Table 2
Linear regression analysis of the association between brain atrophy and low-intensity physical activity.

Variables	Model 1		Model 2		Model 3	
	β	*P*	β	*P*	β	*P*
LPA	−0.209	<0.001	−0.120	0.062	−0.102	0.136
Age	–	–	0.206	0.001	0.116	0.048
Sex	–	–	0.110	0.089	0.115	0.065
BMI	–	–	−0.030	0.584	−0.034	0.528
MCI subtype	–	–	−0.008	0.887	0.015	0.766
Hypertension	–	–	0.065	0.233	0.055	0.295
Diabetes mellitus	–	–	0.049	0.356	0.037	0.473
Lipidemia	–	–	−0.021	0.692	−0.017	0.736
TUG	–	–	0.164	0.006	0.166	0.003
WML	–	–	–	–	0.287	<0.001
ΔR^2	–		0.111		0.073	
R^2	–	–			0.228	

LPA: low-intensity physical activity; BMI: body mass index; MCI: mild cognitive impairment; TUG: timed up and go test; WML: white matter lesions.

each model was calculated. All analyses were performed using commercially available software (IBM SPSS statistics software, Version 20; IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

3. Results

Overall, 323 subjects fulfilled with the eligibility criteria and were divided into those with severe WML ($n = 60$) or non-severe WML ($n = 263$). The characteristics of each group are summarized in Table 1. Age, TUG, and brain atrophy were significantly different between the two groups ($P < 0.05$). The proportions of time in LPA and MVPA were also significantly different between the two WML groups ($P < 0.05$).

Correlations between PA and brain atrophy in each WML group are shown in Fig. 1 for LPA and Fig. 2 for MPA. The simple correlation analysis revealed that more LPA ($r = -0.20$, $P < 0.001$) and MVPA ($r = -0.20$, $P < 0.001$) correlated with a lower rate of atrophy. Partial correlation analysis that controlled age, sex, and TUG showed that LPA was not significantly associated with brain atrophy ($pr = -0.10$, $P = 0.069$), but that MVPA was ($pr = -0.15$, $P = 0.006$). The results of the regression analysis of LPA against brain atrophy are shown in Table 2. In Model 1, brain atrophy was negatively associated with LPA ($\beta = -0.209$, $P < 0.001$). However, adjusting for demographic data in Model 2 and WML in Model 3 revealed that LPA itself was not independently correlated with atrophy (Model 2: $\beta = -0.120$, $P = 0.062$; Model 3: $\beta = -0.092$, $P = 0.136$). In contrast, MVPA was significantly associated with brain atrophy in Model 1 ($\beta = -0.202$, $P < 0.001$, Table 3), and remained so in Model 2 ($\beta = -0.148$, $P = 0.007$) and Model 3 ($\beta = -0.126$, $P = 0.015$).

Table 3
Linear regression analysis of the association between brain atrophy and moderate-to-vigorous intensity physical activity.

Variables	Model 1		Model 2		Model 3	
	β	*P*	β	*P*	β	*P*
MVPA	−0.202	<0.001	−0.148	0.007	−0.126	0.015
Age	–	–	0.206	<0.001	0.117	0.045
Sex	–	–	0.182	0.001	0.170	0.002
BMI	–	–	−0.020	0.713	−0.027	0.608
MCI subtype	–	–	−0.009	0.871	0.014	0.784
Hypertension	–	–	0.064	0.233	0.054	0.295
Diabetes mellitus	–	–	0.054	0.304	0.041	0.420
Lipidemia	–	–	−0.020	0.704	−0.017	0.744
TUG			0.135	0.025	0.142	0.014
WML	–	–	–	–	0.284	<0.001
ΔR^2	–		0.103		0.072	
R^2	–		–		0.213	

MVPA: moderate-to-vigorous intensity physical activity; BMI: body mass index; MCI: mild cognitive impairment; TUG: timed up and go test; WML: white matter lesions.

4. Discussion

The proportions of time spent in LPA and MVPA were lower in subjects with severe WML than in those without severe WML. Subjects with severe WML were older, had less mobility and more extensive brain atrophy. Our study revealed that in this cohort of subjects with MCI, objectively measured PA was associated with brain atrophy, independent of WML. Specifically, multivariate regression models showed that greater MVPA was associated with less extensive brain atrophy, even after adjusting for WML. In contrast, the amount of LPA could not explain the amount of brain atrophy better than the other covariates.

The results of studies using objectively measured PA, including our study, provide evidence for sustained protective effects of PA in preserving brain health. Some studies have shown that PA is associated with macrostructural brain measures (Benedict et al., 2013; Burzynska et al., 2014; Erickson et al., 2010; Flöel et al., 2010; Gow et al., 2012). Most of those studies assessed PA using questionnaires. For example, it was found that the self-reported duration and frequency of PA were associated with gray matter and white matter volume (Benedict et al., 2013) and greater walking distance at baseline was related to greater gray matter volume 9 years later in older adults (Erickson et al., 2010). In contrast, there is less evidence of a relationship between objectively measured PA and brain health. Burzynska et al. (2014) focused on the association between white matter and PA among low-fit older adults. Their findings showed that more MVPA was associated with a smaller volume of white matter hyperintensities and that sedentary time was associated with lower white mater integrity. In contrast, the LPA was less associated with these brain measures than with other covariates. Additionally, they reported that the correlation between PA and brain health depended on the intensity of the PA. However, these studies did not investigate the effects of PA among older adults with MCI. Thus, our results provide further insight into the benefits of PA on maintaining brain health, even among subjects with MCI.

Based on the hypothesis that PA has a positive impact on brain health, several intervention studies have examined the effects of introducing exercise or enhancing PA on improving cognition in subjects with MCI (Gates et al., 2013). However, a consensus has not been reached, partly because the intensity of the interventions varied among studies. An intervention aimed at promoting PA helped to maintain cognitive function, although the effect was dependent on the severity of cognitive impairment (Lautenschlager et al., 2008). By contrast, a walking program aimed at enhancing PA had limited effects on cognition in subjects with MCI (van Uffelen et al., 2008). In other studies, aerobic exercise at moderate to high intensities had a positive impact on hippocampus volume in older adults (Erickson et al., 2011) and cognitive function in subjects with MCI (Baker et al., 2012). Thus, our results suggest that the benefits of PA, especially MVPA, on brain health extend to older adults with MCI.

The strength of our study is that we performed multivariate analysis, which included WML. WML are thought to represent the loss of myelin, axons, oligodendrocytes, and other glial cells in the subcortical white matter because of ischemic damage caused by underlying small-vessel disease (Brun and Englund, 1986) or other explanations, such as Wallerian degeneration (Leys et al., 1991). The presence of WML is thought to be a strong mediating factor for brain atrophy. The coexistence of WML and brain atrophy is a common age-related change in the brain, even in people without overt diseases, because disturbances in white matter integrity contributes to the pathogenesis of brain atrophy (Appelman et al., 2009). Additionally, WML may be associated with PA, although the results published to date are conflicting (Gow et al., 2012; Podewils et al., 2007; Wirth et al., 2014). Thus, when investigating the factors associated with brain atrophy, it is important to consider the

severity of WML. Additionally, neuroimaging studies have revealed that brain atrophy and white matter lesions are typical age-related structural changes in the brain (Seidler et al., 2010), while physical performance, particularly mobility, is correlated with gray matter volume and WML (de Laat et al., 2012; Rosano et al., 2010). Based on this evidence that brain structure is associated with age and mobility, we included age, TUG, and other demographic data as covariates in this study. Higher age, being male, and low mobility were associated with more brain atrophy. Results of the partial correlation and multivariate analysis indicated that age and TUG could explain atrophy better than LPA, but also supported the association between MVPA and brain measures even after adjusting for other factors.

