Hypertension Research (2017) 40, 665–670

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ORIGINAL ARTICLE

Longitudinal association of hypertension and diabetes mellitus with cognitive functioning in a general 70-year-old population: the SONIC study

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Both hypertension and diabetes in middle-aged individuals have been suggested to be predictive indicators of cognitive decline. However, the association of hypertension, diabetes and their combination with cognitive functioning is still controversial in older people. The purpose of this study was to investigate the association between cognitive decline and hypertension, diabetes, and their combination in 70-year-old people based on a 3-year longitudinal analysis. Four hundred and fifty-four people aged 70 (±1) years who participated in the Japanese longitudinal cohort study of Septuagenarians, Octogenarians and Nonagenarians Investigation with Centenarians (SONIC) were recruited randomly from a general population and were monitored for 3 years. The data, including most of the demographics, cognitive functioning measured by the Montreal Cognitive Assessment Japanese version (MoCA-J), blood pressure, blood chemistry and other medical histories, were collected at baseline and during the follow-up. The prevalence of hypertension noted in the follow-up survey was significantly higher than than noted at baseline. The mean MoCA-J score at follow-up was not significantly different from the score obtained at baseline. However, the participants with diabetes, especially combined with hypertension at baseline, had significantly lower MoCA-J scores than those without lifestyle-related diseases. The combination of hypertension and diabetes was still a significant risk factor for cognitive decline, considering the MoCA-J scores obtained during the follow-up after adjustments at baseline, relative to sex, body mass index, dyslipidemia, smoking, excessive alcohol intake, antihypertensive treatment and education level ($\beta = -0.14$; $P < 0.01$). Our findings indicate that diabetes and the combination of hypertension and diabetes are clear risk factors for future cognitive decline in elderly individuals who are 70 years of age.
Hypertension Research (2017) **40,** 665–670; doi:10.1038/hr.2017.15; published online 23 February 2017

Keywords: cognitive functioning; diabetes mellitus; older population

INTRODUCTION

Midlife hypertension (HT) is thought to be associated with lower cognitive functioning in later life, and HT-related changes in cognition have been well-documented.[1–4] In contrast, it is still controversial whether HT affects cognitive decline at an older age based on the results of most cross-sectional analyses.[1,2,5–7] In a cross-sectional investigation, our group recently reported that HT might be associated with cognitive decline at ~70 years of age but not in individuals ~80 years of age.[5] This finding may indicate that aging influences cognitive decline in the presence of lifestyle-related diseases, such as HT and diabetes mellitus (DM).

According to several longitudinal studies, high blood pressure (BP) in midlife significantly increases the risk of cognitive decline in later life.[1,2,8–10] Meanwhile, several reports have indicated that the influence of HT and elevated BP on the progression of cognitive decline was attenuated in general populations of those aged 70 years or older.[1,2,5–7,11,12]

Similar findings were reported in several previous studies of HT, obesity and cognitive performance, in which the effects of these risk factors on cognitive decline were additive.[1,13,14] Regarding the relationship between DM and cognitive decline, there have been many population-based longitudinal studies, including both middle-aged

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Received 18 October 2016; revised 14 December 2016; accepted 25 December 2016; published online 23 February 2017

and older populations.[15,16] With the finding of significant multiplicative interactions between HT and DM in previous studies, the combined presence of these lifestyle-related diseases might be associated with lower-level cognitive functioning compared with the presence of either alone. However, the majority of studies were limited to Caucasians and involved elderly populations, in which these associations tended to be weak.[1,13,17–19]

The aim of this study was to investigate the 3-year longitudinal effect of HT and additive risk factors on cognitive functioning in individuals ~70 years of age. There was a clear influence of high BP on cognitive decline in our previous study, involving a general Japanese population in a narrow age range cohort study: the Septuagenarians, Octogenarians and Nonagenarians Investigation with Centenarians (SONIC) study, a longitudinal cohort study targeting older ages.[5,20–22]

METHODS

Study population

This study was a longitudinal examination involving a 3-year follow-up investigating health and longevity. Named the SONIC study, our longitudinal cohort study targeted older individuals aged 70, 80, 90 and over 100 years, and included medical and social variables.[5,20–22] The participants were 1000 independently living volunteers (excluding institutionalized individuals) aged 69–71 years (52.1% were women) from the following four areas of Japan: Itami City, Hyogo (Western-urban); Asago City, Hyogo (Western-rural); Itabashi ward, Tokyo (Eastern-urban); and Nishitama County, Tokyo (Eastern-rural). The participants were selected randomly from the local resident registration performed in 2010. We invited 4307 people among the targeted age range in the four surveyed regions. We estimated the participation ratio for the 70 s cohort as 25%. Consequently, 1000 people participated in our survey.[23] Six hundred and thirty-four people (50.5% were women) participated in the baseline and 3-year follow-up survey. We excluded 180 participants from our analyses who had histories of stroke, cardiovascular disease, kidney disease and dementia. We examined 454 people (53.7% were women) who participated in the baseline and 3-year follow-up surveys.

