosso et al., 2013). To date, however, only one population-based study has examined the brain imaging regions shared by gait slowing and cognitive impairment (Rosso et al., 2017). Clearly, further investigations will be needed to fully address this issue.

The objectives of this study were to evaluate the association between gait speed and the regional gray matter volume (GMV) or white matter hyperintensities volume (WMHV), and to investigate the association between gait speed levels and the development of dementia and its subtypes, taking the influence of the regional GMV and WMHV on the association into account.

2. Methods

2.1. Study population

The Hisayama Study is an ongoing population-based prospective cohort study of cerebrovascular and cardiovascular diseases, which was established in 1961 in the town of Hisayama, a suburb of Fukuoka City in southern Japan (Ninomiya, 2018) Health examinations of physical and neurological conditions have been repeated in this town every 1–2 years. In addition, comprehensive surveys of dementia in the older residents have been conducted every 5–7 years since 1985. In 2012–2013, a total of 1906 individuals (93.6%) among 2036 residents aged ≥65 years participated in the screening survey, of which 1342 participants underwent brain MRI scanning (Hirabayashi et al., 2022). For the present study, we selected the analyzed participants according to the flow shown in Supplementary Fig. 1. First, 44 individuals who did not consent to participate in the study, 2 individuals without available data of cognitive function, 2 individuals with disturbance of consciousness or mental retardation, and 339 individuals with dementia at baseline were excluded from the 1906 participants in order to select the study participants who consented to participate in the study and did not have dementia at baseline. Next, from the remaining 1519 individuals, 356 participants without available data of maximum gait speed, 41 participants without available brain MRI data (16 without T1-weighted three-dimensional images, 3 without fluid attenuated inversion recovery images, 4 with metal artifacts, 2 with excessive motion artifact, 1 who did not consent to use the MRI data, and 15 who did not undergo brain MRI scanning) were excluded. As a result, 1122 individuals (499 men and 623 women) were finally enrolled in this study. In the analysis of the association of maximum gait speed and the data from brain MRI, participants with cortical or cerebellar infarcts ($n = 39$) were additionally excluded to avoid measurement error.

2.2. Follow-up surveys

The participants were followed for a median of 5.0 years (interquartile range 4.9–5.1 years) from the baseline examination. We have reported details of the procedures for screening potential dementia events elsewhere (Ohara et al., 2017) Except for deceased cases, no participants were lost to follow-up. Additionally, a comprehensive neuropsychological screening for dementia was conducted in 2017–2018 to detect dementia cases as accurately as possible, which 95.7% of the study participants underwent. In the baseline survey at 2012–2013 and the follow-up survey at 2017–2018, dementia was diagnosed using a two-step diagnostic system, where the screening survey was conducted by trained doctors, public health nurses, nurses and clinical psychologists using the Mini-Mental State Examination (MMSE), (Folstein et al., 1975) followed by comprehensive investigations based on physical and neurological examinations including the Wechsler Memory Scale of logical memory (Wechsler, 1987) by a specialized psychiatrist for participants with suspected dementia.

2.3. Assessment of maximum gait speed

Maximum gait speed was measured twice on a 5 m course at baseline in 2012–2013, and the faster of the two measurements was used for the analysis. Participants were encouraged to walk as fast as possible. The time in seconds was measured using a digital stopwatch and gait speed was expressed in meters by seconds (m/s). The participants were divided into four categories based on age- and sex-specific quartiles of maximum gait speed, where the age-groups were categorized by 5-year intervals in order to control for the confounding caused by a rapid decrease in the gait speed with aging (Supplementary Table 1).

2.4. Diagnosis of dementia

The diagnosis of dementia was made based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (American Psychiatric Association, 1987). Participants diagnosed as having Alzheimer's disease (AD) met the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984) and participants diagnosed with vascular dementia (VaD) met the criteria of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et I'Enseignement en Neurosciences criteria (Román et al., 1993). The diagnosis of probable or possible dementia subtypes was based on the clinical information and morphological analysis of neuroimages, such as brain computed tomography and MRI. For autopsied participants with dementia, we also made a diagnosis of definite dementia subtypes based on neuropathological and clinical information. All dementia cases were adjudicated by expert psychiatrists and stroke physicians on the study team.

2.5. Brain MRI analysis

The details of brain MRI data acquisition and processing were described previously (Nakazawa et al., 2022; Yamasaki et al., 2020). In the present study, we analyzed each regional brain volume as the sum of the left and right values. The intracranial volume (ICV) was calculated as the sum of the gray matter, white matter, and cerebrospinal fluid volumes. Cerebrovascular lesions were defined as brain infarction or hemorrhage on MRI regardless of the presence or absence of neurological symptoms. Each MRI scan was checked by two trained stroke physicians blinded to the clinical information (inter-rater agreement ratio: 74.8% for the brain infarctions, 83.7% for the brain hemorrhages) (Nakazawa et al., 2022) In the case of conflicting interpretations, a third stroke physician checked the scan and decided.