Some limitations must be mentioned. Because of the cross-sectional design, we could not assess the causal relationship between PA and brain structure in these subjects with MCI. Further prospective studies are required to address this issue. In addition, other brain measures including Aβ burden and white matter integrity might mediate the association between PA and MCI. Additionally, we used a voxel-based analysis to assess gray matter atrophy of the entire brain. The possibility that PA has differential effects depending on brain region should be investigated in future studies.

5. Conclusion

Our study showed that PA, particularly MVPA, was negatively associated with the extent of brain atrophy in older adults with MCI. This association was independent of the severity of WML. These results support the possibility that enhancing PA could contribute to brain health. Further studies, including interventions, are needed to confirm the benefits of PA on cognition and brain health.

Conflict of interest

The authors declare that they have no competing interests.

Acknowledgments

We wish to thank the Obu office for help with subject recruitment. This work was supported by Grants; Comprehensive Research on Aging and Health from Health and Labor Sciences Research Grants; a Grant-in-Aid for Scientific Research (B) (grant number 23300205); a Grant-in-Aid for JSPS Fellows 259435; and Research Funding for Longevity Sciences (22-16) from the National Center for Geriatrics and Gerontology, Japan.

References

Appelman, A.P., Exalto, L.G., van der Graaf, Y., Biessels, G.J., Mali, W.P., Geerlings, M.I., 2009. White matter lesions and brain atrophy: more than shared risk factors? A systematic review. Cerebrovasc. Dis. 28 (3), 227–242. http://dx.doi.org/10.1159/000226774.

Baker, L.D., Barsness, S.M., Borson, S., Merriam, G.R., Friedman, S.D., Craft, S., Vitiello, M.V., 2012. Effects of growth hormone-releasing hormone on cognitive function in adults with mild cognitive impairment and healthy older adults: results of a controlled trial. Arch. Neurol. 69 (11), 1420–1429. http://dx.doi.org/10.1001/archneurol.2012.1970.

Barnes, D.E., Yaffe, K., 2011. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 10 (9), 819–828. http://dx.doi.org/10.1016/s1474-4422(11)70072-2.

Benedict, C., Brooks, S.J., Kullberg, J., Nordenskjold, R., Burgos, J., Le Greves, M., Kilander, L., Larsson, E.M., Johansson, L., Ahlstrom, H., Lind, L., Schioth, H.B., 2013. Association between physical activity and brain health in older adults. Neurobiol. Aging 34 (1), 83–90. http://dx.doi.org/10.1016/j.neurobiolaging.2012.04.013.

Brodaty, H., Heffernan, M., Kochan, N.A., Draper, B., Trollor, J.N., Reppermund, S., Slavin, M.J., Sachdev, P.S., 2013. Mild cognitive impairment in a community sample: the Sydney Memory and Ageing Study. Alzheimers Dement. 9 (3), 310–317. http://dx.doi.org/10.1016/j.jalz.2011.11.010 (e1).

Brown, B.M., Peiffer, J.J., Sohrabi, H.R., Mondal, A., Gupta, V.B., Rainey-Smith, S.R., Taddei, K., Burnham, S., Ellis, K.A., Szoeke, C., Masters, C.L., Ames, D., Rowe, C.C., Martins, R.N., 2012. Intense physical activity is associated with cognitive performance in the elderly. Transl. Psychiatry 2, e191. http://dx.doi.org/10.1038/tp.2012.118.

Brun, A., Englund, E., 1986. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. Ann. Neurol. 19 (3), 253–262. http://dx.doi.org/10.1002/ana.410190306.

Buchman, A.S., Wilson, R.S., Bennett, D.A., 2008. Total daily activity is associated with cognition in older persons. Am. J. Geriatr. Psychiatry 16 (8), 697–701. http://dx.doi.org/10.1097/JGP.0b013e31817945f6.

Burzynska, A.Z., Chaddock-Heyman, L., Voss, M.W., Wong, C.N., Gothe, N.P., Olson, E.A., Knecht, A., Lewis, A., Monti, J.M., Cooke, G.E., Wojcicki, T.R., Fanning, J., Chung, H.D., Awick, E., McAuley, E., Kramer, A.F., 2014. Physical activity and cardiorespiratory fitness are beneficial for white matter in low-fit older adults. PLoS One 9 (9), e107413. http://dx.doi.org/10.1371/journal.pone.0107413.

de Laat, K.F., Reid, A.T., Grim, D.C., Evans, A.C., Kotter, R., van Norden, A.G., de Leeuw, F.E., 2012. Cortical thickness is associated with gait disturbances in cerebral small vessel disease. Neuroimage 59 (2), 1478–1484. http://dx.doi.org/10.1016/j.neuroimage.2011.08.005.

Erickson, K.I., Raji, C.A., Lopez, O.L., Becker, J.T., Rosano, C., Newman, A.B., Gach, H.M., Thompson, P.M., Ho, A.J., Kuller, L.H., 2010. Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. Neurology 75 (16), 1415–1422. http://dx.doi.org/10.1212/WNL.0b013e3181f88359.

Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., Wojcicki, T.R., Mailey, E., Vieira, V.J., Martin, S.A., Pence, B.D., Woods, J.A., McAuley, E., Kramer, A.F., 2011. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. U. S. A. 108 (7), 3017–3022. http://dx.doi.org/10.1073/pnas.1015950108.

Fazekas, F., Kleinert, R., Offenbacher, H., Schmidt, R., Kleinert, G., Payer, F., Radner, H., Lechner, H., 1993. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 43 (9), 1683–1689.

Flöel, A., Ruscheweyh, R., Kruger, K., Willemer, C., Winter, B., Volker, K., Lohmann, H., Zitzmann, M., Mooren, F., Breitenstein, C., Knecht, S., 2010. Physical activity and memory functions: are neurotrophins and cerebral gray matter volume the missing link? Neuroimage 49 (3), 2756–2763. http://dx.doi.org/10.1016/j.neuroimage.2009.10.043.

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. J. Psychiatr. Res. 12 (3), 189–198 (0022-3956(75)90026-6 [pii]).

Gates, N., Fiatarone Singh, M.A., Sachdev, P.S., Valenzuela, M., 2013. The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. Am. J. Geriatr. Psychiatry 21 (11), 1086–1097. http://dx.doi.org/10.1016/j.jagp.2013.02.018.

Gow, A.J., Bastin, M.E., Munoz Maniega, S., Valdes Hernandez, M.C., Morris, Z., Murray, C., Royle, N.A., Starr, J.M., Deary, I.J., Wardlaw, J.M., 2012. Neuroprotective lifestyles and the aging brain: activity, atrophy, and white matter integrity. Neurology 79 (17), 1802–1808. http://dx.doi.org/10.1212/WNL.0b013e3182703fd2.

Hagstromer, M., Ainsworth, B.E., Oja, P., Sjostrom, M., 2010. Comparison of a subjective and an objective measure of physical activity in a population sample. J. Phys. Act. Health 7 (4), 541–550.

Hirata, Y., Matsuda, H., Nemoto, K., Ohnishi, T., Hirao, K., Yamashita, F., Asada, T., Iwabuchi, S., Samejima, H., 2005. Voxel-based morphometry to discriminate early Alzheimer's disease from controls. Neurosci. Lett. 382 (3), 269–274. http://dx.doi.org/10.1016/j.neulet.2005.03.038.

