Journal of the Neurological Sciences 397 (2019) 129–134

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Cognitive impairment, brain ischemia and shorter telomeres are predictors of mortality in the Japanese elderly: A 13-year prospective community-based study

Ryosuke Igari[a,1], Philip Davy[b], Hidenori Sato[a], Yoshimi Takahashi[a], Chifumi Iseki[a], Hajime Kato[a], Hiroyasu Sato[a], Shingo Koyama[a], Kenichi Ishizawa[a], Richard Allsopp[b,1], Takeo Kato[a,*,1]

[a] Division of Neurology and Clinical Neuroscience, Department of Internal Medicine III, Yamagata University School of Medicine, Yamagata, Japan
[b] Institute for Biogenesis Research, John A Burns School of Medicine, University of Hawaii, Honolulu, United States

ABSTRACT

Objective: To examine whether cognitive impairment, deep white matter hyperintensity (DWMH) on brain MRI, and shorter telomere length would be predictors of mortality in community-dwelling Japanese elderly.
Methods: We followed 259 individuals (74% of all the residents at age 70) from age 70 to 83 years. The mean observation period was 133 ± 34 months. The key clinical characteristics examined included DWMH on brain MRI and cognitive function. Telomere length was also measured in 81 subjects. Both univariate and multivariate analyses were performed.
Results: Of the 259 subjects, 69 subjects (30 men, 39 women; 26.6%) died during the follow-up period. Cognitive impairment, smoking habits, diabetes mellitus, and moderate to severe DWMH were significant predictors of total mortality in univariate analysis. However, only cognitive impairment and moderate to severe DWMH remained as significant independent predictors of death in multivariate analysis. The rate of mortality increased with additional number of risk factors (cognitive impairment and DWMH). The total mortality of subjects with both cognitive impairment and DWMH was 71.4%. The median telomere length was 7.8 kb in the deceased and 8.2 kb in the living subjects. The deceased subjects had significantly shorter telomere length ($P = .0025$) than the living subjects. Telomere length with moderate to severe DWMH was higher than without moderate to severe DWMH on brain MRI ($P = .017$).
Conclusions: The present study revealed that cognitive impairment, DWMH, and shorter telomere length were significant predictors of total mortality in the community-dwelling Japanese elderly. Furthermore, the combination of cognitive impairment and DWMH increased the mortality rate, as compared with a single risk factor. It is also clarified that a significant difference was present in telomere length by severity of DWMH.

1. Introduction

In many countries, including Japan, the major causes of death in adults are cancer, cardiovascular disease (CVD), and pneumonia. To reduce CVD, it is important to prevent and treat their risk factors, such as hypertension (HT), diabetes mellitus (DM), and hyperlipidemia (HL). Moderate exercise and well-balanced meals are also important to prevent such conditions.

As compared with studies on the causes of death, there have been relatively fewer studies about the predictive factors of mortality in the elderly, especially in Japanese people, because the determination of predictors of mortality requires time-consuming, longitudinal studies, whereas the cause of death can be determined by cross-sectional studies. Nevertheless, a considerable number of studies have reported several predictive factors of mortality, including medical history (obesity [1], treatment of hyperlipidemia [2], self-reported health in men and a previous cancer diagnosis in women [3], socioecomonic conditions and a history of vascular diseases [4], disease factors such as coronary heart disease, other heart diseases, peripheral arterial disease, stroke, chronic obstructive pulmonary disease, and diabetes mellitus [5]), lifestyle factors [6], physical function related factors [7–9], abnormalities of laboratory tests (IL-6 and carotid plaques [10], albuminuria [11], higher plasma renin activity [12], cardiac troponin I levels [13]), and cognitive impairment [14–18]. However, there have been no previous studies showing a cumulative effect of cognitive impairment and brain ischemia using MRI on total mortality in community-dwelling elderly people.

Telomeres are essential genetic components that protect the ends of chromosomes. The gradual erosion of telomeres is now established as a universal feature of aging in mammalian species. Telomere length has

* Corresponding author at: Division of Neurology and Clinical Neuroscience, Department of Internal Medicine III, Yamagata University School of Medicine, 2-2-2, Iida-nishi, Yamagata 990-9585, Japan.
E-mail address: tkato@med.id.yamagata-u.ac.jp (T. Kato).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.jns.2018.12.038
Received 7 March 2018; Received in revised form 7 December 2018; Accepted 31 December 2018
Available online 31 December 2018
0022-510X/