2.6. Risk factor measurements

Detailed definitions of the risk factors obtained in the baseline survey are provided in online supplemental material.

2.7. Statistical analysis

The WMHV/ICV (%) was natural log transformed because its

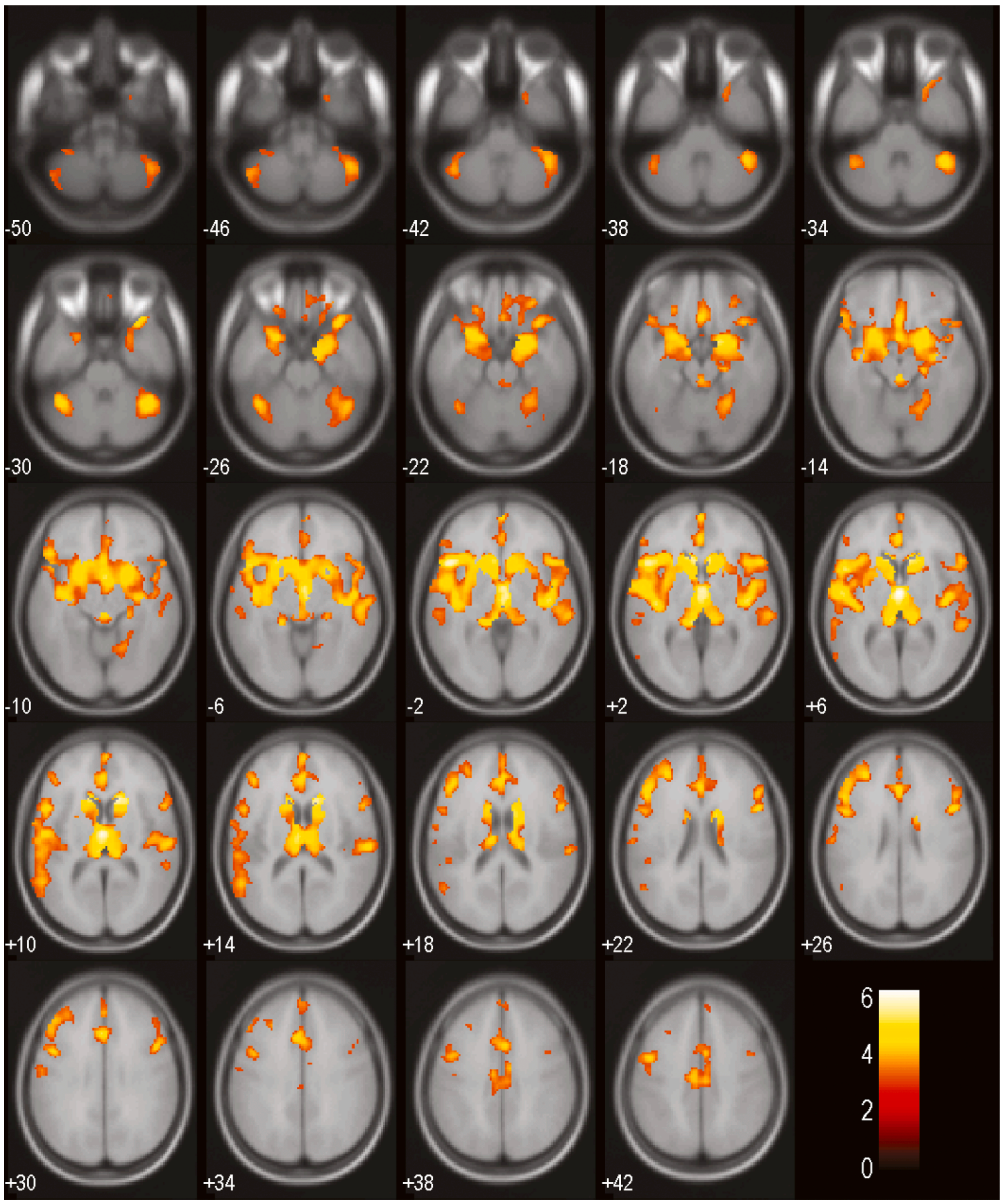

Fig. 1. Association between maximum gait speed levels and gray matter volume based on voxel-based morphometry analysis.
Areas where gait speed level and brain volume are positively correlated are colored. The region of smaller gray matter volume mainly involved the frontal, temporal, and medial temporal lobe, and the cingulate, insular, hippocampus, accumbens, amygdala, caudate, putamen, thalamus, and cerebellum. Adjusted for covariates: age, sex, education level, systolic blood pressure, antihypertensive agents, diabetes, serum total cholesterol, body mass index, electrocardiogram abnormalities, cerebrovascular lesions on MRI, smoking habit, alcohol intake, and regular exercise.
Participants with cortical or cerebellar infarcts (n = 39) and participants with missing covariates data (n = 29) were excluded from the analysis.
Statistical parametric mappings were thresholded at uncorrected $P < 0.001$ at the peak level combined with a familywise error rate correction of $P < 0.05$ at the cluster level.