Kerr, J., Marshall, S.J., Patterson, R.E., Marinac, C.R., Natarajan, L., Rosenberg, D., Wasilenko, K., Crist, K., 2013. Objectively measured physical activity is related to cognitive function in older adults. J. Am. Geriatr. Soc. 61 (11), 1927–1931. http://dx.doi.org/10.1111/jgs.12524.

Kim, J., Tanabe, K., Yokoyama, N., Zempo, H., Kuno, S., 2013. Objectively measured light-intensity lifestyle activity and sedentary time are independently associated with metabolic syndrome: a cross-sectional study of Japanese adults. Int. J. Behav. Nutr. Phys. Act. 10, 30. http://dx.doi.org/10.1186/1479-5868-10-30.

Kooistra, M., Boss, H.M., van der Graaf, Y., Kappelle, L.J., Biessels, G.J., Geerlings, M.I., 2014. Physical activity, structural brain changes and cognitive decline. The SMART-MR study. Atherosclerosis 234 (1), 47–53. http://dx.doi.org/10.1016/j.atherosclerosis.2014.02.003.

Lautenschlager, N.T., Cox, K.L., Flicker, L., Foster, J.K., van Bockxmeer, F.M., Xiao, J.G., Greenop, K.R., Almeida, O.P., 2008. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease – a randomized trial. JAMA J. Am. Med. Assoc. 300 (9), 1027–1037. http://dx.doi.org/10.1001/jama.300.9.1027.

Lautenschlager, N.T., Cox, K., Kurz, A.F., 2010. Physical activity and mild cognitive impairment and Alzheimer's disease. Curr. Neurol. Neurosci. Rep. 10 (5), 352–358. http://dx.doi.org/10.1007/s11910-010-0121-7.

Leys, D., Pruvo, J.P., Parent, M., Vermersch, P., Soetaert, G., Steinling, M., Delacourte, A., Defossez, A., Rapoport, A., Clarisse, J., et al., 1991. Could Wallerian degeneration contribute to "leuko-araiosis" in subjects free of any vascular disorder? J. Neurol. Neurosurg. Psychiatry 54 (1), 46–50.

Makizako, H., Shimada, H., Park, H., Doi, T., Yoshida, D., Uemura, K., Tsutsumimoto, K., Suzuki, T., 2013. Evaluation of multidimensional neurocognitive function using a tablet personal computer: test-retest reliability and validity in community-dwelling older adults. Geriatr. Gerontol. Int. 13 (4), 860–866. http://dx.doi.org/10.1111/ggi.12014.

Makizako, H., Liu-Ambrose, T., Shimada, H., Doi, T., Park, H., Tsutsumimoto, K., Uemura, K., Suzuki, T., 2014. Moderate-intensity physical activity, hippocampal volume, and memory in older adults with mild cognitive impairment. J. Gerontol. A Biol. Sci. Med. Sci. http://dx.doi.org/10.1093/gerona/glu136.

Matsuda, H., Mizumura, S., Nemoto, K., Yamashita, F., Imabayashi, E., Sato, N., Asada, T., 2012. Automatic voxel-based morphometry of structural MRI by SPM8 plus diffeomorphic anatomic registration through exponentiated lie algebra improves

the diagnosis of probable Alzheimer disease. AJNR Am. J. Neuroradiol. 33 (6), 1109–1114. http://dx.doi.org/10.3174/ajnr.A2935.

Oshima, Y., Kawaguchi, K., Tanaka, S., Ohkawara, K., Hikihara, Y., Ishikawa-Takata, K., Tabata, I., 2010. Classifying household and locomotive activities using a triaxial accelerometer. Gait Posture 31 (3), 370–374. http://dx.doi.org/10.1016/j.gaitpost.2010.01.005.

Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J. Intern. Med. 256 (3), 183–194. http://dx.doi.org/10.1111/j.1365-2796.2004.01388.x (JIM1388 [pii]).

Podewils, L.J., Guallar, E., Beauchamp, N., Lyketsos, C.G., Kuller, L.H., Scheltens, P., 2007. Physical activity and white matter lesion progression: assessment using MRI. Neurology 68 (15), 1223–1226. http://dx.doi.org/10.1212/01.wnl.0000259063.50219.3e.

Podsiadlo, D., Richardson, S., 1991. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J. Am. Geriatr. Soc. 39 (2), 142–148.

Rosano, C., Sigurdsson, S., Siggeirsdottir, K., Phillips, C.L., Garcia, M., Jonsson, P.V., Eiriksdottir, G., Newman, A.B., Harris, T.B., van Buchem, M.A., Gudnason, V., Launer, L.J., 2010. Magnetization transfer imaging, white matter hyperintensities, brain atrophy and slower gait in older men and women. Neurobiol. Aging 31 (7), 1197–1204. http://dx.doi.org/10.1016/j.neurobiolaging.2008.08.004.

Seidler, R.D., Bernard, J.A., Burutolu, T.B., Fling, B.W., Gordon, M.T., Gwin, J.T., Kwak, Y., Lipps, D.B., 2010. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. Neurosci. Biobehav. Rev. 34 (5), 721–733. http://dx.doi.org/10.1016/j.neubiorev.2009.10.005.

Shimada, H., Makizako, H., Doi, T., Yoshida, D., Tsutsumimoto, K., Anan, Y., Uemura, K., Ito, T., Lee, S., Park, H., Suzuki, T., 2013. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people. J. Am. Med. Dir. Assoc. 14 (7), 518–524. http://dx.doi.org/10.1016/j.jamda.2013.03.010.

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G.F., Casini, A., Macchi, C., 2011. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. J. Intern. Med. 269 (1), 107–117. http://dx.doi.org/10.1111/j.1365-2796.2010.02281.x.

Tsutsui, T., Muramatsu, N., 2007. Japan's universal long-term care system reform of 2005: containing costs and realizing a vision. J. Am. Geriatr. Soc. 55 (9), 1458–1463. http://dx.doi.org/10.1111/j.1532-5415.2007.01281.x.

van Uffelen, J.G.Z., Chinapaw, M.J.M., van Mechelen, W., Hopman-Rock, M., 2008. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. Br. J. Sports Med. 42 (5), 344. http://dx.doi.org/10.1136/bjsm.2007.044735.

Wirth, M., Haase, C.M., Villeneuve, S., Vogel, J., Jagust, W.J., 2014. Neuroprotective pathways: lifestyle activity, brain pathology, and cognition in cognitively normal older adults. Neurobiol. Aging http://dx.doi.org/10.1016/j.neurobiolaging.2014.02.015.

Yesavage, J.A., 1988. Geriatric Depression Scale. Psychopharmacol. Bull. 24 (4), 709–711.

Neurobiology of Aging 36 (2015) 942–947

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Association of insulin-like growth factor-1 with mild cognitive impairment and slow gait speed

Takehiko Doi [a,b,c,*], Hiroyuki Shimada [a], Hyuma Makizako [a,b,c], Kota Tsutsumimoto [a], Ryo Hotta [a], Sho Nakakubo [a], Takao Suzuki [c]

[a] Department of Functioning Activation, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan
[b] Japan Society for the Promotion of Science, Tokyo, Japan
[c] Research Institute, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan

ARTICLE INFO

Article history:
Received 17 July 2014
Received in revised form 15 October 2014
Accepted 27 October 2014
Available online 1 November 2014

Keywords:
IGF-1
MCI
Cognitive function
Gait speed

ABSTRACT

The decrease in serum insulin-like growth factor-1 (IGF-I) with aging is related to the neurobiological processes in Alzheimer's disease. IGF-1 mediates effects of physical exercise on the brain, and cognition has a common pathophysiology with physical function, particularly with gait. The aim of this study was to examine whether mild cognitive impairment (MCI) and slow gait are associated with the serum IGF-1 level. A population survey was conducted in 3355 participants (mean age, 71.4 years). Cognitive functions (attention, executive function, processing speed, visuospatial skill, and memory), gait speed, and demographic variables were measured. All cognitive functions and gait speed were associated with the IGF-1 level ($p < 0.001$). The association of IGF-1 with slow gait was weakened by adjustment for covariates, but MCI and the combination of MCI and slow gait were independently related to the IGF-1 level in multivariate analysis ($p < 0.05$). Our findings support the association of a low IGF-1 level with reduced cognitive function and gait speed, particularly with a combination of MCI and slow gait.