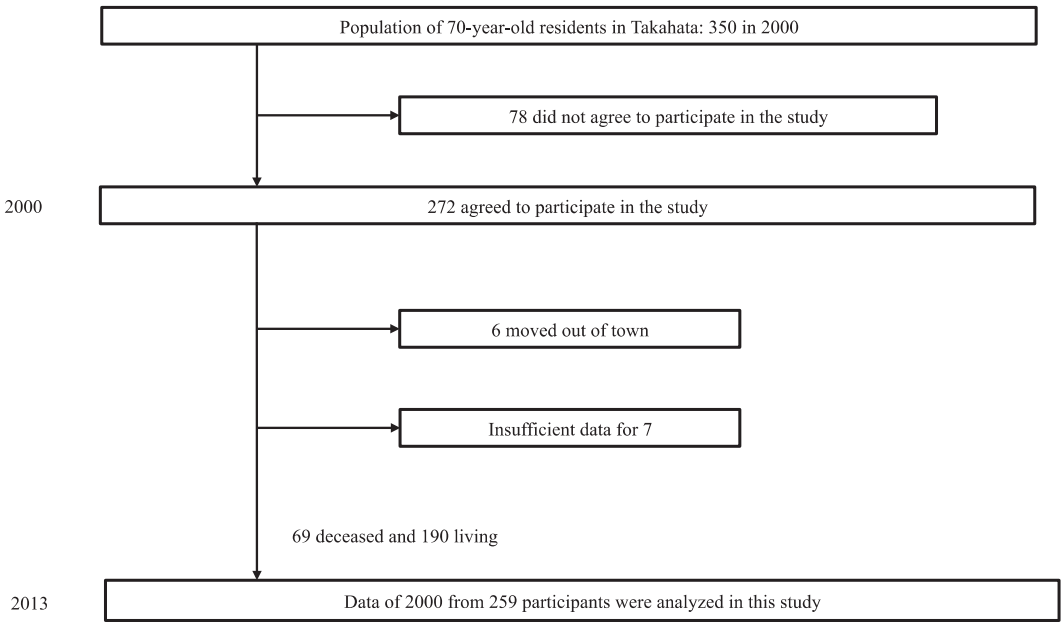

Fig. 1. Study population selection.

recently been shown to be a predictor of mortality [19–21] as well as certain age-related diseases such as CVD [22] in humans. However, it remains unclear whether or not telomere length is associated with other predictors of mortality such as cognitive impairment.

In 2000, we started a prospective, community-based study of elderly people in Takahata, a town in Japan, to determine mortality-predicting factors [23–27]. The present 13-year cohort study aims to examine whether or not cognitive impairment, brain ischemia on MRI, and shorter telomere could influence a lifespan of community-dwelling Japanese elderly.

2. Methods

2.1. Subjects

Fig. 1 shows the protocol and number of participants in this study. In 2000, we began a prospective, community-based investigation of elderly residents in Takahata, a town in a rural area of Yamagata Prefecture, Japan [10–14]. All residents aged 70 years in the town (n = 350) were invited to participate; 272 subjects (77.7%: 101 men, 172 women) were enrolled in the study. All the participants seemed to have independent activities of daily living, because they were able to come from home to the venue of medical examinations without support. The subjects were followed up for 13 years to the age of 83 years. The mean observation period of the participants was 133 ± 34 months. During that period, six subjects moved out of the town; we were unable to obtain sufficient data from seven subjects. Thus, after excluding those 13 subjects, 259 participants (74.0% of the 70-year-old residents of the town: 95 men, 164 women) were evaluated in this study.

The information of death of the participants was obtained from the local government (Takahata Town Office). After the informed consent was given by the families of the deceased participants, the causes of death were examined. In case of a subject who saw a doctor regularly, the cause of death was identified by closely examining his/her medical record. In case of necessity, we interviewed their families. The study was approved by the Medical Ethics Committee of the Yamagata University School of Medicine. All participants gave their written informed consent.

2.2. Clinical and laboratory examinations

At the baseline examinations in 2000, a medical interview, health check, assessment of cognitive function, and brain MRI examination were performed. The face-to-face medical interview included medical history of CVD, HT, DM, and HL as well as educational level, smoking habits, and alcohol consumption. Alcohol consumption was calculated on the basis of ethanol volume; heavy drinkers were defined as those who consumed > 210 g of ethanol weekly [27]. The health check included measurements of blood pressure, neurological examination, blood examination (including HbA_{1c}), and electrocardiogram. HT was defined as casual blood pressure (BP) of ≥140/90 mmHg. HL was defined as a total cholesterol level of ≥220 mg/dL. In accordance with the National Glycohemoglobin Standardization Program, DM was defined as an HbA_{1c} level of ≥6.5% [28]. CVD was defined as the presence of a past history of cardiovascular disease. Subjects were also defined as having HT, HL, DM, or CVD if they were taking medications for those conditions. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2. The eGFR was calculated from the serum creatinine value and age using the abbreviated Modification of Diet in Renal Disease equation modified by the Japanese coefficient [29]. Each subject also underwent the Mini-Mental State Examination (MMSE) as a global measure for cognitive function. Subjects with an MMSE score of 23 or less were classified as cognitively impaired.

2.3. Brain MRI examination

Brain MRI examination was performed using a 0.3 Tesla system (Airias, Hitachi-Medico, Japan), and the images were evaluated by four trained neurologists. Deep white matter hyperintensity (DWMH) lesion was defined as a hyperintensity lesion in the cerebral white matter on fluid-attenuated inversion recovery images. The Fazekas scale was used to evaluate the severity (grades 0–3) of DWMH. That scale has been shown to reflect the pathological severity of cerebral ischemic lesions in postmortem examinations [30]. Grades 2 and 3 of the Fazekas scale were regarded as moderate and severe DWMH, respectively.

2.4. Measurement of telomere length

Blood samples for telomere length measurement were obtained in 2000. Genomic DNA was extracted from peripheral leukocytes using a QIAamp DNA blood kit (Qiagen, Tokyo, Japan). For all samples, telomere length was measured using Southern blot analysis of terminal restriction fragment (TRF) length, as previously described [31], with the following modifications. In brief, DNA was digested with restriction enzymes *Rsa* I and *Hinf*I and quantified by UV spectroscopy. One microgram was resolved by electrophoresis in 0.5% agarose gels for 600–700 V-hr, followed by transfer to nylon membranes. Hybridization of ^{32}P-oligonucleotide probes to the membranes was performed [32]. The membranes were incubated in 5 x standard saline/citrate (SSC) at 37 °C with ^{32}P-endlabeled (TTAGGG)4 for 8–12 h and exposed PhosphorImager screens for 1–2 days after washing three times with 0.34 x SSC plus 0.1% sodium dodecyl sulfate at room temperature (10 min each). The mean TRF length was assessed as previously described [33].