distribution was skewed. The linear trends of the mean values or frequencies of risk factors across maximum gait speed levels were tested using linear or logistic regression analysis. The statistical parametric mapping of the association between maximum gait speed levels and GMV was generated using a multiple regression model with potential confounding factors and ICV as covariates in the voxel-based correlation analysis. Statistical parametric mappings were thresholded at uncorrected $P < 0.001$ at the peak level combined with a familywise error rate correction of $P < 0.05$ at the cluster level. The details of the statistical parametric mapping have been described elsewhere (Hirabayashi et al., 2022) In addition, the multivariable-adjusted mean values of total GMV/ICV, GMV/ICV of the brain regions related to maximum gait speed in voxel-based analysis and WMHV/ICV were estimated using an analysis of covariates, and their trends were tested with linear regression analysis. The incidences of total dementia and its subtypes were calculated using the person-year method. The hazard ratios (HRs) and their 95% confidence intervals (CIs) of total dementia and its subtypes across the maximum gait speed levels were estimated using a Cox proportional hazards model. In the multivariable-adjusting analysis, the following covariates were added to the relevant model: age, sex, education level, systolic blood pressure, antihypertensive agents, diabetes, serum total cholesterol, body mass index, history of stroke, electrocardiogram abnormalities, smoking habit, alcohol intake, and regular exercise. Instead of adding history of stroke, cerebrovascular lesions on MRI were added to the above covariates for the analysis of the association between maximum gait speed levels and mean values of GMV/ICV and WMHV/ICV. In addition, mediation analysis was conducted to quantify the role of changes in regional brain volumes in the association between maximum gait speed and incident dementia. As the brain regions of interest in this analysis, we selected the following gait- and dementia-related brain regions based on previous studies (Nakazawa et al., 2022; Wilson et al., 2019): the total gray matter, medial temporal lobe, insula, hippocampus, amygdala, and white matter hyperintensities. The mediation effect of the brain region was estimated using a SAS macro developed by Valeri and VanderWeele that allows for mediation analysis using Cox regression (Valeri & VanderWeele, 2015) These statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC). P values < 0.05 were considered significant.

Table 1
Adjusted mean values of the regional gray matter volume / intracranial volume and white matter hyperintensity volume / intracranial volume according to age- and sex-specific quartile levels of maximum gait speed.

	Maximum gait speed levels				
	Q1 (lowest)	Q2	Q3	Q4 (highest)	
	(n = 233)	(n = 244)	(n = 281)	(n = 296)	P for trend
Total GMV/ICV,%	38.365** (0.163)	38.875* (0.156)	38.997 (0.145)	39.469 (0.144)	<0.001
Frontal GMV/ICV, %	9.761** (0.051)	9.918* (0.049)	9.938 (0.046)	10.086 (0.045)	<0.001
Temporal GMV/ ICV,%	7.139** (0.039)	7.256 (0.037)	7.266 (0.035)	7.356 (0.034)	<0.001
Cingulate GMV/ ICV,%	1.764** (0.008)	1.787 (0.007)	1.794 (0.007)	1.810 (0.007)	<0.001
Insular GMV/ICV, %	0.846** (0.006)	0.878 (0.005)	0.863 (0.005)	0.881 (0.005)	0.001
Hippocampal GMV/ICV,%	0.628** (0.004)	0.642 (0.004)	0.641 (0.003)	0.645 (0.003)	0.002
Medial temporal GMV/ICV,%	0.653* (0.004)	0.658 (0.004)	0.661 (0.004)	0.667 (0.004)	0.01
Amygdala GMV/ ICV,%	0.177** (0.001)	0.180 (0.001)	0.180 (0.001)	0.184 (0.001)	<0.001
Basal ganglia GMV/ICV,%	0.689** (0.011)	0.724** (0.011)	0.725** (0.010)	0.769 (0.010)	<0.001
Thalamus GMV/ ICV,%	0.547** (0.005)	0.567* (0.005)	0.575 (0.005)	0.585 (0.005)	<0.001
Cerebellum GMV/ ICV,%	5.802* (0.045)	5.874 (0.043)	5.929 (0.040)	5.987 (0.040)	0.002
WMHV/ICV,%	0.258** (0.081)	0.167 (0.078)	0.193 (0.072)	0.163 (0.071)	0.001

Abbreviations: GMV, gray matter volume; ICV, intracranial volume; WMHV, white matter hyperintensity volume.
Values are shown as adjusted mean values (standard error).
Participants with cortical or cerebellar infarcts (n = 39) and participants with missing covariates data (n = 29) were excluded from the multivariable-adjusted analyses.
The values were adjusted for covariates: age, sex, education level, systolic blood pressure, antihypertensive agents, diabetes, serum total cholesterol, body mass index, electrocardiogram abnormalities, smoking habit, alcohol intake, regular exercise, and cerebrovascular lesions on MRI.
*P < 0.05, **P < 0.01 vs. Q4.