1. Introduction

Insulin-like growth factor-1 (IGF-1) is an important mediator of growth hormone effects in body growth and tissue remodeling (Nishijima et al., 2010) and contributes to the promotion of neuronal plasticity and skeletal muscle (Clegg et al., 2013; Florini et al., 1991; van Dam et al., 2000). IGF-1 also has protective effects on the neurobiological processes that are compromised by aging and Alzheimer's disease (AD), including those with potent neurotrophic and neuroprotective actions (Baker et al., 2012; de la Monte and Wands, 2005; Deak and Sonntag, 2012; Sonntag et al., 2005). A decrease in IGF-1 may be related to the pathology of AD because IGF-1 increases clearance of amyloid beta (Aβ) in the brain and upregulates Aβ carriers and transport of Aβ-carrier protein complexes (Carro et al., 2002, 2006). In humans, low levels of serum IGF-1 are a risk for AD and dementia (Watanabe et al., 2005; Westwood et al., 2014).

Mild cognitive impairment (MCI) is a prodromal status in the course of AD. Subjects with MCI have characteristics between healthy subjects and AD, including pathology, biomarkers, brain function, and cognitive function (Petersen, 2004, 2011). The common features of MCI, particularly in cases showing progression to AD, are higher levels of Aβ42 and tau, brain atrophy, and reduced cognitive function (Petersen, 2011). Subcutaneous injections of growth hormone–releasing hormone enhances the IGF-1 level and improves cognitive function in MCI subjects (Baker et al., 2012), but it is unclear whether lower levels of serum IGF-1 are a characteristic of MCI.

Cognitive impairment has a strong link with physical frailty, especially with slow gait linked with worsening of cognitive function. Slow gait has been associated with the cognitive decline (Mielke et al., 2013) and with accumulation of brain pathology related to AD at autopsy (Buchman et al., 2013), whereas longitudinal studies indicate that slow gait precedes MCI and dementia (Buracchio et al., 2010; Solfrizzi et al., 2013). Importantly, a combined status of slow gait and cognitive impairment increases the risk for dementia compared with each status alone (Waite et al., 2005). The mechanism of the association between physical and cognitive impairment was not examined, but IGF-1 may mediate this association.

The mechanism underlying the benefit of exercise on cognition is also thought to involve IGF-1 (Liu-Ambrose et al., 2012). Exercise-dependent stimulation of angiogenesis and neurogenesis seems to

* Corresponding author at: Department of Functioning Activation, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka, Obu, Aichi 474-8511, Japan. Tel.: +81 562 44 5651; fax: +81 562 46 8294.
E-mail address: take-d@ncgg.go.jp (T. Doi).

0197-4580/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.10.035

be regulated by IGF-1 (Cotman et al., 2007), whereas a peripheral increase in IGF-1 appears to be required for exercise-induced neurogenesis in the brain (Trejo et al., 2001). IGF-I is also an important modulator of muscle mass and function (Barbieri et al., 2003). Low IGF-I levels may also be associated with physical frailty represented by muscle weakness and slow gait speed (Cappola et al., 2001; Onder et al., 2006). Therefore, an improved understanding of the association of IGF-1 with physical and cognitive functioning may contribute to the clarification of mechanisms associated with aging.

The aim of this study was to examine the association between serum IGF-1 and MCI and to determine whether slow gait affects this association. We hypothesized that lower levels of serum IGF-1 are associated with reduced cognitive function and gait speed and that a combined status of MCI + slow gait speed would be sensitively associated with a lower IGF-1 level. Assessments of cognitive function require the use of a variety of cognitive domains (Albert et al., 2011) because there is some debate over which cognitive functions are related to IGF-1 levels (Dik et al., 2003; Sanders et al., 2014). In contrast, confirmed covariates in older adults, such as age and body mass index (BMI), are known to weaken the association between mobility and IGF-1 (Cappola et al., 2001; Kaplan et al., 2008; Sanders et al., 2014). Thus, we conducted a population survey in a large cohort with adjustment for covariates in multivariate analysis.

2. Material and methods

2.1. Participants

Subjects eligible for this study were participants in the population-based cohort of the Obu Study of Health Promotion for the Elderly (OSHPE), which was conducted from August 2011 to February 2012. Inclusion criteria for the OSHPE required each participant to be 65 years or older at the time of examination and to reside in Obu city; a total of 15,974 individuals were eligible for participation. Before recruitment, 1661 people were excluded because they had participated in other similar studies, were hospitalized or in residential care, or were certified at levels 3–5 to require support or care by the Japanese public long-term care insurance system. Recruitment was conducted via a letter sent to 14,313 individuals, and 5104 of these individuals participated in the OSHPE. In the present study, we included participants who were independent for basic activities of daily living, as confirmed by interview, and not certified by long-term care insurance, and were cognitively normal (no objective cognitive impairment and Mini-Mental State Examination [MMSE] score >23, Folstein et al., 1975) or met the criteria for MCI. MCI criteria followed those established and revised by Petersen (2004); in particular, subjects satisfied the following conditions: subjective memory complaints, objective cognitive impairment, no dementia, and independent in activity of daily living. No dementia was defined as not meeting clinical criteria for dementia, and intact global cognitive function was defined as an MMSE score >23 (Folstein et al., 1975). Cognitive function was also assessed in multiple domains using the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al., 2013), and objective cognitive impairment was defined as having a cognitive function of >1.5 standard deviation lower than the normal data (Shimada et al., 2013a). Subjects were classified into subtypes of amnestic MCI (aMCI) and nonamnestic MCI (naMCI). Those with objective cognitive impairment in memory were defined as aMCI and others were defined as naMCI, based on the published criteria (Petersen, 2004). Participants were excluded based on a history of cerebrovascular disease, Parkinson disease, depression or dementia, or an MMSE score of ≤23 (Folstein et al., 1975). Finally, 3355 participants were judged to be eligible for the study and completed all assessments, including blood tests. The Ethics Committee of the National Center for Geriatrics and Gerontology approved this study.

2.2. Gait speed

Gait speed was measured as an indicator of motor function. Participants were asked to walk on a straight walkway of 6.6 m in length on a flat floor under their usual gait speed. Gait duration was measured using a stopwatch over a 2.4-m distance between marks at 2.1 and 4.5 m from the start of the walkway, and the mean gait speed (minute per second) was calculated. The measurement protocol of using a stopwatch has been validated elsewhere (Peters et al., 2013). The cutoff value (1.0 m/s) for a slow gait speed was based on the threshold value for discrimination of functional decline found in a previous study (Shimada et al., 2013b).