2.5. Statistical analyses

We compared categorical variables with the chi-square test when appropriate. We compared continuous variables with Student's *t*-test or Mann-Whitney *U* test on the basis of the distribution. We used the Kaplan-Meier method to estimate cumulative survival rates and assessed differences with the log-rank test. We assessed differences of cumulative survival rates with Cochran-Armitage test. We compared telomere length as a function of DWMH grade with one-way ANOVA. We used Spearman's rank correlation coefficient to evaluate correlation between MMSE score and telomere length. We used a univariate Cox proportional model to estimate the hazard ratio of death. We also used a multivariate Cox proportional hazards model to estimate the hazard ratio of death by adjusting for sex, HT, DM, HL, education level, smoking habits, alcohol consumption, CKD, DWMH, and cognitive impairment. A probability value of $P < .05$ was considered significant. All analyses were performed using the R package 3.2.0 (http://www.r-project.org/) and EZR [34].

3. Results

Of the 259 study participants, 69 subjects (26.6%: 30 men, 39 women) died during the 13-year observation period from 2000 to 2013. In 2013, 190 subjects (73.4%: 65 men, 125 women) were alive (Fig. 1). We found the major causes of death to be cancer and respiratory disease. The proportion of major causes of death was similar between subjects with and without cognitive impairment (Fig. 2A).

The baseline characteristics of the deceased and living subjects appear in Table 1. The frequencies of DM, moderate to severe DWMH (grades 2 and 3 of the Fazekas scale), and cognitive impairment were significantly higher in deceased than in living subjects. By analysis of the univariate Cox proportional hazards model, we found cognitive impairment, smoking habits, DM, and moderate to severe DWMH to be significant predictors of death during the 13-year observation period (Table 2). The Kaplan-Meier analyses also supported those results (Fig. 2B). However, analysis of the multivariate Cox proportional hazards model showed that only cognitive impairment and moderate to severe DWMH remained as significant independent predictors of death (Table 2). As evident in Fig. 3A, the rate of mortality increased with an additive effect of the DWMH and cognitive impairment risk factors.

The telomere length was measured in 81 randomly chosen samples selected from the 259 subjects: 32 from the 69 deceased and 49 from the 190 living subjects. The average telomere length at age 70 years was significantly shorter in deceased than in living subjects: 7.8 kb (median, range 3.7–10.6) versus 8.2 kb (median, range 5.0–11.3); $P = .0025$ (Fig. 3B). We next evaluated the relationship between telomere length, DWMH grade and cognitive impairment. As shown in Fig. 3C, telomere length was significantly shorter in participants with moderate to high DWMH grade ($P = .017$). However, we observed no correlation between telomere length and MMSE score (Fig. 3D).

4. Discussion

In this study, we followed elderly Japanese residents (70 years of age) for 13 years. We found that cognitive impairment and DWMH were significant predictors of total mortality in the community-dwelling Japanese elderly. The present study confirms previous findings of cognitive impairment being associated with increased risk of mortality [35–40]. This study also revealed that the combination of cognitive impairment and DWMH increased the mortality rate, as compared with a single risk factor. It is also observed that the length of telomere decreased significantly with an increase in the severity of DWMH.

In univariate Cox proportional hazards model, DM and smoking habit were significant risk factors of total mortality, but not in multivariate Cox proportional hazards model. The participants with DM showed significantly higher grades of Fazekas scale for DWMH than those without DM (data not shown), suggesting DM as a cofounding factor. With regard to smoking habit, only among subjects without alcohol consumption, smokers showed a significantly higher mortality than non-smokers; no significant difference was observed between smokers and non-smokers with alcohol consumption (data not shown), suggesting a limited power of the present study.

In clinical settings, brain MRI examinations are essential for effective evaluation of cognitive impairment and dementia. In previous community-based studies, the relationship between cognitive impairment and mortality was evaluated without brain MRI examinations [35–40]. In a hospital-based study involving brain MRI examinations performed on neurologically asymptomatic subjects, with an average follow-up of 6.3 years (range 1–15 years), subcortical white matter lesions graded by the Fazekas scale were not a significant predictor of mortality [41]. The reason for the discrepancy between that study and ours remains unclear. However, the differences in study design (hospital- versus community-based), ages of the subjects (mean age of 58 ± 7 years at entry versus all 70 years), and the follow-up periods (6.3 years on average versus 13 years) may have had a substantial effect.

One advantage of the present study is that we recruited subjects of the same age (all 70 years). In a study on mortality, differences in the participants' age are a confounding factor; thus, age adjustment is needed in statistical analysis. In this regard, only two studies on mortality recruited subjects of the same age. Börjesson-Hanson et al. enrolled participants of the same age (all 95 years) and followed them for 5 years until the age of 100 [15]. The authors found that the mortality rate during the observation period was significantly higher in subjects with dementia than in those without (96.0% versus 73.2%; $P < .0001$) [15]. Takata et al. recruited residents all aged 85 years from several communities in Japan. The authors found that cognitive impairment was a predictor of mortality for 10 years [42]. Those studies and ours indicate that cognitive impairment is a predictor of mortality for the elderly.

There are several reasons for the association between cognitive impairment and mortality. First, individuals with cognitive impairment may have poor ability to recognize their own symptoms and signs of diseases, resulting in delay in medical assistance and eventual death through advancement of the major age-related diseases: cancer or vascular disease. Second, cognitive impairment may be a surrogate marker for frailty—a well-known predictor of total mortality in the elderly [43]. Boyle et al. [44] reported that frailty is a risk factor for mild cognitive impairment. Therefore, cognitive impairment would reflect frailty, which is associated with total mortality. Third, cognitive impairment/dementia due to Alzheimer's disease or other dementing illnesses may lead to lethal diseases such as pneumonia.