The study protocol was approved by the Institutional Review Board of Osaka University Graduate School of Medicine, Dentistry, Human Sciences, and Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology (approval numbers 266, H22-E9, 22018 and 38, respectively). All of the subjects provided their written informed consent to participate in the study.

Measurements

BP measurement and classification. A physician or trained nurse, using a mercury sphygmomanometer or electronic monitor two times, obtained BP measurements from the left and right arms of the patients while they sat after at least 1 min of rest, and the mean of the 2 measurements of both arms were used in the analysis. According to the criteria of the Japanese Society of Hypertension guidelines for the management of HT (JSH 2014), the diagnosis of HT was based on BP values >140/90 mm Hg and use of antihypertensive treatment at the time of the first contact.[4] BP measurements were classified into 2 categories: the uncontrolled BP group was defined as individuals with systolic BP (SBP) values of 140 mm Hg or greater and diastolic BP (DBP) values of 90 mm Hg or greater, and the controlled BP group was defined as individuals with SBP values <140 mm Hg and DBP values <90 mm Hg according to the guidelines. Individuals receiving antihypertensive treatment at the time of the first contact were classified as treated, and of these subjects, those having SBP values <140 mm Hg or DBP <90 mm Hg were considered to be hypertensive but controlled. The pulse pressure (PP) was calculated by subtracting DBP from SBP.

Other factor measurements. The participants were interviewed at the time of the study enrollment and follow-up using questionnaires covering demographics, clinical information and psychosocial characteristics. The blood samples were drawn after overnight fasting. The levels of total cholesterol, high-density lipoprotein cholesterol, triglycerides, serum albumin and fasting/casual blood glucose were determined by biochemical examinations. DM was defined by fasting blood glucose concentrations $\geqslant 7.0$ mmol l^{-1} (126 mg dl^{-1}), casual blood glucose concentrations $\geqslant 11.1$ mmol l^{-1} (200 mg dl^{-1}), HbA1c (NGSP) $\geqslant 6.5\%$ or taking medications for diabetes according to the World Health Organization criteria for epidemiologic studies of DM. Dyslipidemia was defined as low-density lipoprotein cholesterol $\geqslant 3.62$ mmol l^{-1} (140 mg dl^{-1}), high-density lipoprotein cholesterol <1.03 mmol l^{-1} (40 mg dl^{-1}), triglyceride $\geqslant 1.69$ mmol l^{-1} (150 mg dl^{-1}) and medications for dyslipidemia. Smoking behavior was based on a questionnaire, which classified subjects into the following three categories: never, past and current. Alcohol consumption was also classified into the following three categories by ethanol units: never, current (1–3 days <3 units per week) and excessive current (≥3 days and ⩾3 units per week).

Assessment of cognitive functioning

We used the Japanese version of the Montreal Cognitive Assessment (MoCA-J) as a general index of the cognitive status.[24] MoCA is a brief cognitive screening tool for detecting mild cognitive impairment in elderly people.[25] MoCA consists of a 1-page 30-point test administered by trained geriatricians and psychologists, with higher scores reflecting more favorable cognitive functioning. MoCA assesses the following domains of cognition: visuospatial abilities (3 points), naming task (3 points), attention task (6 points), language (3 points), abstraction task (2 points), delayed recall (5 points) and orientation (6 points). The MoCA-J showed a favorable reliability and better validity for predicting mild cognitive impairment than conventional cognitive tests.[24] We used the MoCA-J total score as a predictor of cognitive functioning.[5]

Statistical analyses

At baseline and follow-up examination, the descriptive data were summarized and presented as the mean ± s.d. values and proportions. Student's *t*-test for two independent groups and the paired *t*-test for two dependent groups were used, and the comparison of proportions between the baseline and follow-up was performed using the McNemar test. Multiple linear regression models were produced for each group to calculate the standardized regression coefficients (β) expressing independent associations between the variables. In these analyses, the data were stratified by the diagnosis of HT and DM, BP category and antihypertensive treatment. When analysis of covariance indicated the effect of the BP category and antihypertensive treatment, pairwise comparisons were used to identify significant differences. All of the statistical analyses were performed using SPSS Statistics 22 (IBM Japan, Tokyo, Japan). All of the reported *P*-values are two-tailed, and $P<0.05$ was considered to be statistically significant.