2.3. Cognitive function

Cognitive function was assessed using the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al., 2013). The test consists of tasks to assess memory, processing speed, attention and executive function, and visuospatial cognition (Figure Selection Task). Memory was assessed using word and story tests. Both tests have 2 sessions (an immediate session and a delayed session). Processing speed was assessed using a tablet version of the Symbol-Digit Substitution Task (Makizako et al., 2013), based on the Symbol-Digit Modality Test (Shum et al., 1990). The score is the number of correct answers chosen within 90 seconds. Attention and executive functions were evaluated using a tablet version of the Trail-Making Test Part A (TMT-A) and Part B (TMT-B, 15 stimuli) (Makizako et al., 2013). The amount of time taken to complete each task was recorded. In the Figure Selection Task, participants were required to select the same figure from 3 choices shown at the bottom of the display (Makizako et al., 2013). This task consists of 9 questions and 1 point is given for each correctly selected figure, with the score being the number of correct answers (0–9). Better performance is represented by lower values on the TMT-A and TMT-B and higher values on the other tests.

2.4. IGF-1

To obtain serum, whole blood samples were allowed to coagulate at room temperature for 30 minutes and then centrifuged at room temperature for 15 minutes at 1000 × *g*. The collected serum was stored in polypropylene tubes at −80 °C until assayed. IGF-1 was quantitatively determined using an IGF-1 Immunoradiometric assay "Daiichi" (TFB Inc, Tokyo, Japan). Measurements were performed in duplicate and averaged to give a value in nanograms per milliliter. The assay was performed by SRL Inc (Tokyo, Japan).

2.5. Demographic and lifestyle data

Demographic data were collected for age, sex, BMI (weight/height^2), educational history, and medication use in a face-to-face interview. Information on lifestyle was also obtained, and sleep quality was assessed using the question "How would you rate your sleepiness in daytime?" on a 4-point scale ranging from "never," "very little," and "sometimes" to "almost always". Subjects who answered never or very little were judged to have good quality of sleep. Depressive symptoms were evaluated using the 15-item Geriatric Depression Scale (Yesavage, 1988). The total amount of time spent walking in a day was used to assess physical activity using a subscale of the International Physical Activity Questionnaire (Murase et al., 2003).

Table 1
Characteristics of subjects in quartiles based on the level of IGF-1

Variables	All	Level of IGF-1 (ng/mL)				p Value for trend
		C1 ≤ 84	C2 85–100	C3 101–120	C4 ≥ 121	
Age, y	71.4 ± 5.2	73.5 ± 5.9	71.3 ± 5.0	70.7 ± 4.4	70.1 ± 4.6	<0.001
Sex, % (F)	53.5	64.4	57.1	48.8	43.2	<0.001
BMI, kg/m^2	23.3 ± 3.1	22.7 ± 3.3	23.3 ± 3.1	23.4 ± 2.9	24.0 ± 2.9	<0.001
Medication use, *n*	1.9 ± 2.0	2.0 ± 2.1	1.9 ± 1.9	1.7 ± 1.9	1.9 ± 2.0	0.406
Education, y	11.6 ± 2.5	11.1 ± 2.5	11.7 ± 2.5	11.8 ± 2.4	12.0 ± 2.5	<0.001
Sleep quality, % (good)	53.3	48.4	55.5	53.8	55.9	0.006
GDS, score	2.7 ± 2.5	3.0 ± 2.7	2.6 ± 2.4	2.6 ± 2.5	2.6 ± 2.4	0.044
Physical activity, min/d	285.7 ± 159.9	288.3 ± 158.2	282.7 ± 161.9	288.1 ± 157.8	283.2 ± 161.9	0.554

Data are shown as mean ± standard deviation or percentage. Variables were compared among IGF-1 levels (C1–C4). *p* Values are from a Cochran-Armitage or Jonckheere-Terpstra trend test.
Key: BMI, body mass index; F, female; GDS, Geriatric Depression Scale; IGF-1, insulin-like growth factor-1.

2.6. Statistical analyses

To examine the association of IGF-1 with subject characteristics, gait speed, and cognitive function, the subjects were divided into quartiles based on the levels of IGF-1 (C1–C4). Comparisons among these groups were conducted by Cochran-Armitage trend test for the categorical data (Mikami et al., 2008) and Jonckheere-Terpstra trend test for the continuous variables (Bansal et al., 2007). To examine the association of the level of IGF-1 with gait and cognition statuses, subjects were first categorized into 4 groups based on their functional status: no cognitive impairment including MCI and no slow gait (control group), slow gait without cognitive impairment (SG group), MCI without slow gait (MCI group), and MCI and slow gait (MCI + SG group). Associations were tested using multinomial logistic regression analysis in a crude model (Model 1) and an adjusted model (Model 2), and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The Cochran-Armitage trend test was performed using JMP9.0J (SAS Institute, Tokyo, Japan), and other tests were performed using SPSS, version 20 (IBM Corp, Chicago, IL, USA). Statistical significance was set at $p < 0.05$ in all the analyses.

3. Results

Subjects were classified into quartiles based on the IGF-1 levels (C1, ≤84 ng/mL [$n = 892$]; C2, 85–100 ng/mL [$n = 800$]; C3, 101–120 ng/mL [$n = 834$]; and C4, ≥121 ng/mL [$n = 829$]). A comparison of characteristics between these groups is shown in Table 1. There were trends for an older age, higher proportion of women, lower BMI, and lower educational history with a decreased level of IGF-1 ($p < 0.001$). Sleep quality increased ($p = 0.006$) and the Geriatric Depression Scale score decreased ($p = 0.044$) with increasing IGF-1, whereas physical activity was not significantly related to the IGF-1 level ($p = 0.554$). Medication use was not associated with the IGF-1 level. The proportion of subtypes in MCI cases (aMCI vs. naMCI) also had no significant association with the IGF-1 level ($p = 0.845$).

Comparisons of gait speed and cognitive functions in the 4 groups based on the IGF-1 levels are shown in Table 2. Subjects with higher IGF-1 had a trend of walking faster ($p < 0.001$). All cognitive functions were reduced with decreased IGF-1 ($p < 0.001$). The distributions of SG, MCI, and MCI + SG subjects in groups C1–C4 differed significantly with that of controls (all $p < 0.001$, Fig. 1): control (C1, 60.4%; C2, 68.0%; C3, 69.2%; and C4, 71.9%), SG (C1, 11.6%; C2, 7.0%; C3, 7.1%; and C4, 7.1%), MCI (C1, 20.6%; C2, 19.6%; C3, 19.8%; and C4, 18.1%), and MCI with SG (C1, 7.4%; C2, 5.4%; C3, 4.0%; and C4, 2.9%).

Multinomial logistic regression analysis was conducted with adjustment for subject characteristics as potential confounders. These results are summarized in Table 3. A crude model (model 1) showed that the IGF-1 level in quartiles C1–C3 relative to the C4 quartile was associated with SG (C1: OR = 1.94, 95% CI = 1.38–2.72, $p < 0.001$), MCI (C1: OR = 1.35, 95% CI = 1.06–1.73, $p = 0.015$), and MCI + SG (C1: OR = 3.05, 95% CI = 1.89–4.94, $p < 0.001$; C2: OR = 1.97, 95% CI = 1.18–3.28, $p = 0.010$) compared with controls. A refined multivariate model (model 2) with adjustment for age, sex, BMI, medication, educational years, sleep quality, physical activity, and depressive symptoms indicated that the IGF-1 level in quartiles C1–C3 relative to the C4 quartile remained associated with MCI (C1: OR = 1.34, 95% CI = 1.04–1.75, $p = 0.027$) and MCI + SG (C1: OR = 1.81, 95% CI = 1.07–3.05, $p = 0.027$; C2: OR = 1.79, 95% CI = 1.05–3.07, $p = 0.034$) compared with controls.