Numerous studies have shown that telomere length decreases during human aging in a variety of proliferative cells; those cells

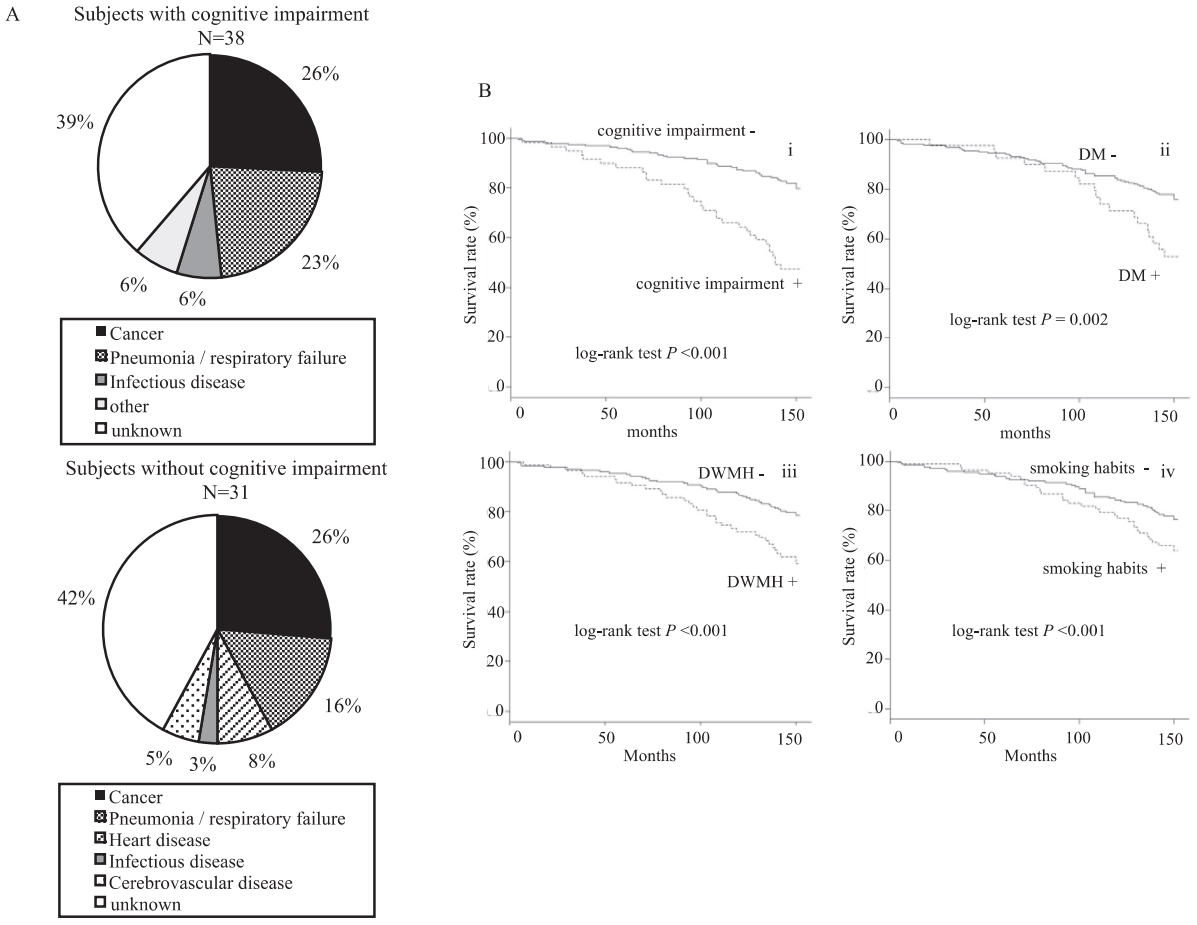

Fig. 2. A. Proportion of major cause of death in subjects with and without cognitive impairment. B. Kaplan-Meier curves for risk factors for survival. i, Subjects with (dotted line) and without (solid line) cognitive impairment; ii, subjects with (dotted line) and without (solid line) DM; iii, subjects with (dotted line) and without (solid line) DWMH; iv, subjects with (dotted line) and without (solid line) smoking habits. DM, diabetes mellitus; DWMH, deep white matter hyperintensity.

Table 1
Baseline characteristics of deceased and living subjects.

	All N = 259		
	Deceased n = 69	Living n = 190	*P* value
Male (%)	43.5	34.2	0.22[b]
Alcohol (%)	40.6	38.4	0.86[b]
Smoking (%)	42.0	28.4	0.054[b]
Education (years, SD)	8.96 (1.68)	9.37 (2.09)	0.14[c]
CKD (%)	18.8	16.8	0.85[b]
CVD (%)	17.4	11.1	0.25
DM (%)	**26.1**	**11.6**	**0.008**[b]
DWMH[a](%)	**47.8**	**26.8**	**0.002**[b]
HL (%)	37.7	34.2	0.71[b]
HT (%)	79.7	77.9	0.89[b]
Cognitive impairment (%)	**44.9**	**14.7**	**< 0.001**[b]

SD, standard deviation; CVD, cardiovascular disease, CKD, chronic kidney disease; DM, diabetes mellitus; DWMH, deep white matter hyperintensity; HL, hyperlipidemia; HT, hypertension.