RESULTS

Characteristics of participants

The characteristics of participants at baseline and follow-up are shown in Table 1. The proportions of those with HT, dyslipidemia and HT medication use were significantly higher in participants at the time of follow-up than in those at baseline. The proportion of those with DM was not significantly different; In addition, the proportion of DM participants with HT at the time of follow-up was not significantly different at baseline. DBP at the time of follow-up was significantly lower than at baseline. The number of patients with new-onset of HT was 56 (41.5% of normotensives at baseline). Serum total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol at the time of follow-up were significantly lower than at baseline, whereas triglyceride and BMI were higher than those at baseline.

The MoCA-J total score at the time of follow-up was not significantly different from the baseline score not only in the total participants but also in the participants with combination of HT and DM (Table 1 and Figure 1). However, those with HT, especially combined with DM at baseline, had a significantly lower MoCA-J total score at the time of follow-up after adjusting for sex and dyslipidemia in the analysis of covariance model (Figure 1). The MoCA-J total score

at baseline was not significantly different between the combinations of HT and DM. In addition, the MoCA-J total score according to the combinations of HT and DM was not significantly different between the baseline and the follow-up scores. According to the SBP category at baseline, the MoCA-J total score of people with stage 3 HT at the time of follow-up was significantly lower than those with optimal, normal, high-normal and stage 1 HT after adjusting for sex, DM and dyslipidemia (Figure 2). The MoCA-J total score at baseline was not significantly different between the SBP categories at baseline. In addition, the MoCA-J total score according to the SBP categories was not significantly different between the baseline and the follow-up scores. According to the BP control level and the treatment status at baseline, the MoCA-J total score at the time of follow-up was not significantly different after adjusting for sex, DM and dyslipidemia; however, there was a marginal difference between those individuals with no HT and those with BP uncontrolled no treatment (Supplementary Figure S1). The distribution of the 3-year change in the MoCA-J total score is shown in Supplementary Figure S2 (skewness = − 0.029, kurtosis = 0.383).

Table 1 Characteristics of study population

N = *454*	*Baseline*	*Follow-up (3 years)*	*Changes*
SBP (mmHg)	139.5 ± 18.9	137.9 ± 18.2	− 1.6 ± 17.7
DBP (mmHg)	79.3 ± 10.4	77.9 ± 11.1	− 1.4 ± 10.2**
PP (mmHg)	60.3 ± 15.0	60.0 ± 14.4	− 0.2 ± 14.3
HTN (%)	64.8	71.4	+6.6*
Taking medication for HTN (%)	33.1	43.0	+9.9***
DM (%)	18.4	17.1	− 1.3
Combined HTN (%)	68.4	73.7	+5.3
Dyslipidemia (%)	63.6	74.3	+10.7***
Serum total cholesterol (mg dl^{-1})	213.3 ± 37.0	207.6 ± 34.4	− 5.7 ± 50.5*
LDL-C (mg dl^{-1})	124.8 ± 29.5	119.5 ± 30.2	− 5.2 ± 26.9***
HDL-C (mg dl^{-1})	63.8 ± 15.7	60.4 ± 14.9	− 3.3 ± 8.6***
TG (mg dl^{-1})	132.5 ± 77.0	139.6 ± 84.4	+7.0 ± 79.9
BMI (kg m^{-2})	22.7 ± 2.8	22.9 ± 3.0	+0.2 ± 1.5*
Serum albumin (g dl^{-1})	4.4 ± 0.3	4.4 ± 0.3	− 0.1 ± 0.4**
MoCA-J total score (0–30)	24.0 ± 3.1	24.1 ± 3.0	+0.1 ± 2.8
Visuospatial/executive (0–5)	4.4 ± 0.8	4.3 ± 0.9	− 0.1 ± 0.9
Naming task (0–3)	2.9 ± 0.4	2.9 ± 0.4	+0.0 ± 0.4
Attention (0–6)	5.1 ± 1.0	5.0 ± 1.1	− 0.0 ± 1.0
Language (0–3)	1.6 ± 0.9	1.5 ± 0.8	− 0.1 ± 1.0
Abstraction (0–2)	1.4 ± 0.7	1.8 ± 0.5	0.4 ± 0.8***
Delayed recall (0–5)	2.1 ± 1.6	2.1 ± 1.6	+0.0 ± 1.8
Orientation (0–6)	5.9 ± 0.4	5.8 ± 0.5	− 0.0 ± 0.6
Current smoking (%)	10.6	13.3	+2.7*
Alcohol consumption (%)			
Never	61.4	60.5	− 0.9
Current	32.9	35.4	+2.5
Current excessive	5.7	4.1	− 1.6

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein-cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein-cholesterol; MoCA-J, Japanese version of Montreal Cognitive Assessment; PP, pulse pressure; SBP, systolic blood pressure; TG, triglyceride.
At both the baseline and follow-up, 454 participants were analyzed after excluding those with missing data.
*P<0.05, **P<0.01 and ***P<0.001.