3. Results

3.1. Participant characteristics

Supplementary Table 2 shows the baseline characteristics of study participants according to the age- and sex-specific maximum gait speed levels. The mean values of BMI and the frequencies of low education, hypertension, use of antihypertensive agents, history of stroke, cerebrovascular lesions on MRI, and cognitive decline increased significantly with lower maximum gait speed levels. Conversely, the frequencies of current alcohol intake and regular exercise decreased significantly with slowing maximum gait speed levels.

3.2. Gait speed and brain regions

Fig. 1 shows the results of the multivariable-adjusted VBM analysis, for which the Montreal Neurological Institute coordinates of cluster are shown in Supplementary Table 3. Lower maximum gait speed was correlated with smaller GMV in the frontal lobe, temporal lobe, medial temporal lobe, cingulate gyrus, insula, hippocampus, amygdala, basal ganglia, thalamus, and cerebellum. Next, we investigated the association of the age- and sex-specific quartile levels of maximum gait speed with multivariable-adjusted mean values of total GMV/ICV, GMV/ICV of the above 10 brain regions and WMHV/ICV. As a result, significant associations were observed for total GMV/ICV, GMV/ICV of all 10 brain regions, and WMHV/ICV (Table 1).

3.3. Gait speed and dementia risk

During the follow-up period, 108 participants (45 men and 63 women) developed total dementia. Among them, one participant had a mixed type of AD and VaD, and this case was counted as an event in the analysis for each subtype. In all, 78 participants developed AD and 14 participants developed VaD. The incidence rates of total dementia and AD increased with decreasing age- and sex-specific quartile levels of maximum gait speed (both P for trend < 0.05), while there was no association between maximum gait speed levels and the development of VaD (P for trend = 0.59) (Fig. 2). Table 2 shows the estimated HRs and 95% CIs for the development of dementia and its subtypes according to the age- and sex-specific quartile levels of maximum gait speed. The

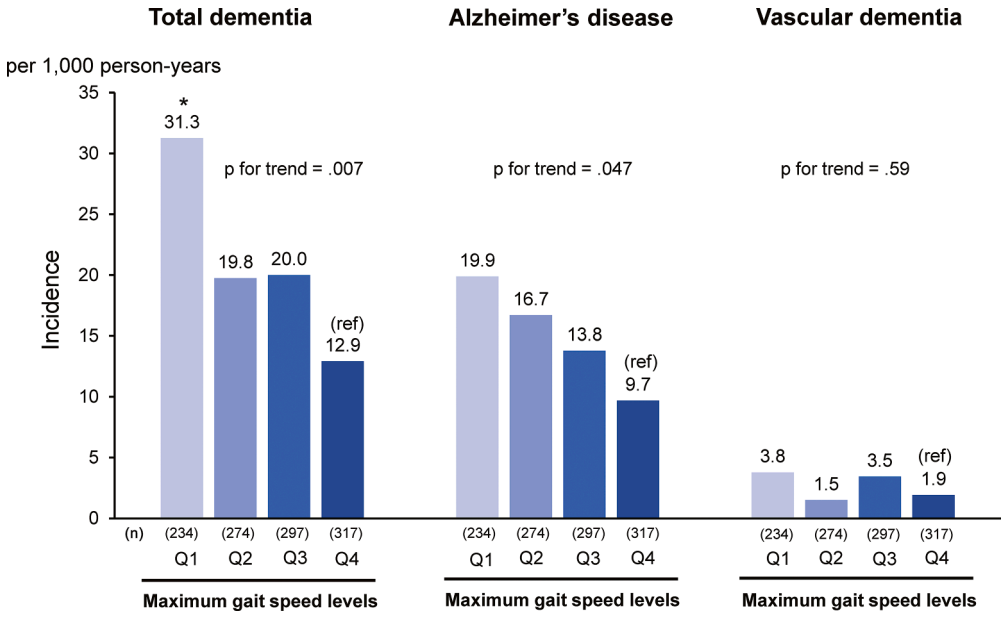

Fig. 2. Crude incidence rate of total dementia, Alzheimer's disease, and vascular dementia according to age- and sex-specific quartile levels of maximum gait speed.
*P < 0.05 vs Q1.

Table 2
Risk of the development of total dementia and its subtypes according to age- and sex-specific quartile levels of maximum gait speed during a 5-year follow-up period, 2012–2017.