[a] moderate to severe DWMH (grades 2 and 3 of Fazekas scale).

[b] chi-square test.

[c] *t* test.

include white blood cells [45], vascular endothelial cells [46], skin cells [47], colon epithelial cells [45], and certain types of stem cells [48]. A number of studies have shown that short telomere length is a risk factor for mortality in the elderly [49]. Moreover, shorter telomeres have been shown to be associated with increased risk of age-related diseases [50], including coronary artery disease [22], cancer [51], Alzheimer's disease [52], and DM [53]. Although the exact relationship between shorter telomeres and these age-related diseases remains to be clarified, our study showed a negative correlation between the severity of DWMH and telomere length. The Fazekas scale reflects the pathological severity of cerebral ischemic lesions in postmortem examinations [30]. Thus, it is possible that moderate to severe DWMH on brain MRI may represent aging of vascular endothelial cells.

The present study has some limitations. First, we used a visual rating scale (Fazekas scale) for white matter lesions on brain MRI. This scale is used worldwide; however, it is possible that the degrees of cerebral white matter lesions were under- or overestimated. Computer-assisted quantitative techniques are needed for objective evaluation of white matter changes. Second, although MMSE is a globally common neuropsychological test, there are several other means of evaluating cognitive function. Further studies are needed to determine which modality of neuropsychological tests is the most sensitive, reliable predictor of mortality in the elderly. Third, in the present study, we did not measure some potential confounding factors such as lifestyle factors and physical function related factors.

5. Conclusions

The present study revealed that cognitive impairment, DWMH, and shorter telomere length were significant predictors of total mortality in the community-dwelling Japanese elderly. Furthermore, the combination of cognitive impairment and DWMH increased the mortality rate, as compared with a single risk factor. It is also clarified that a significant negative correlation was present between telomere length and

Table 2
Hazard ratios of death during the 13-year observation period (Cox proportional hazards model).

	Univariate Cox proportional hazards model			Multivariate Cox proportional hazards model[b]		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Cognitive impairment	**3.48**	**2.16–5.61**	**< 0.001**	**3.34**	**2.00–5.59**	**< 0.001**
Male (%)	1.46	0.90–2.35	0.12	1.13	0.44–2.95	0.80
Alcohol (%)	1.03	0.63–1.68	0.90	0.69	0.36–1.31	0.26
Smoking (%)	**1.65**	**1.02–2.67**	**0.042**	1.79	0.78–4.11	0.15
Education (years, SD)	0.92	0.82–1.05	0.20	0.96	0.84–1.11	0.61
CKD (%)	0.98	0.52–1.83	0.95	0.88	0.47–1.67	0.70
CVD (%)	1.75	0.94–3.27	0.08	1.70	0.90–3.21	0.10
DM (%)	**2.23**	**1.30–3.83**	**0.0035**	1.41	0.80–2.50	0.24
DWMH[a](%)	**2.10**	**1.31–3.39**	**0.0022**	**2.02**	**1.24–3.30**	**0.0045**
HL (%)	1.10	0.67–1.8	0.71	1.52	0.89–2.60	0.13
HT (%)	1.11	0.62–2.01	0.71	1.39	0.75–2.60	0.29

CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease, DM, diabetes mellitus; DWMH, deep white matter hyperintensity; HL, hyperlipidemia; HT, hypertension. Bold letters/numbers indicate significant predictors of death during the 13-year observation period.

[a] moderate to severe DWMH (grades 2 and 3 of Fazekas scale).

[b] adjustment for all co-variables.

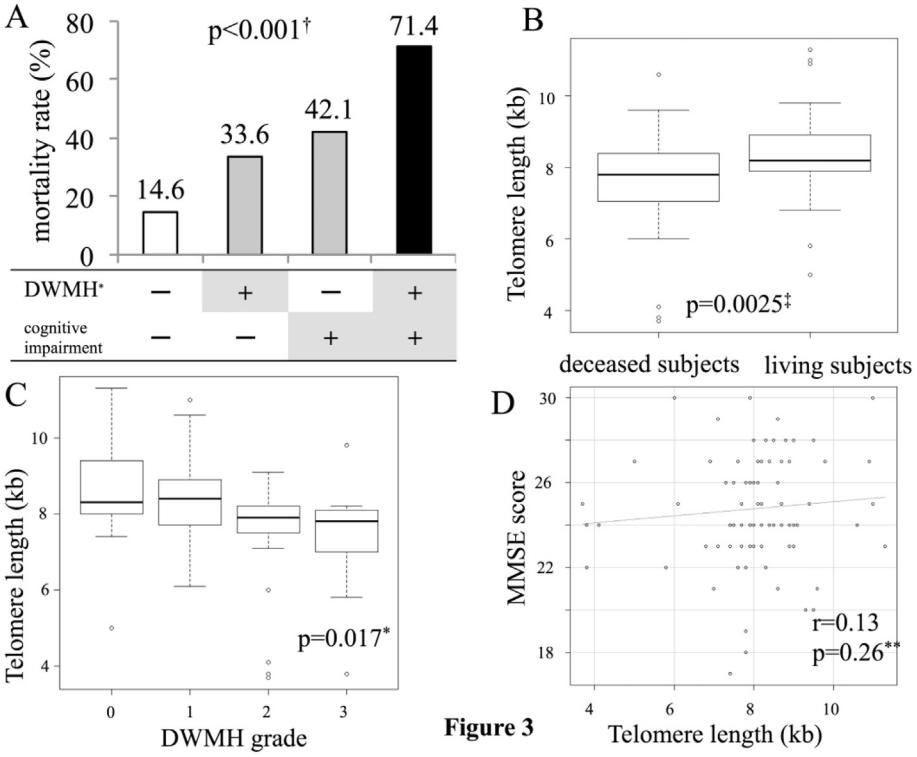

Fig. 3. A. Mortality rate in the presence or absence of deep white matter hyperintensity (DWMH) and cognitive impairment. †Cochran-Armitage test for trend in proportions. B. Telomere length in deceased and living subjects at the age of 70. ‡Mann-Whitney *U* test. C. Association between DWMH grade and telomere length. *One-way ANOVA. D. Relationship between MMSE score and telomere length. **Spearman's rank correlation coefficient.