4. Discussion

This population-based survey showed that serum IGF-1 levels are related to gait speed and cognitive function in multiple domains. Compared with controls, higher percentages of subjects

Table 2
Gait speed and cognitive function among quartiles based on level of IGF-1

Variables	Level of IGF-1 (ng/mL)				p Value for trend
	C1 ≤ 84	C2 85–100	C3 101–120	C4 ≥ 121	
Gait speed, m/s	1.18 ± 0.22	1.23 ± 0.21	1.24 ± 0.21	1.25 ± 0.20	<0.001
Cognitive function					
TMT-A, s	21.40 ± 6.46	20.13 ± 5.68	19.81 ± 4.84	19.41 ± 5.23	<0.001
TMT-B, s	42.92 ± 15.99	39.81 ± 16.17	38.64 ± 14.08	37.55 ± 13.23	<0.001
SDST, score	37.24 ± 7.92	40.08 ± 7.79	40.49 ± 7.54	41.21 ± 6.99	<0.001
Figure selection, score	5.22 ± 1.44	5.37 ± 1.41	5.46 ± 1.39	5.54 ± 1.42	<0.001
Word recall, score	3.82 ± 1.86	4.09 ± 1.88	4.27 ± 1.74	4.20 ± 1.79	<0.001
Story memory, score	6.66 ± 1.78	7.04 ± 1.78	7.20 ± 1.73	7.36 ± 1.63	<0.001

Variables were compared among IGF-1 levels (C1-C4). *p* values are from a Jonckheere-Terpstra trend test.
IGF-1, insulin-like growth factor-1; SDST, Symbol-Digit Substitution Task; TMT-A, Trail-Making Test Part A; TMT-B, Trail-Making Test Part B.

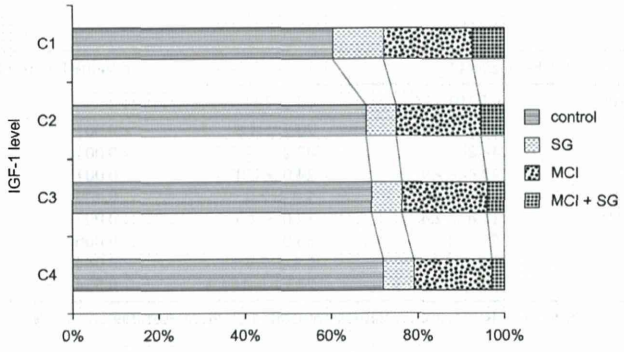

Fig. 1. Quartiles of insulin-like growth factor-1 (IGF-1) levels (C1, ≤84 ng/mL; C2, 85–100 ng/mL; C3, 101–120 ng/mL; and C4, ≥121 ng/mL) and percentages of control, slow gait without cognitive impairment (SG), MCI without slow gait (MCI), and MCI and slow gait (MCI + SG) subjects in each quartile.

with SG, MCI, and MCI + SG had lower levels of IGF-1. The association between serum IGF-1 levels and slow gait was not significant after adjusting for covariates, but those for MCI and MCI + SG remained after adjustment.

All domains of cognitive function, including attention, executive function, processing speed, visuospatial skill, and memory, were related to IGF-1 levels. Most studies of the relationship of cognitive function with IGF-1 have focused on global cognition using, for example, the MMSE. Lower levels of IGF-1 are predictive of global cognition (Kalmijn et al., 2000), and changes of IGF-1 over time are related to changes of global cognition (Sanders et al., 2014). Regarding specific cognitive domains, there are conflicting results on the association with IGF-1. Lower IGF-1 has been associated with orientation, memory, praxis, and frontal functions (Angelini et al., 2009), whereas Dik et al. (2003) found that a reduced level of IGF-1 is predictive for a decline in the processing speed alone. These results were discussed in the context of the sensitivity of neuropsychological measures against biological factors (Dik et al., 2003). Our results showed a trend in the association between cognitive function and IGF-1 that was not related to a specific cognitive domain. Additionally, subtypes of MCI (aMCI vs. naMCI) were not associated with the IGF-1 level. In a human study, a higher serum IGF-1 level was related to a larger total cerebral brain volume (Westwood et al., 2014). An autopsy study suggested a role of IGF-I in compensatory plasticity and survival of susceptible neurons in the frontal cortex and hippocampus of AD brains (Jafferali et al., 2000). IGF-I receptors are widely expressed not only in the brain, specifically in the hippocampus and parahippocampal areas, olfactory bulb, and cerebellar cortex, but also in the amygdala, prefrontal cortex, and hypothalamus and dorsal thalamic nuclei (Adem et al., 1989; Bondy and Cheng, 2004). Studies regarding multiple-domain neuropsychological assessments also tend to have been conducted in relatively small cohorts and have produced some conflicting results (Aleman and Torres-Aleman, 2009; Angelini et al., 2009; Arwert et al., 2005). Our findings from a population-based survey with a large sample size may help to clarify these previous results.

Our results showed that serum IGF-1 levels are associated with MCI after adjusting for covariates. This is the first evidence of an association between IGF-1 and MCI. In human studies, a lower IGF-1 level has been associated with AD (Duron et al., 2012), and longitudinal population studies have also shown that lower IGF-1 is a risk factor for dementia and AD (Watanabe et al., 2005; Westwood et al., 2014). IGF-1 also promotes neuronal survival in the hippocampus and entorhinal cortex, decreases regulation of tau phosphorylation (Hong and Lee, 1997), and reduces protection against the neurotoxic effects of Aβ (Dore et al., 1997). IGF-I also increases clearance of Aβ in the brain and upregulates brain levels of Aβ carriers and transport of Aβ carrier protein complexes (Carro et al., 2002, 2006). On the contrary, some studies have indicated that an increased serum IGF-1 level is associated with AD (Johansson et al., 2013; van Exel et al., 2014; Vardy et al., 2007). This discrepancy may be partly dependent on study design, samples, and disease course. Most of these studies were conducted in small samples, although a few population-based surveys have used large samples (Watanabe et al., 2005; Westwood et al., 2014). Additionally, the discrepancy may be attributable to disease course. Vardy et al. (2007) indicated that the linkage between serum IGF-1 level and AD may depend on disease course based on the idea that IGF-I decreases with the progressive stages of the disease. Studies of IGF-1 levels among MCI subjects have been based on clinical cohorts, rather than population cohorts, and have used relatively small samples (Duron et al., 2012; Johansson et al., 2013). MCI has heterogeneity in pathology and clinical signatures and thus is vulnerable to effects of sampling bias. To avoid the influence of heterogeneity in MCI, a standardized protocol to define MCI and population studies with a large cohort are required.