Maximum gait speed levels	No. of events / participants	Crude HR (95% CI)	*P* value	Multivariable-adjusted* HR (95% CI)	*P* value
Total dementia					
Q4 (highest)	20 / 317	1.00 (reference)		1.00 (reference)	
Q3	29 / 297	1.54 (0.87–2.72)	0.14	1.39 (0.78–2.48)	0.26
Q2	26 / 274	1.44 (0.81–2.59)	0.22	1.24 (0.67–2.29)	0.50
Q1 (lowest)	33 / 234	2.26 (1.30–3.95)	0.004	2.01 (1.11–3.61)	0.02
P for trend			0.007		0.03
Per 0.1 m/s decrement		1.16 (1.11–1.21)	<0.001	1.10 (1.03–1.16)	0.002
Alzheimer's disease					
Q4 (highest)	15 / 317	1.00 (reference)		1.00 (reference)	
Q3	20 / 297	1.41 (0.72–2.75)	0.32	1.29 (0.66–2.54)	0.46
Q2	22 / 274	1.63 (0.84–3.14)	0.15	1.47 (0.73–2.93)	0.28
Q1 (lowest)	21 / 234	1.93 (0.99–3.74)	0.05	1.76 (0.88–3.52)	0.11
P for trend			0.05		0.11
Per 0.1 m/s decrement		1.16 (1.1–1.22)	<0.001	1.08 (1.01–1.16)	0.02
Vascular dementia					
Q4 (highest)	3 / 317	1.00 (reference)		1.00 (reference)	
Q3	5 / 297	1.79 (0.43–7.50)	0.42	1.73 (0.41–7.34)	0.46
Q2	2 / 274	0.79 (0.13–4.73)	0.80	0.62 (0.10–3.96)	0.62
Q1 (lowest)	4 / 234	2.01 (0.45–8.96)	0.36	1.34 (0.26–7.02)	0.73
P for trend			0.59		1.00
Per 0.1 m/s decrement		1.12 (0.98–1.27)	0.09	1.09 (0.92–1.28)	0.31

Abbreviations: MMSE; Mini-Mental State Examination; HR, hazard ratio; CI, confidence interval.
*HRs and 95% CIs were adjusted for age, sex, education level, systolic blood pressure, use of antihypertensive agents, diabetes, serum total cholesterol, body mass index, history of stroke, electrocardiogram abnormalities, smoking habit, alcohol intake, and regular exercise, where 29 individuals with missing covariates data were excluded from the analyses.

crude HRs for total dementia (HR 2.26, 95% CI 1.30–3.95 for the first quartile against the fourth quartile) and AD (HR 1.93, 95% CI 0.99–3.74) increased with lower maximum gait speed levels. These excess risks of developing total dementia were observed after adjusting for potential confounding factors (HR 2.01, 95% CI 1.11–3.61). Every 0.1 m/s decrement in maximum gait speed was associated significantly with 10% (95% CI 3–16%) and 8% (95% CI 1–16%) increased multivariable-adjusted risk of developing total dementia and AD, respectively. In the sensitivity analyses after excluding participants with an MMSE of <24 or those who developed dementia within one year, the findings were not altered substantially (Supplementary Table 4).

3.4. Mediation analysis

Finally, we conducted mediation analysis to exam whether and to what extent the specific brain regions mediated the association between maximum gait speed and dementia risk. When the GMV/ICV of hippocampus or insula, or WMHV/ICV was used as the mediating variable in the analysis, the natural direct effect was not statistically significant and the percentage of the total association between maximum gait speed and dementia risk mediated by each was over 20% (Table 3).

Table 3
Association of maximum gait speed and risk of dementia mediated by the gait- and dementia-related brain regions.

Mediator	Hazard ratio (95% confidence interval)[a] Total effect	Natural direct effect	Natural indirect effect	% Mediated
Total GMV/ICV,%	2.09 (1.16–3.77)	1.92 (1.07–3.46)	1.09 (1.00–1.18)	15.4%
Medial temporal GMV/ICV,%	2.10 (1.17–3.80)	1.96 (1.09–3.53)	1.07 (1.00–1.15)	12.7%
Insular GMV/ICV, %	1.99 (1.10–3.59)	1.76 (0.97–3.18)	1.13 (1.03–1.24)	23.3%
Hippocampal GMV/ICV,%	1.98 (1.09–3.58)	1.70 (0.94–3.08)	1.16 (1.05–1.27)	27.8%
Amygdala GMV/ICV,%	2.11 (1.17–3.81)	1.90 (1.06–3.42)	1.11 (1.03–1.20)	19.1%
WMHV/ICV,%	2.04 (1.13–3.68)	1.74 (0.96–3.15)	1.17 (1.03–1.33)	28.8%

Abbreviations: GMV, gray matter volume; ICV, intracranial volume; WMHV, white matter hyperintensity volume.
(a) Hazard ratios and their 95% confidence intervals of the first against the fourth age- and sex-specific quartile levels of maximum gait speed are shown. The model was adjusted for age, sex, education level, systolic blood pressure, use of antihypertensive agents, diabetes, serum total cholesterol, body mass index, history of stroke, electrocardiogram abnormalities, smoking habit, alcohol intake, and regular exercise.