Figure 3

the severity of DWMH. Further studies are needed to confirm our results in other ethnicities and races.

Acknowledgments

We thank the participants in the present study and the staff of Takahata Town Office for helping us perform the medical check-up and follow up the participants. The present study was supported in part by a Grant-in-Aid from the 21st Century Center of Excellence (COE) Program (#F03) ("Molecular Epidemiological Study Utilizing Regional Characteristics", Yamagata University) of the Japan Society for the Promotion of Science (T. Kato).

References

[1] K.M. Flegal, B.K. Kit, H. Orpana, B.I. Graubard, Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis, JAMA 309 (1) (2013) 71–82.

[2] M. Daimon, T. Oizumi, W. Kameda, J. Matsui, H. Murakami, Y. Ueno, I. Kubota, H. Yamashita, T. Kayama, T. Kato, Association of treatment for hyperlipidemia with decreased total mortality in Japanese individuals: the Yamagata (Takahata) study, J. Atheroscler. Thromb. 22 (10) (2015) 1030–1039.

[3] A. Ganna, E. Ingelsson, 5 year mortality predictors in 498,103 UK Biobank participants: a prospective population-based study, Lancet 386 (9993) (2015) 533–540.

[4] Michael Hurd, Daniel McFadden, Angela Merrill, Predictors of mortality among the elderly. Nber working paper No. 7440 Issued in December 1999, NBER Program(s), Aging (1999), http://www.nber.org/papers/w7440.

[5] A. Menotti, H. Blackburn, F. Seccareccia, D. Kromhout, A. Nissinen, C. Aravanis, S. Giampaoli, I. Mohacek, S. Nedeljkovic, H. Toshima, The relation of chronic diseases to all-cause mortality risk—the seven Countries Study, Ann. Med. 29 (2) (1997) 135–141.

[6] L.P. Fried, R.A. Kronmal, A.B. Newman, D.E. Bild, M.B. Mittelmark, J.F. Polak, J.A. Robbins, J.M. Gardin, Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study, JAMA 279 (8) (1998) 585–592.

[7] G. Kojima, Frailty defined by FRAIL scale as a predictor of mortality: a systematic review and meta-analysis, J. Am. Med. Dir. Assoc. 19 (6) (2018) 480–483.

[8] S. Studenski, S. Perera, K. Patel, C. Rosano, K. Faulkner, M. Inzitari, J. Brach, J. Chandler, P. Cawthon, E.B. Connor, M. Nevitt, M. Visser, S. Kritchevsky, S. Badinelli, T. Harris, A.B. Newman, J. Cauley, L. Ferrucci, J. Guralnik, Gait speed