Multiple regression analysis

Table 2 shows the standardized univariate coefficients and multi-regression coefficients as predictors of the MoCA-J total score at the time of follow-up. In model 1, the combination of HT and DM was a significant risk factor for the MoCA-J total score at the 3-year follow-up after adjusting for the MoCA-J total score at the baseline, sex, BMI, dyslipidemia, smoking, excessive alcohol intake, antihypertensive medications and educational level at baseline ($\beta = -0.14$; $P<0.01$). In model 2, DM at baseline correlated significantly with the MoCA-J total score at the time of follow-up ($\beta = -0.12$; $P<0.01$). DM at baseline was a significant predictor of the MoCA-J total score at the time of follow-up in the multi-regression analyses, whereas SBP and PP at baseline were not significant predictors (models 3 and 4). Table 3 shows DM at baseline was a significant predictor of the change in the MoCA-J total score between baseline and follow-up scores (models 2, 3 and 4).

DISCUSSION

Previous cross-sectional studies, including our report, indicated a significant correlation between a high SBP and an increased risk of cognitive decline.[1,5–7,26] The present longitudinal study indicated that DM and the combination of HT and DM but not HT only in later life at ~70 years of age might be a risk factor for cognitive decline after a 3-year follow-up. In our results, the prevalence of HT at the time of follow-up was significantly higher than at baseline in the community-dwelling Japanese participants ~70 years old, whereas SBP was not significantly different and the mean SBP was controlled. This finding may be due to the significantly increasing use of antihypertensive medication at the time of follow-up compared with HT medication use at baseline; therefore, BP control of follow-up participants might be adequate in the present study. One of the previous studies on the relationship between HT and dementia suggested that a higher SBP developed 4 years before the onset of Alzheimer's disease in community-dwelling people aged 75 or younger.[27] In addition, several previous studies using longitudinal observation performed a longer

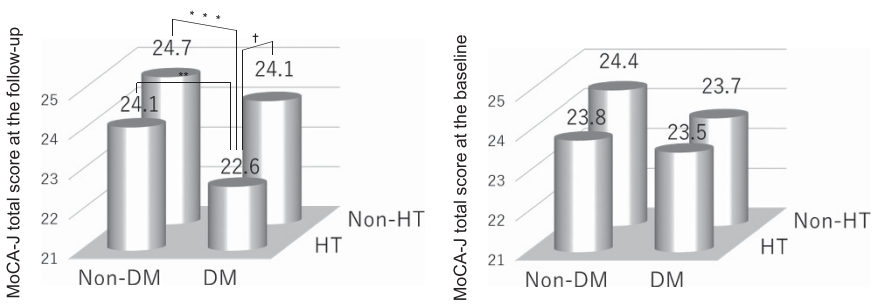

Figure 1 MoCA-J total score at the time of follow-up and at baseline associated with the combination of hypertension (HT) and diabetes mellitus (DM) at baseline after adjusting for sex and dyslipidemia in the analysis of covariance model. †P<0.1, **P<0.01 and ***P<0.001.

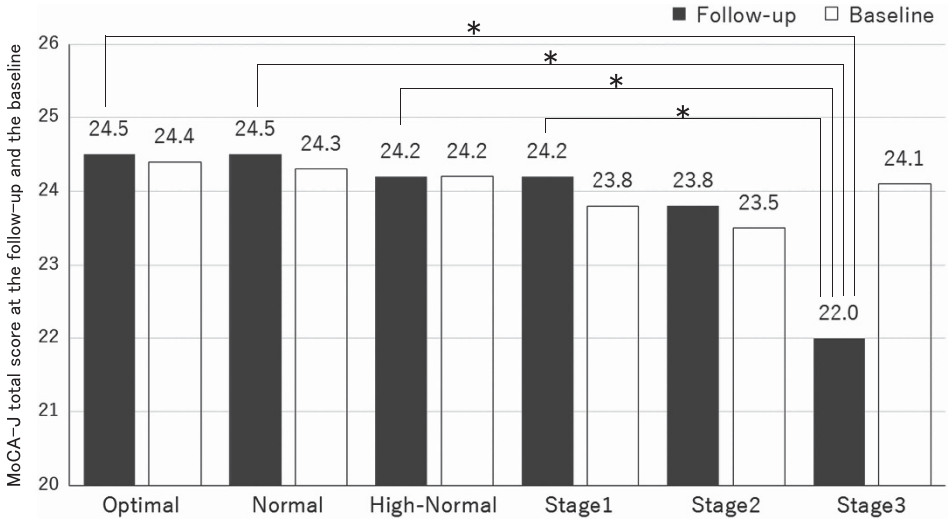

Figure 2 Sex-, diabetes mellitus- (DM) and dyslipidemia-adjusted MoCA-J total scores at the time of follow-up and at baseline according to the systolic blood pressure (SBP) category at baseline using analysis of covariance. *$P<0.05$.