4. Discussion

The present study demonstrated that lower maximum gait speed was significantly associated with lower GMV in the limbic system (hippocampus, amygdala, cingulate gyrus), basal ganglia, frontal lobe, temporal lobe, insula, and cerebellum and also was significantly associated with higher WMHV in a general older Japanese population. In addition, lower maximum gait speed was significantly associated with an increased risk of total dementia during a 5-year follow-up. This association was partially mediated by the reduced GMV of the hippocampus and insula, or the increase in WMHV. These findings suggest that decreasing gait speed may be one of the clinical signs for the brain changes related to cognitive function and subsequent future dementia risk.

Our findings raise the possibility that any common neural basis for low gait speed and cognitive decline may exist in these brain structural changes (Supplementary Fig. 2). Several previous studies have reported a significant association of usual or maximum gait speed with GMV. Most of these studies showed that lower gait speed was associated with lower GMV in the total gray matter, frontal lobe, basal ganglia, and hippocampus, although the brain regions reported in each study varied (Allali et al., 2019; Callisaya et al., 2014; Dumurgier et al., 2012; Wilson et al., 2019). Additionally, an association between higher WMHV and lower gait speed has also been reported (Bolandzadeh., 2014; Willey., 2013; Wilson., 2019; Zheng., 2011) The brain regions that showed a significant association in the present study were consistent with those in previous reports. There are many previous studies on usual or maximum gait speed and the development of dementia (Beauchet et al., 2016; Kuate-Tegueu et al., 2017; Peel et al., 2019; Quan et al., 2017). The Three-City Study reported an association between gait speed and risk of AD and VaD (Kuate-Tegueu et al., 2017). The present study also found a significant association between maximum gait speed and risk of total dementia and AD. In addition, several studies have reported that a decreased GMV and an increased WMHV are significantly associated with increased risk of dementia (Nakazawa et al., 2022; Wu et al., 2019). In the Health Aging and Body Composition study, a longitudinal study of

the general population, lower usual gait speed was significantly associated with cognitive impairment, and this significant association disappeared when the right hippocampus volume was adjusted (Rosso et al., 2017). Based on this finding, the authors note that right hippocampus volume may be a neural substrate shared by slowing gait speed and cognitive impairment. The present study also revealed via the mediation analysis that the hippocampal volume, insular volume, and WMHV were likely to be involved in the association between reduced maximal walking speed and dementia risk.

Although the mechanism by which common brain structural changes affect both lower gait speed and the risk of dementia is not completely clear, there are possible explanations. Animal models with damage to the hippocampus showed impairments in learning and memory as well as motor coordination and balance (Paylor et al., 2001). Atrophy of the insula has been implicated in neurodegenerative diseases, including dementia, and it has been reported that this region serves as a hub for multiple cortical networks involved in behavioral control and multimodal sensor processing as well as emotional and cognitive functions (Benarroch, 2019; Fathy et al., 2020). As for white matter hyperintensities, the disturbances in the brain microenvironment and intercortical networks may be involved in both gait slowing and cognitive decline (Bolandzadeh et al., 2014) As another possible mechanism, since gait speed may be affected by several factors, such as muscle strength, skeletal system disease, cerebrovascular disease, and heart disease, the accumulation of these factors could cause brain atrophy and subsequent future dementia (Grande et al., 2019).

The strengths of the present study include its population-based prospective cohort study design with a high participation rate at baseline and perfect follow-up for dementia, the large sample size of the MRI scan, and the accurate diagnosis of dementia and its subtypes. However, several limitations of the present study should also be noted. First, 397 participants were excluded from this study because they lacked available data of MRI or gait speed, which likely led to a selection bias. Since the participants without available data of MRI or gait speed were likely to have lower activity of daily living and MMSE score than those with MRI data (Supplementary Table 5), such selection bias may have tended to weaken the association of gait speed with brain changes and dementia risk. Second, there was a possibility that cases of the prodromal stage of dementia were more likely to be included in participants with lower gait speed level at baseline. However, our sensitivity analyses excluding participants with an MMSE <24, or those who developed dementia within one year did not alter the results substantially. Third, the association of usual gait speed with dementia risk could not be assessed in the present study, because the relevant data were not collected. Fourth, the generalizability of these findings was limited, because the participants of the present study were recruited from one town in Japan. Fifth, we did not collect information on some potential confounding factors that were shown to be risk factors, such as musculoskeletal diseases.

5. Conclusions

In conclusion, the present study demonstrated that lower gait speed was significantly associated with the development of dementia in a general older population of Japanese, and that a smaller volume of the hippocampus or insula, and a larger volume of white matter hyperintensity were likely to be involved in this association. These findings suggest that gait speed may be a clinical sign for the brain structural changes and the future onset of dementia.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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References

Allali, G., Montembeault, M., Brambati, S. M., et al. (2019). Brain structure covariance associated with gait control in aging. *The Journals of Gerontology Series A Biological Sciences, 74*, 705–713. https://doi.org/10.1093/gerona/gly123

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: American Psychiatric Association. revised.