and survival in older adults, JAMA 305 (1) (2011) 50–58.
[9] W. Zhao, S. Ukawa, K. Tsushita, T. Kawamura, K. Wakai, M. Ando, A. Tamakoshi, Association of gait speed with mortality among the Japanese elderly in the New Integrated Suburban Seniority Investigation Project: a prospective cohort study, Age Ageing 44 (1) (2015) 153–157.
[10] S. Stork, R.A. Feelders, A.W. van den Beld, E.W. Steyerberg, H.F. Savelkoul, S.W. Lamberts, D.E. Grobbee, M.L. Bots, Prediction of mortality risk in the elderly, Am. J. Med. 119 (6) (2006) 519–525.
[11] T. Konta, K. Kudo, H. Sato, K. Ichikawa, A. Ikeda, K. Suzuki, A. Hirayama, Y. Shibata, T. Watanabe, M. Daimon, T. Kato, Y. Ueno, T. Kayama, I. Kubota, Albuminuria is an independent predictor of all-cause and cardiovascular mortality in the Japanese population: the Takahata study, Clin. Exp. Nephrol. 17 (6) (2013) 805–810.
[12] M. Daimon, T. Konta, T. Oizumi, S. Karasawa, W. Kaino, K. Takase, Y. Jimbu, K. Wada, W. Kameda, S. Susa, T. Saito, I. Kubota, T. Kayama, T. Kato, Higher plasma renin activity is a risk factor for total mortality in older Japanese individuals: the Takahata study, Metab. Clin. Exp. 61 (4) (2012) 504–511.
[13] K.M. Eggers, P. Venge, B. Lindahl, L. Lind, Cardiac troponin I levels measured with a high-sensitive assay increase over time and are strong predictors of mortality in an elderly population, J. Am. Coll. Cardiol. 61 (18) (2013) 1906–1913.
[14] J.T. Tschanz, C. Corcoran, I. Skoog, A.S. Khachaturian, J. Herrick, K.M. Hayden, K.A. Welsh-Bohmer, T. Calvert, M.C. Norton, P. Zandi, J.C. Breitner, G. Cache County Study, Dementia: the leading predictor of death in a defined elderly population: the Cache County Study, Neurology 62 (7) (2004) 1156–1162.
[15] A. Borjesson-Hanson, D. Gustafson, I. Skoog, Five-year mortality in relation to dementia and cognitive function in 95-year-olds, Neurology 69 (22) (2007) 2069–2075.
[16] L.L. Lavery, H.H. Dodge, B. Snitz, M. Ganguli, Cognitive decline and mortality in a community-based cohort: the Monongahela Valley Independent Elders Survey, J. Am. Geriatr. Soc. 57 (1) (2009) 94–100.
[17] T. Luck, S. Roehr, F. Jessen, A. Villringer, M.C. Angermeyer, S.G. Riedel-Heller, Mortality in individuals with Subjective Cognitive Decline: results of the Leipzig Longitudinal Study of the Aged (LEILA75+), J. Alzheimers Dis. 48 (Suppl. 1) (2015) S33–S42.
[18] S. Roehr, T. Luck, H. Bickel, C. Brettschneider, A. Ernst, A. Fuchs, K. Heser, H.H. Konig, F. Jessen, C. Lange, E. Mosch, M. Pentzek, S. Steinmann, S. Weyerer, J. Werle, B. Wiese, M. Scherer, W. Maier, S.G. Riedel-Heller, G. AgeCoDe Study, Mortality in incident dementia - results from the German Study on Aging, Cognition, and Dementia in primary Care patients, Acta Psychiatr. Scand. 132 (4) (2015) 257–269.
[19] R.M. Cawthon, K.R. Smith, E. O'Brien, A. Sivatchenko, R.A. Kerber, Association between telomere length in blood and mortality in people aged 60 years or older, Lancet 361 (9355) (2003) 393–395.
[20] W. Chen, M. Kimura, S. Kim, X. Cao, S.R. Srinivasan, G.S. Berenson, J.D. Kark, A. Aviv, Longitudinal versus cross-sectional evaluations of leukocyte telomere length dynamics: age-dependent telomere shortening is the rule, J. Gerontol. A Biol. Sci. Med. Sci. 66 (3) (2011) 312–319.
[21] J.L. Sanders, A.B. Newman, Telomere length in epidemiology: a biomarker of aging, age-related disease, both, or neither? Epidemiol. Rev. 35 (2013) 112–131.
[22] N.J. Samani, R. Boultby, R. Butler, J.R. Thompson, A.H. Goodall, Telomere shortening in atherosclerosis, Lancet 358 (9280) (2001) 472–473.
[23] Y. Takahashi, C. Iseki, M. Wada, T. Momma, M. Ueki, T. Kawanami, M. Daimon, K. Suzuki, G. Tamiya, T. Kato, Impaired glucose metabolism slows executive function independent of cerebral ischemic lesions in Japanese elderly: the Takahata study, Intern. Med. (Tokyo, Japan) 50 (16) (2011) 1671–1678.
[24] M. Wada, Y. Takahashi, C. Iseki, T. Kawanami, M. Daimon, T. Kato, Plasma fibrinogen, global cognitive function, and cerebral small vessel disease: results of a cross-sectional study in community-dwelling Japanese elderly, Intern. Med. (Tokyo, Japan) 50 (9) (2011) 999–1007.
[25] M. Wada, H. Nagasawa, T. Kawanami, K. Kurita, M. Daimon, I. Kubota, T. Kayama, T. Kato, Cystatin C as an index of cerebral small vessel disease: results of a cross-sectional study in community-based Japanese elderly, Eur. J. Neurol. 17 (3) (2010) 383–390.
[26] M. Wada, M. Daimon, M. Emi, H. Iijima, H. Sato, S. Koyano, K. Tajima, T. Kawanami, K. Kurita, S.C. Hunt, P.N. Hopkins, I. Kubota, S. Kawata, T. Kato, Genetic association between aldehyde dehydrogenase 2 (ALDH2) variation and high-density lipoprotein cholesterol (HDL-C) among non-drinkers in two large population samples in Japan, J. Atheroscler. Thromb. 15 (4) (2008) 179–184.
[27] H. Nagasawa, M. Wada, S. Arawaka, T. Kawanami, K. Kurita, M. Daimon, M. Adachi, T. Hosoya, M. Emi, M. Muramatsu, T. Kato, A polymorphism of the aldehyde dehydrogenase 2 gene is a risk factor for multiple lacunar infarcts in Japanese men: the Takahata Study, Eur. J. Neurol. 14 (4) (2007) 428–434.