The association of MCI + SG with IGF-1 had a higher OR than that for MCI alone, and both of these associations remained after adjusting for covariates. However, the association between lower levels of serum IGF-1 and slower gait speed only was not significant after adjusting for covariates. These results partially support our hypothesis. There are limited evidences for an association between IGF-1 and gait speed. Lower IGF-I in older women is associated with poor knee extensor muscle strength and slow gait speed (Cappola et al., 2001), and higher IGF-I is associated with robust gait among older adults with obesity (Onder et al., 2006). On the contrary, a prospective study of the relationships of changes in several biomarkers with physical and cognitive function showed that changes in IGF-1 were associated with cognition, but not with gait speed (Sanders et al., 2014). However, in our study, the combination of MCI and slower gait was more sensitive to the IGF level than either condition alone. Robust gait represents the capacity for

Table 3
Multinomial logistic regression analysis of the relationship between status (SG, MCI, or MCI + SG) and IGF-1 levels compared with the control group

IGF-1 level	Model 1			Model 2		
	SG	MCI	MCI + SG	SG	MCI	MCI + SG
C1 (lowest)	1.94 (1.38–2.72)[b]	1.35 (1.06–1.73)[a]	3.05 (1.89–4.94)[b]	1.27 (0.87–1.85)	1.34 (1.04–1.75)[a]	1.81 (1.07–3.05)[a]
C2	1.04 (0.71–1.53)	1.15 (0.89–1.48)	1.97 (1.18–3.28)[a]	0.90 (0.60–1.35)	1.16 (0.89–1.50)	1.79 (1.05–3.07)[a]
C3	1.03 (0.71–1.51)	1.14 (0.89–1.46)	1.42 (0.83–2.43)	1.01 (0.68–1.51)	1.13 (0.87–1.46)	1.43 (0.81–2.51)
C4 (highest)	Reference	Reference	Reference	Reference	Reference	Reference

Data are shown as odds ratio (95% confidence interval). Model 1: crude model; model 2: adjusted for age, sex, body mass index, medication, years of education, sleep quality, physical activity, and depressive symptoms.
IGF-1, insulin-like growth factor-1; MCI, mild cognitive impairment without slow gait; MCI + SG, MCI and slow gait; SG, slow gait without cognitive impairment.
[a] $p < 0.05$.
[b] $p < 0.01$.

physical activity, and decreasing mobility induces a vicious cycle of reduced physical activity among older adults. Our results further support the idea of an effect of IGF-1 on mediating exercise and cognition. Both brain and muscle are regarded as major target organs for blood-borne IGF-I (Trejo et al., 2001), and IGF-1 is increased in the periphery by exercise and crosses the blood-brain barrier to enter the brain (Lopez-Lopez et al., 2004; Trejo et al., 2001). This peripheral increase in IGF-1 appears to be essential for exercise-induced neurogenesis in the brain. In fact, blocking entrance of circulating IGF-I into the brain prevents exercise-induced proliferation of neural precursors (Trejo et al., 2001), and serum IGF-I-deficient mice do not show cognitive enhancement after exercise unless they are treated with IGF-I (Trejo et al., 2008). Thus, serum IGF-1 may have mediation effects on the association between exercise and cognition. The mechanisms underlying this linkage are unclear, but our findings suggest a possible pathway. Further studies are required to examine this possible linkage between physical and cognitive functions.

The present study had not only several strong points but also some limitations. The cohort was large, and MCI was defined using a validated neuropsychological assessment tool, but the cross-sectional design does not allow examination of causal relationships. Next, IGF-1 is not commonly measured in a large cohort, but the role of IGF-1 in older adults is still uncertain, and improved examination of cognition among older adults requires brain neuroimaging to identify age-related changes based on brain atrophy or white-matter hyperintensities. Within these limitations, we found that the serum IGF-1 level was associated with cognitive functions in multiple domains, gait speed, and MCI. The associations of serum IGF-1 with MCI alone and MCI + SG were retained in multivariate models but that between serum IGF-1 and slow gait alone was not significant. A further study is required to examine the mechanisms underlying the linkages among serum IGF-1, gait, and cognition. In addition, other biomarkers, for example, brain-derived neurotrophic factor and vascular endothelial growth factor, may mediate the association between cognition and physical exercise (Voss et al., 2013). To compare these markers, an understanding of the mediation effects of biomarkers is required. Furthermore, it is unclear if the IGF-1 level is related to reversion from MCI to dementia, although combined gait and cognitive impairment is thought to be a high risk factor for dementia (Verghese et al., 2014; Waite et al., 2005). A longitudinal study is required to examine the relationship between IGF-1 level and future risk of dementia, in comparison with established disease markers such as Aβ and tau.

Disclosure statement

None of the authors have any financial, personal, or potential conflicts of interest.

Acknowledgements

This work was supported by Health and Labor Sciences Research Grants (Comprehensive Research on Aging and Health); a Grant-in-Aid for Scientific Research (B) (grant number 23300205); and Research Funding for Longevity Sciences (22-16) from the National Center for Geriatrics and Gerontology.

References

Adem, A., Jossan, S.S., d'Argy, R., Gillberg, P.G., Nordberg, A., Winblad, B., Sara, V., 1989. Insulin-like growth factor 1 (IGF-1) receptors in the human brain: quantitative autoradiographic localization. Brain Res. 503, 299–303.

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 270–279.

Aleman, A., Torres-Aleman, I., 2009. Circulating insulin-like growth factor I and cognitive function: neuromodulation throughout the lifespan. Prog. Neurobiol. 89, 256–265.

Angelini, A., Bendini, C., Neviani, F., Bergamini, L., Manni, B., Trenti, T., Rovati, R., Neri, M., 2009. Insulin-like growth factor-1 (IGF-1): relation with cognitive functioning and neuroimaging marker of brain damage in a sample of hypertensive elderly subjects. Arch. Gerontol. Geriatr. 49 (Suppl 1), 5–12.

Arwert, L.I., Deijen, J.B., Drent, M.L., 2005. The relation between insulin-like growth factor I levels and cognition in healthy elderly: a meta-analysis. Growth Hormone IGF Res. 15, 416–422.

Baker, L.D., Barsness, S.M., Borson, S., Merriam, G.R., Friedman, S.D., Craft, S., Vitiello, M.V., 2012. Effects of growth hormone-releasing hormone on cognitive function in adults with mild cognitive impairment and healthy older adults: results of a controlled trial. Arch. Neurol. 69, 1420–1429.

Bansal, S., Buring, J.E., Rifai, N., Mora, S., Sacks, F.M., Ridker, P.M., 2007. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA 298, 309–316.

Barbieri, M., Ferrucci, L., Ragno, E., Corsi, A., Bandinelli, S., Bonafe, M., Olivieri, F., Giovagnetti, S., Franceschi, C., Guralnik, J.M., Paolisso, G., 2003. Chronic inflammation and the effect of IGF-I on muscle strength and power in older persons. Am. J. Physiol. Endocrinol. Metab. 284, E481–E487.

Bondy, C.A., Cheng, C.M., 2004. Signaling by insulin-like growth factor 1 in brain. Eur. J. Pharmacol. 490, 25–31.

Buchman, A.S., Yu, L., Wilson, R.S., Schneider, J.A., Bennett, D.A., 2013. Association of brain pathology with the progression of frailty in older adults. Neurology 80, 2055–2061.

Buracchio, T., Dodge, H.H., Howieson, D., Wasserman, D., Kaye, J., 2010. The trajectory of gait speed preceding mild cognitive impairment. Arch. Neurol. 67, 980–986.

Cappola, A.R., Bandeen-Roche, K., Wand, G.S., Volpato, S., Fried, L.P., 2001. Association of IGF-I levels with muscle strength and mobility in older women. J. Clin. Endocrinol. Metab. 86, 4139–4146.

Carro, E., Trejo, J.L., Gerber, A., Loetscher, H., Torrado, J., Metzger, F., Torres-Aleman, I., 2006. Therapeutic actions of insulin-like growth factor I on APP/PS2 mice with severe brain amyloidosis. Neurobiol. Aging 27, 1250–1257.

Carro, E., Trejo, J.L., Gomez-Isla, T., LeRoith, D., Torres-Aleman, I., 2002. Serum insulin-like growth factor I regulates brain amyloid-beta levels. Nat. Med. 8, 1390–1397.

Clegg, A., Young, J., Iliffe, S., Rikkert, M.O., Rockwood, K., 2013. Frailty in elderly people. Lancet 381, 752–762.