Beauchet, O., Annweiler, C., Callisaya, M. L., et al. (2016). Poor gait performance and prediction of dementia: Results from a meta-analysis. *Journal of the American Medical Directors Association, 17*, 482–490. https://doi.org/10.1016/j.jamda.2015.12.092

Benarroch, E. E. (2019). Insular cortex: Functional complexity and clinical correlations. *Neurology, 93*, 932–938. https://doi.org/10.1212/wnl.0000000000008525

Bolandzadeh, N., Liu-Ambrose, T., Aizenstein, H., et al. (2014). Pathways linking regional hyperintensities in the brain and slower gait. *Neuroimage, 99*, 7–13. https://doi.org/10.1016/j.neuroimage.2014.05.017

Callisaya, M. L., Beare, R., Phan, T. G., et al. (2014). Global and regional associations of smaller cerebral gray and white matter volumes with gait in older people. *PLoS ONE, 9*(1), E84909. https://doi.org/10.1371/journal.pone.0084909

Dumurgier, J., Crivello, F., Mazoyer, B., et al. (2012). MRI atrophy of the caudate nucleus and slower walking speed in the elderly. *Neuroimage, 60*, 871–878. https://doi.org/10.1016/j.neuroimage.2012.01.102

Fathy, Y. Y., Hoogers, S. E., Berendse, H. W., et al. (2020). Differential insular cortex subregional atrophy in neurodegenerative diseases: A systematic review and meta-analysis. *Brain Imaging and Behavior, 14*, 2799–2816. https://doi.org/10.1007/s11682-019-00099-3

Ferrucci, L., Bandinelli, S., Benvenuti, E., et al. (2000). Subsystems contributing to the decline in ability to walk: Bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *Journal of the American Geriatrics Society, 48*, 1618–1625. https://doi.org/10.1111/j.1532-5415.2000.tb03873.x

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state" a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Grande, G., Triolo, F., Nuara, A., et al. (2019). Measuring gait speed to better identify prodromal dementia. *Experimental Gerontology, 124*, Article 110625. https://doi.org/10.1016/j.exger.2019.05.014

Hirabayashi, N., Hata, J., Furuta, Y., et al. (2022). Association between diabetes and gray matter atrophy patterns in a general older Japanese population: The Hisayama study. *Diabetes Care, 45*, 1364–1371. https://doi.org/10.2337/dc21-1911

Kuate-Tegueu, C., Avila-Funes, J. A., Simo, N., et al. (2017). Association of gait speed, psychomotor speed, and dementia. *Journal of Alzheimer's Disease, 60*, 585–592. https://doi.org/10.3233/jad-170267

McKhann, G., Drachman, D., Folstein, M., et al. (1984). Clinical diagnosis of Alzheimer's disease report of the NINCDS-ADRDA Work Group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurolog, 34*, 939–944. https://doi.org/10.1212/wnl.34.7.939

Middleton, A., Fritz, S. L., & Lusardi, M. (2015). Walking speed: The functional vital sign. *Journal of Aging and Physical Activity, 23*, 314–322. https://doi.org/10.1123/japa.2013-0236

Montero-Odasso, M., & Hachinski, V. (2014). Preludes to brain failure: Executive dysfunction and gait disturbances. *Neurological Sciences, 35*, 601–604. https://doi.org/10.1007/s10072-013-1613-4

Nakazawa, T., Ohara, T., Hirabayashi, N., et al. (2022). Multiple-region grey matter atrophy as a predictor for the development of dementia in a community: The Hisayama study. *Journal of Neurology Neurosurgery, and Psychiatry, 93*, 263–271. https://doi.org/10.1136/jnnp-2021-326611

Ninomiya, T. (2018). Japanese legacy cohort studies: The Hisayama Study. *Journal of epidemiology Japan Epidemiological Association, 28*, 444–451. https://doi.org/10.2188/jea.je20180150

Norton, S., Matthews, F. E., Barnes, D. E., et al. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *The Lancet. Neurology, 13*, 788–794. https://doi.org/10.1016/s1474-4422(14)70136-x

Ohara, T., Hata, J., Yoshida, D., et al. (2017). Trends in dementia prevalence, incidence, and survival rate in a Japanese community. *Neurology, 88*, 1925–1932. https://doi.org/10.1212/wnl.0000000000003932

Paylor, R., Zhao, Y., Libbey, M., et al. (2001). Learning impairments and motor dysfunctions in adult Lhx5-deficient mice displaying hippocampal disorganization. *Physiology & Behavior, 73*, 781–792. https://doi.org/10.1016/s0031-9384(01)00515-7