Table 2 Standardized multi-regression coefficients (β) as predictors of MoCA-J total score at follow-up

		Multi-regression coefficients (β)			
	Univariate coefficients	*Model 1*	*Model 2*	*Model 3*	*Model 4*
Combination of HT and DM	−0.18***	−0.14**	–	–	–
HT	−0.10*	–	−0.07	–	–
DM	−0.15**	–	−0.12**	−0.12**	−0.12**
SBP	−0.08	–	–	−0.03	–
PP	−0.10*	–	–	–	−0.05

Abbreviations: BMI, body mass index; DM, diabetes mellitus; HT, hypertension; MoCA-J, Japanese version of the Montreal Cognitive Assessment; PP, pulse pressure; SBP, systolic blood pressure.
We defined the categorical variables as following; non-HT and non-DM = 0, HT or DM = 1, HT and DM = 2.
The covariates of models 1 are including MoCA-J total score at the baseline, sex, dyslipidemia, BMI, smoking, excessive alcohol intake, antihypertensives and educational level.
The covariates of models 2 are including MoCA-J total score at the baseline, sex, dyslipidemia, BMI, smoking, excessive alcohol intake, antihypertensives and educational level.
The covariates of models 3 are including MoCA-J total score at the baseline, sex, dyslipidemia, BMI, smoking, excessive alcohol intake, antihypertensives and educational level.
The covariates of models 4 are including MoCA-J total score at the baseline, sex, dyslipidemia, BMI, smoking, excessive alcohol intake, antihypertensives and educational level.
Parameter estimates (β) can be interpreted as differences in MoCA-J total scores for each 10-mmHg increase in SBP and PP.
*$P<0.05$, **$P<0.01$, ***$P<0.001$.

Table 3 Standardized multi-regression coefficients (β) as predictors of change of MoCA-J total score between baseline and follow-up

		Multi-regression coefficients (β)			
	Univariate coefficients	*Model 1*	*Model 2*	*Model 3*	*Model 4*
Combination of HT and DM	−0.05	−0.09	–	–	–
HT	0.02	–	−0.02	–	–
DM	−0.08	–	−0.11*	−0.11*	−0.11*
SBP	0.03	–	–	0.00	–
PP	0.01	–	–	–	−0.02

Abbreviations: BMI, body mass index; DM, diabetes mellitus; HT, hypertension; MoCA-J, Japanese version of the Montreal Cognitive Assessment; PP, pulse pressure; SBP, systolic blood pressure.
We defined the categorical variables as following: non-HT and non-DM = 0, HT or DM = 1, and HT and DM = 2.
Models 1–4 are adjusted for sex, dyslipidemia, BMI, smoking, excessive alcohol intake, antihypertensives and educational level.
Parameter estimates (β) can be interpreted as differences in MoCA-J total scores for each 10-mmHg increase in SBP and PP.

follow-up and included subjects with higher BP values at baseline than in our study; therefore, the results of the present study might not be concordant with those of previous studies.[11,27] Another reason for the discrepancy with previous studies involves the characteristics of participants in the SONIC study, whereas the participants in this study may be healthier than those in previous studies because most are community dwellers, and they were able to come to the investigation site by themselves.

Interestingly, HT, DM and PP at baseline were correlated with the MoCA-J total score at the time of follow-up, as shown in Table 2; however, in multi-regression models, DM and its combination with HT were significantly correlated with the cognitive functioning evaluated by MoCA-J in community-dwelling elderly aged ~70 years after adjusting for the MoCA-J total score and other confounders excluding stroke, cardiovascular disease, kidney disease and dementia at baseline (Table 2). These findings are novel. From these results, we suggest that DM combined with HT may have a stronger influence on future cognitive decline compared with DM only. Comparing the findings of significant multiplicative interactions between HT and DM in previous studies, we note that our results indicated that the combination of HT and DM had a more additive effect, but not a more interactive effect, than the presence of a higher BP and DM alone.[1,11,17] Previous longitudinal studies, which reported on the association of combined HT and DM in community-dwelling elderly, suggested that HT and DM were associated with different cognitive domains.[11,17] Our study examined cognitive functioning using MoCA-J, which is appropriate for the evaluation of early and mild cognitive decline. Since we could not perform imaging examinations, such as MRI, to determine subtypes of dementia because the survey was conducted at a community center and not a hospital, we could not discuss the causes of cognitive decline. However, our study may support additive effects whereby the combination of HT and DM impairs the cognitive functioning in different domains. In addition, the standardized multi-regression coefficient as a predictor of the MoCA-J total score at the time of follow-up was larger than those of previous cross-sectional and longitudinal studies; therefore, the prevention of both HT and DM was more effective for the prevention of cognitive decline at the 3-year follow-up in later life at approximately age 70.[5,7,17]