[28] A. Kashiwagi, M. Kasuga, E. Araki, Y. Oka, T. Hanafusa, H. Ito, M. Tominaga, S. Oikawa, M. Noda, T. Kawamura, T. Sanke, M. Namba, M. Hashiramoto, T. Sasahara, Y. Nishio, K. Kuwa, K. Ueki, I. Takei, M. Umemoto, M. Murakami, M. Yamakado, Y. Yatomi, H. Ohashi, S. Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes, International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values, J. Diabetes Investig. 3 (1) (2012) 39–40.
[29] E. Imai, M. Horio, K. Nitta, K. Yamagata, K. Iseki, Y. Tsukamoto, S. Ito, H. Makino, A. Hishida, S. Matsuo, Modification of the Modification of Diet in Renal Disease (MDRD) Study equation for Japan, Am. J. Kidney Dis. 50 (6) (2007) 927–937.
[30] F. Fazekas, J.B. Chawluk, A. Alavi, H.I. Hurtig, R.A. Zimmerman, MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging, AJR Am. J. Roentgenol. 149 (2) (1987) 351–356.
[31] R.C. Allsopp, H. Vaziri, C. Patterson, S. Goldstein, E.V. Younglai, A.B. Futcher, C.W. Greider, C.B. Harley, Telomere length predicts replicative capacity of human fibroblasts, Proc. Natl. Acad. Sci. U. S. A. 89 (21) (1992) 10114–10118.
[32] M.W. Mather, Base composition-independent hybridization in dried agarose gels: screening and recovery for cloning of genomic DNA fragments, BioTechniques 6 (5) (1988) 444–447.
[33] H. Vaziri, F. Schachter, I. Uchida, L. Wei, X. Zhu, R. Effros, D. Cohen, C.B. Harley, Loss of telomeric DNA during aging of normal and trisomy 21 human lymphocytes, Am. J. Hum. Genet. 52 (4) (1993) 661–667.
[34] Y. Kanda, Investigation of the freely available easy-to-use software 'EZR' for medical statistics, Bone Marrow Transplant. 48 (3) (2013) 452–458.
[35] J. Xie, C. Brayne, F.E. Matthews, F. Medical Research, Council Cognitive, c. Ageing Study, Survival times in people with dementia: analysis from population based cohort study with 14 year follow-up, BMJ 336 (7638) (2008) 258–262.
[36] R.S. Wilson, N.T. Aggarwal, L.L. Barnes, J.L. Bienias, C.F. Mendes de Leon, D.A. Evans, Biracial population study of mortality in mild cognitive impairment and Alzheimer disease, Arch. Neurol. 66 (6) (2009) 767–772.
[37] G.A. Sachs, R. Carter, L.R. Holtz, F. Smith, T.E. Stump, W. Tu, C.M. Callahan, Cognitive impairment: an independent predictor of excess mortality: a cohort study, Ann. Intern. Med. 155 (5) (2011) 300–308.
[38] S.I. Chaudhry, T.E. Murphy, E. Gahbauer, L.S. Sussman, H.G. Allore, T.M. Gill, Restricting symptoms in the last year of life: a prospective cohort study, JAMA Intern. Med. 173 (16) (2013) 1534–1540.
[39] J. Benito-Leon, J.P. Romero, E.D. Louis, F. Bermejo-Pareja, Faster cognitive decline in elders without dementia and decreased risk of cancer mortality: NEDICES Study, Neurology 82 (16) (2014) 1441–1448.
[40] K.B. Rajan, N.T. Aggarwal, R.S. Wilson, S.A. Everson-Rose, D.A. Evans, Association of cognitive functioning, incident stroke, and mortality in older adults, Stroke 45 (9) (2014) 2563–2567.
[41] H. Bokura, S. Kobayashi, S. Yamaguchi, K. Iijima, A. Nagai, G. Toyoda, H. Oguro, K. Takahashi, Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: a prospective cohort study, J. Stroke Cerebrovasc. Dis. 15 (2) (2006) 57–63.
[42] Y. Takata, T. Ansai, I. Soh, S. Awano, I. Nakamichi, S. Akifusa, K. Goto, A. Yoshida, H. Fujii, R. Fujisawa, K. Sonoki, Cognitive function and 10 year mortality in an 85 year-old community-dwelling population, Clin. Interv. Aging 9 (2014) 1691–1699.
[43] K.E. Ensrud, S.K. Ewing, B.C. Taylor, H.A. Fink, P.M. Cawthon, K.L. Stone, T.A. Hillier, J.A. Cauley, M.C. Hochberg, N. Rodondi, J.K. Tracy, S.R. Cummings, Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women, Arch. Intern. Med. 168 (4) (2008) 382–389.
[44] P.A. Boyle, A.S. Buchman, R.S. Wilson, S.E. Leurgans, D.A. Bennett, Physical frailty is associated with incident mild cognitive impairment in community-based older persons, J. Am. Geriatr. Soc. 58 (2) (2010) 248–255.
[45] N.D. Hastie, M. Dempster, M.G. Dunlop, A.M. Thompson, D.K. Green, R.C. Allshire, Telomere reduction in human colorectal carcinoma and with ageing, Nature 346 (6287) (1990) 866–868.
[46] E. Chang, C.B. Harley, Telomere length and replicative aging in human vascular tissues, Proc. Natl. Acad. Sci. U. S. A. 92 (24) (1995) 11190–11194.
[47] J. Lindsey, N.I. McGill, L.A. Lindsey, D.K. Green, H.J. Cooke, In vivo loss of telomeric repeats with age in humans, Mutat. Res. 256 (1) (1991) 45–48.
[48] H. Vaziri, W. Dragowska, R.C. Allsopp, T.E. Thomas, C.B. Harley, P.M. Lansdorp, Evidence for a mitotic clock in human hematopoietic stem cells: loss of telomeric DNA with age, Proc. Natl. Acad. Sci. U. S. A. 91 (21) (1994) 9857–9860.
[49] E.H. Blackburn, E.S. Epel, J. Lin, Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection, Science 350 (6265) (2015) 1193–1198.
[50] M. Armanios, E.H. Blackburn, The telomere syndromes, Nat. Rev. Genet. 13 (10) (2012) 693–704.
[51] B. Martinez-Delgado, K. Yanowsky, L. Inglada-Perez, S. Domingo, M. Urioste, A. Osorio, J. Benitez, Genetic anticipation is associated with telomere shortening in hereditary breast cancer, PLoS Genet. 7 (7) (2011) e1002182.
[52] V. Boccardi, L. Pelini, S. Ercolani, C. Ruggiero, P. Mecocci, From cellular senescence to Alzheimer's disease: the role of telomere shortening, Ageing Res. Rev. 22 (2015) 1–8.
[53] H. Mulder, Is shortening of telomeres the missing link between aging and the Type 2 Diabetes epidemic? Aging (Albany NY) 2 (10) (2010) 634–636.