Peel, N. M., Alapatt, L. J., Jones, L. V., et al. (2019). The association between gait speed and cognitive status in community-dwelling older people: A systematic review and meta-analysis. *The Journals of Gerontology Series A Biological Sciences, 74*, 943–948. https://doi.org/10.1093/gerona/gly140

Peel, N. M., Kuys, S. S., & Klein, K. (2013). Gait speed as a measure in geriatric assessment in clinical settings: A systematic review. *The Journals of Gerontology Series A Biological Sciences, 68*, 39–46. https://doi.org/10.1093/gerona/gls174

Perera, S., Patel, K. V., Rosano, C., et al. (2016). Gait speed predicts incident disability: A pooled analysis. *The Journals of Gerontology Series A Biological Sciences, 71*, 63–71. https://doi.org/10.1093/gerona/glv126

Prins, N. D., & Scheltens, P. (2015). White matter hyperintensities, cognitive impairment and dementia: An update. *Nature reviews. Neurology, 11*, 157–165. https://doi.org/10.1038/nrneurol.2015.10

Quan, M., Xun, P., Chen, C., et al. (2017). Walking pace and the risk of cognitive decline and dementia in elderly populations: A meta-analysis of prospective cohort studies. *The Journals of Gerontology Series A Biological Sciences, 72*, 266–270. https://doi.org/10.1093/gerona/glw121

Román, G. C., Tatemichi, T. K., Erkinjuntti, T., et al. (1993). Vascular dementia: Diagnostic criteria for research studies: Report of the NINDS-AIREN International Workshop. *Neurolog, 43*, 250–260. https://doi.org/10.1212/wnl.43.2.250

Rosso, A. L., Sanders, J. L., Arnold, A. M., et al. (2015). Multisystem physiologic impairments and changes in gait speed of older adults. *The Journals of Gerontology Series A Biological Sciences, 70*, 319–324. https://doi.org/10.1093/gerona/glu176

Rosso, A. L., Studenski, S. A., Chen, W. G., et al. (2013). Aging, the central nervous system, and mobility. *The Journals of Gerontology Series A Biological Sciences, 68*, 1379–1386. https://doi.org/10.1093/gerona/glt089

Rosso, A. L., Verghese, J., Metti, A. L., et al. (2017). Slowing gait and risk for cognitive impairment: The hippocampus as a shared neural substrate. *Neurology, 89*, 336–342. https://doi.org/10.1212/wnl.0000000000004153

Stijntjes, M., De Craen, A. J. M., Van Der Grond, J., et al. (2016). Cerebral microbleeds and lacunar infarcts are associated with walking speed independent of cognitive performance in middle-aged to older adults. *Gerontology, 62*, 500–507. https://doi.org/10.1159/000444583

Studenski, S., Perera, S., Patel, K., et al. (2011). Gait speed and survival in older adults. *Jama, 305*, 50–58. https://doi.org/10.1001/jama.2010.1923

Valeri, L., & VanderWeele, T. J. (2015). SAS macro for causal mediation analysis with survival data. *Epidemiology, 26*(2), e23–e24. https://doi.org/10.1097/EDE.0000000000000253 (Cambridge, Mass.).

Wechsler, D. (1987). *Manual for the Wechsler memory scale-revised*. San Antonio: The Psychological Corporation.

Willey, J. Z., Scarmeas, N., Provenzano, F. A., et al. (2013). White matter hyperintensity volume and impaired mobility among older adults. *Journal of Neurology, 260*, 884–890. https://doi.org/10.1007/s00415-012-6731-z

Wilson, J., Allcock, L., Mc Ardle, R., et al. (2019). The neural correlates of discrete gait characteristics in ageing: A structured review. *Neuroscience and Biobehavioral Reviews, 100*, 344–369. https://doi.org/10.1016/j.neubiorev.2018.12.017. Elsevier.

World Alzheimer Report (2015). The global impact of dementia. Accessed Jun 23,2022. https://www.alzint.org/resource/world-alzheimer-report-2015.

Wu, A., Sharrett, A. R., Gottesman, R. F., et al. (2019). Association of brain magnetic resonance imaging signs with cognitive outcomes in persons with nonimpaired cognition and mild cognitive impairment. *JAMA Network Open, 2*, Article E193359. https://doi.org/10.1148/radiol.2482070938

Yamasaki, K., Hata, J., Furuta, Y., et al. (2020). Association of albuminuria with white matter hyperintensities volume on brain magnetic resonance imaging in elderly Japanese: The Hisayama study. *Circulation Journal, 84*, 935–942. https://doi.org/10.1253/circj.cj-19-1069

Zheng, J. J. J., Delbaere, K., Close, J. C. T., Sachdev, P. S., & Lord, S. R. (2011). Impact of white matter lesions on physical functioning and fall risk in older people: A systematic review. *Stroke; A Journal of Cerebral Circulation, 42*, 2086–2090. https://doi.org/10.1161/strokeaha.110.610360