The key strength of our SONIC study was that we investigated a cohort study involving community-dwelling participants within a narrow age range to specify predictors under conditions that minimize the influence of age.[5,20–22] We could consider the influence of age, and to our knowledge, this narrow age approach in a longitudinal study may clarify the differences in the influence of aging on the association between HT and cognitive functioning in later life. The age range of participants in previous studies was relatively wide; therefore, one of our hypotheses was that the results were controversial because of the study design. The design of our SONIC study enabled us to clarify the differences in the association of HT and cognitive functioning among participants ranging in age between 70 and 80 years.[5] In addition, the MoCA-J score was sensitive compared with Mini Mental State Examination; therefore, we provided additional outcomes to examine the longitudinal association between HT and cognitive functioning.

Our study has several limitations. First, DM, especially combined with HT, did not predict the change of the MoCA-J total score between baseline and follow-up. Our results showed that DM, especially combined with HT at baseline, predicted the mean of the MoCA-J total score at the time of follow-up after adjusting for the MoCA-J total score and other confounders at baseline, whereas HT at baseline did not predict how the MoCA-J total score would change for 3 years. Second, the total follow-up participants ($n=634$) had significantly lower SBP values ($P=0.006$), a lower proportion of participants with DM ($P=0.003$), a lower prevalence of being house-bound ($P=0.004$) and a higher MoCA-J total score ($P<0.001$) after the follow-up examination than the excluded participants and Japanese national survey data from the Ministry of Health, Labour and Welfare (Supplementary Table S1).[28] This finding might underestimate the influence of SBP and DM on the cognitive functioning of participants in our cohort study. In fact, people with SBP in stage 3 HT at baseline had a lower MoCA-J total score at the time of follow-up than those who were normotensive or had stage 1 HT (Figure 2). In addition, the follow-up rate in our study seemed to be low (634/1000) because there were several expected reasons for dropout from the follow-up survey, such as the following: they had no time to participate in the study, they moved out of the area we surveyed or they could not participate in the follow-up study because of poor health conditions. It is also likely that we missed a few cases in the participants who died or were institutionalized in nursing homes before the follow-up survey. This situation would tend to bias our results toward an underestimation of the influence of HT and DM on cognitive functioning. Third, our study did not clarify the period of HT and DM, considering midlife HT and DM in relation to later-life cognitive decline. Consequently, our study helps to clarify the association between a later-life onset of HT and DM and cognitive decline over the age of 70 years. Fourth, we examined the association between SBP and cognitive functioning for participants aged 80; however, the longitudinal results for participants aged 80 were not reported.[5] Because no association of HT, DM and SBP with cognitive functioning was observed longitudinally, we excluded the results. Fifth, since we could not perform any imaging examinations to diagnose the subtypes of dementia, we could not discuss the causes of cognitive decline and the mechanism for such a link to cognitive functioning. One likely mechanism is that both HT and DM reduce the hippocampal volume and increase a white matter hyperintensity.[29–31] In previous cohort studies of subjects aged 70 years and older, a high BP was associated with an increased progression of structural changes in the brain.[29,31] In addition, a longer duration of DM is a risk factor for brain atrophy, particularly hippocampal atrophy.[30] Our results might suggest that based on these mixed findings, the association between HT and DM and cognitive functioning is complex, depending on coexisting vascular diseases, which we excluded in our analyses. Finally, the differences in the MoCA-J total score between baseline and follow-up among HT and DM participants were significant but not strong because of the standardized regression coefficients. However, we compared our results with previous cross-sectional and longitudinal studies; larger coefficients were observed with similar and larger sample sizes.[5,7,11] Our interpretation is also based on the epidemiological meaning; that is, replication analyses were needed for community-dwelling elderly to assess the inconsistencies of association between HT and cognitive functioning on stratifying the age range. In addition, the differences of the MoCA-J total score between baseline and follow-up could be observed for only 3 years because of the favorable reliability and better validity for predicting mild cognitive impairment than conventional cognitive tests.[24,25] Although the duration of the follow-up was not longer than in previous studies, the follow-up of people with both HT and DM would be important to prevent cognitive decline.[8–10,15,16]

In conclusion, our present study indicated that people with DM, especially combined with HT, had a longitudinal risk factor of cognitive decline in those aged 70 years after a 3-year follow-up. Thus, we recommend the treatment of HT and DM for not only the prevention of cardiovascular diseases but also the attenuation of cognitive decline in the elderly population ~70 years of age.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We sincerely thank all staff involved in the SONIC study, especially Prof Shin-ichi Satoh, Ms Yoshiko Ishioka, Ms Megumi Tabuchi, Ms Yukiko Tatsuhira and Ms Marina Kozono at Osaka University, Graduate School of Human Sciences; Prof Yoshinobu Maeda, Prof Shin-ya Murakami, Dr Masahiro Kitamura, Dr Ryosuke Kagawa, Dr Ken-ichi Matsuda, Dr Tadashi Okada, Dr Chisato Inomata, Dr Hajime Takeshita, Dr Yusuke Mihara and Dr Masahiro Uota at Osaka University Graduate School of Dentistry; and Ms Madoka Ogawa and Takeshi Kurinobu at Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology. We also thank Ms Yasuyo Takamine and Ms Yumiko Aoshima at Osaka University, Graduate School of Medicine for secretarial work. We sincerely appreciate all SONIC participants for their kind cooperation. This study was supported in part by grants-in-aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (KK: 22510211,15K08910), Pfizer Health Care Research Foundation (KK) and Sakamoto Foundation for Medical Research (MT).

1 Elias MF, Goodell AL, Dore GA. Hypertension and cognitive functioning: a perspective in historical context. *Hypertension* 2012; **60**: 260–268.
2 Deckers K, van Boxtel MP, Schiepers OJ, de Vugt M, Muñoz Sánchez JL, Anstey KJ, Brayne C, Dartigues JF, Engedal K, Kivipelto M, Ritchie K, Starr JM, Yaffe K, Irving K, Verhey FR, Köhler S. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry* 2015; **30**: 234–246.
3 Nagai M, Hoshide S, Kario K. Hypertension and dementia. *Am J Hypertens* 2010; **23**: 116–124.
4 Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension. Japanese society of hypertension guidelines for the management of hypertension (JSH 2014). *Hypertens Res* 2014; **37**: 253–390.
5 Ryuno H, Kamide K, Gondo Y, Nakama C, Oguro R, Kabayama M, Kawai T, Kusunoki H, Yokoyama S, Imaizumi Y, Takeya M, Yamamoto H, Takeda M, Takami Y, Itoh N, Yamamoto K, Takeya Y, Sugimoto K, Nakagawa T, Ikebe K, Inagaki H, Masui Y, Ishizaki T, Takayama M, Arai Y, Takahashi R, Rakugi H. Differences in the association between high blood pressure and cognitive functioning among the general Japanese population aged 70 and 80 years: The SONIC study. *Hypertens Res* 2016; **39**: 557–563.
6 Obisesan TO, Obisesan OA, Martins S, Alamgir L, Bond V, Maxwell C, Gillum RF. High blood pressure, hypertension, and high pulse pressure are associated with poorer cognitive function in persons aged 60 and older: the Third National Health and Nutrition Examination Survey. *J Am Geriatr Soc* 2008; **56**: 501–509.
7 Seux ML, Thijs L, Forette F, Staessen JA, Birkenhäger WH, Bulpitt CJ, Girerd X, Jääskivi M, Vanhanen H, Kivinen P, Yodfat Y, Vänskä O, Antikainen R, Laks T, Webster JR, Hakamäki T, Lehtomäki E, Lilov E, Grigorov M, Janculova K, Halonen K, Kohonen-Jalonen P, Kermowa R, Nachev C, Tuomilehto J. Correlates of cognitive status of old patients with isolated systolic hypertension: the Syst-Eur Vascular Dementia Project. *J Hypertens* 1998; **16**: 963–969.
8 Elias PK, Elias MF, Robbins MA, Budge MM. Blood pressure-related cognitive decline: does age make a difference? *Hypertension* 2004; **44**: 631–636.
9 Ninomiya T, Ohara T, Hirakawa Y, Yoshida D, Doi Y, Hata J, Kanba S, Iwaki T, Kiyohara Y. Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama Study. *Hypertension* 2011; **58**: 22–28.
10 Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* 2005; **4**: 487–499.
11 Kuo HK, Jones RN, Milberg WP, Tennstedt S, Talbot L, Morris JN, Lipsitz LA. Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: a longitudinal analysis of the ACTIVE cohort. *J Am Geriatr Soc* 2005; **53**: 1154–1161.
12 Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Odén A, Svanborg A. 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996; **347**: 1141–1145.
13 Kivipelto M, Helkala EL, Hänninen T, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study. *Neurology* 2001; **56**: 1683–1689.
14 Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: the Framingham Heart Study. *Int J Obes Relat Metab Disord* 2003; **27**: 260–268.
15 Ohara T, Doi Y, Ninomiya T, Hirakawa Y, Hata J, Iwaki T, Kanba S, Kiyohara Y. Glucose tolerance status and risk of dementia in the community The Hisayama Study. *Neurology* 2011; **77**: 1126–1134.
16 Rawlings AM, Sharrett AR, Schneider AL, Coresh J, Albert M, Couper D, Griswold M, Gottesman RF, Wagenknecht LE, Windham BG, Selvin E. Diabetes in midlife and cognitive change over 20 years: a cohort study. *Ann Intern Med* 2014; **161**: 785–793.
17 Kelly A, Calamia M, Koval A, Terrera GM, Piccinin AM, Clouston S, Hassing LB, Bennett DA, Johansson B, Hofer SM. Independent and interactive impacts of hypertension and diabetes mellitus on verbal memory: a coordinated analysis of longitudinal data from England, Sweden, and the United States. *Psychol Aging* 2016; **31**: 262–273.
18 Elias PK, Elias MF, D'Agostino RB, Cupples LA, Wilson PW, Silbershatz H, Wolf PA. NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. *Diabetes Care* 1997; **20**: 1388–1395.
19 Alonso A, Mosley TH Jr, Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. *J Neurol Neurosurg Psychiatry* 2009; **80**: 1194–1201.
20 Inomata C, Ikebe K, Kagawa R, Okubo H, Sasaki S, Okada T, Takeshita H, Tada S, Matsuda K, Kurushima Y, Kitamura M, Murakami S, Gondo Y, Kamide K, Masui Y, Takahashi R, Arai Y, Maeda Y. Significance of occlusal force for dietary fibre and vitamin intakes in independently living 70-year-old Japanese: from SONIC Study. *J Dent* 2014; **42**: 556–564.
21 Okada T, Ikebe K, Kagawa R, Inomata C, Takeshita H, Gondo Y, Ishioka Y, Okubo H, Kamide K, Masui Y, Takahashi R, Arai Y, Thomson WM, Maeda Y. Lower protein intake mediates association between lower occlusal force and slower walking speed: from the septuagenarians, octogenarians, nonagenarians investigation with centenarians study. *J Am Geriatr Soc* 2015; **63**: 2383–2387.
22 Takeshita H, Ikebe K, Kagawa R, Okada T, Gondo Y, Nakagawa T, Ishioka Y, Inomata C, Tada S, Matsuda K, Kurushima Y, Enoki K, Kamide K, Masui Y, Takahashi R, Arai Y, Maeda Y. Association of personality traits with oral health-related quality of life independently of objective oral health status: a study of community-dwelling elderly Japanese. *J Dent* 2015; **43**: 342–349.
23 Gondo Y, Masui Y, Kamide K, Ikebe K, Arai Y, Ishizaki T. SONIC study: a longitudinal cohort study of the older people as part of a centenarian study. In Pachana NA (ed.), *Encyclopedia of Geropsychology*, Springer Science+Business Media Singapore, Singapore, 2016. doi 10.1007/978-981-287-080-3_182-1 (e-pub ahead of print).
24 Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53**: 695–699.
25 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999; **56**: 303–308.
26 Wu L, He Y, Jiang B, Liu M, Wang J, Yang S, Wang Y. The association between the prevalence, treatment and control of hypertension and the risk of mild cognitive impairment in an elderly urban population in China. *Hypertens Res* 2016; **39**: 367–375.
27 Li G, Rhew IC, Shofer JB, Kukull WA, Breitner JC, Peskind E, Bowen JD, McCormick W, Teri L, Crane PK, Larson EB. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. *J Am Geriatr Soc* 2007; **55**: 1161–1167.
28 Ministry of Health Welfare Japan (2011). Life-Style Related Diseases Control General Affairs Division. Report On The Survey Of National Health And Nutrition Survey. http://www.mhlw.go.jp/stf/houdou/2r9852000002q1st-att/2r9852000002q1wo.pdf. Accessed on 29 July 2016 (in Japanese).
29 Firbank MJ, Wiseman RM, Burton EJ, Saxby BK, O'Brien JT, Ford GA. Brain atrophy and white matter hyperintensity change in older adults and relationship to blood pressure. Brain atrophy, WMH change and blood pressure. *J Neurol* 2007; **254**: 713–721.
30 Hirabayashi N, Hata J, Ohara T, Mukai N, Nagata M, Shibata M, Gotoh S, Furuta Y, Yamashita F, Yoshihara K, Kitazono T, Sudo N, Kiyohara Y, Ninomiya T. Association between diabetes and hippocampal atrophy in elderly Japanese: the Hisayama study. *Diabetes Care* 2016 Jul 6 **39**: 1543–1549.
31 Liu Z, Zhao Y, Zhang H, Chai Q, Cui Y, Diao Y, Xiu J, Sun X, Jiang G. Excessive variability in systolic blood pressure that is self-measured at home exacerbates the progression of brain white matter lesions and cognitive impairment in the oldest old. *Hypertens Res* 2016; **39**: 245–253.

Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)