Cotman, C.W., Berchtold, N.C., Christie, L.A., 2007. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 30, 464–472.

de la Monte, S.M., Wands, J.R., 2005. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. J. Alzheimers Dis. 7, 45–61.

Deak, F., Sonntag, W.E., 2012. Aging, synaptic dysfunction, and insulin-like growth factor (IGF)-1. J. Gerontol. A Biol. Sci. Med. Sci. 67, 611–625.

Dik, M.G., Pluijm, S.M., Jonker, C., Deeg, D.J., Lomecky, M.Z., Lips, P., 2003. Insulin-like growth factor I (IGF-I) and cognitive decline in older persons. Neurobiol. Aging 24, 573–581.

Dore, S., Kar, S., Quirion, R., 1997. Insulin-like growth factor I protects and rescues hippocampal neurons against beta-amyloid- and human amylin-induced toxicity. Proc. Natl. Acad. Sci. U. S. A. 94, 4772–4777.

Duron, E., Funalot, B., Brunel, N., Coste, J., Quinquis, L., Viollet, C., Belmin, J., Jouanny, P., Pasquier, F., Treluyer, J.M., Epelbaum, J., le Bouc, Y., Hanon, O., 2012. Insulin-like growth factor-I and insulin-like growth factor binding protein-3 in Alzheimer's disease. J. Clin. Endocrinol. Metab. 97, 4673–4681.

Florini, J.R., Ewton, D.Z., Magri, K.A., 1991. Hormones, growth factors, and myogenic differentiation. Annu. Rev. Physiol. 53, 201–216.

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. J. Psychiatr. Res. 12, 189–198.

Hong, M., Lee, V.M., 1997. Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. J. Biol. Chem. 272, 19547–19553.

Jafferali, S., Dumont, Y., Sotty, F., Robitaille, Y., Quirion, R., Kar, S., 2000. Insulin-like growth factor-I and its receptor in the frontal cortex, hippocampus, and cerebellum of normal human and Alzheimer disease brains. Synapse 38, 450–459.

Johansson, P., Aberg, D., Johansson, J.O., Mattsson, N., Hansson, O., Ahren, B., Isgaard, J., Aberg, N.D., Blennow, K., Zetterberg, H., Wallin, A., Svensson, J., 2013. Serum but not cerebrospinal fluid levels of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) are increased in Alzheimer's disease. Psychoneuroendocrinology 38, 1729–1737.

Kalmijn, S., Janssen, J.A., Pols, H.A., Lamberts, S.W., Breteler, M.M., 2000. A prospective study on circulating insulin-like growth factor I (IGF-I), IGF-binding proteins, and cognitive function in the elderly. J. Clin. Endocrinol. Metab. 85, 4551–4555.

Kaplan, R.C., McGinn, A.P., Pollak, M.N., Kuller, L., Strickler, H.D., Rohan, T.E., Xue, X., Kritchevsky, S.B., Newman, A.B., Psaty, B.M., 2008. Total insulin-like growth

factor 1 and insulin-like growth factor binding protein levels, functional status, and mortality in older adults. J. Am. Geriatr. Soc. 56, 652–660.
Liu-Ambrose, T., Nagamatsu, L.S., Voss, M.W., Khan, K.M., Handy, T.C., 2012. Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. Neurobiol. Aging 33, 1690–1698.
Lopez-Lopez, C., LeRoith, D., Torres-Aleman, I., 2004. Insulin-like growth factor I is required for vessel remodeling in the adult brain. Proc. Natl. Acad. Sci. U. S. A. 101, 9833–9838.
Makizako, H., Shimada, H., Park, H., Doi, T., Yoshida, D., Uemura, K., Tsutsumimoto, K., Suzuki, T., 2013. Evaluation of multidimensional neurocognitive function using a tablet personal computer: test-retest reliability and validity in community-dwelling older adults. Geriatr. Gerontol. Int. 13, 860–866.
Mielke, M.M., Roberts, R.O., Savica, R., Cha, R., Drubach, D.I., Christianson, T., Pankratz, V.S., Geda, Y.E., Machulda, M.M., Ivnik, R.J., Knopman, D.S., Boeve, B.F., Rocca, W.A., Petersen, R.C., 2013. Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the Mayo Clinic Study of Aging. J. Gerontol. A Biol. Sci. Med. Sci. 68, 929–937.
Mikami, S., Hamano, T., Fujii, N., Nagasawa, Y., Isaka, Y., Moriyama, T., Matsuhisa, M., Ito, T., Imai, E., Hori, M., 2008. Serum osteoprotegerin as a screening tool for coronary artery calcification score in diabetic pre-dialysis patients. Hypertens. Res. 31, 1163–1170.
Murase, N., Katsumura, T., Ueda, C., Inoue, S., Shimomitsu, T., 2003. International standardization of physical activity level: reliability and validity study of the Japanese version of the International Physical Activity Questionnaire (IPAQ) (Kosei no Shihyo). J. Health Welfare Stat. 49, 9.
Nishijima, T., Piriz, J., Duflot, S., Fernandez, A.M., Gaitan, G., Gomez-Pinedo, U., Verdugo, J.M., Leroy, F., Soya, H., Nunez, A., Torres-Aleman, I., 2010. Neuronal activity drives localized blood-brain-barrier transport of serum insulin-like growth factor-I into the CNS. Neuron 67, 834–846.
Onder, G., Liperoti, R., Russo, A., Soldato, M., Capoluongo, E., Volpato, S., Cesari, M., Ameglio, F., Bernabei, R., Landi, F., 2006. Body mass index, free insulin-like growth factor I, and physical function among older adults: results from the ilSIRENTE study. Am. J. Physiol. Endocrinol. Metab. 291, E829–E834.
Peters, D.M., Fritz, S.L., Krotish, D.E., 2013. Assessing the reliability and validity of a shorter walk test compared with the 10-Meter Walk Test for measurements of gait speed in healthy, older adults. J. Geriatr. Phys. Ther. 36, 24–30.
Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J. Intern. Med. 256, 183–194.
Petersen, R.C., 2011. Clinical practice. Mild cognitive impairment. N. Engl. J. Med. 364, 2227–2234.
Sanders, J.L., Ding, V., Arnold, A.M., Kaplan, R.C., Cappola, A.R., Kizer, J.R., Boudreau, R.M., Cushman, M., Newman, A.B., 2014. Do changes in circulating biomarkers track with each other and with functional changes in older adults? J. Gerontol. A Biol. Sci. Med. Sci. 69, 174–181.
Shimada, H., Makizako, H., Doi, T., Yoshida, D., Tsutsumimoto, K., Anan, Y., Uemura, K., Ito, T., Lee, S., Park, H., Suzuki, T., 2013a. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people. J. Am. Med. Dir. Assoc. 14, 518–524.
Shimada, H., Suzuki, T., Suzukawa, M., Makizako, H., Doi, T., Yoshida, D., Tsutsumimoto, K., Anan, Y., Uemura, K., Ito, T., Lee, S., Park, H., 2013b. Performance-based assessments and demand for personal care in older Japanese people: a cross-sectional study. BMJ Open 3:e002424.
Shum, D.H.K., McFarland, K.A., Bain, J.D., 1990. Construct validity of eight tests of attention: comparison of normal and closed head injured samples. Clin. Neuropsychol. 4, 151–162.
Solfrizzi, V., Scafato, E., Frisardi, V., Seripa, D., Logroscino, G., Maggi, S., Imbimbo, B.P., Galluzzo, L., Baldereschi, M., Gandin, C., Di Carlo, A., Inzitari, D., Crepaldi, G., Pilotto, A., Panza, F., 2013. Frailty syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Aging. Alzheimers Dement. 9, 113–122.
Sonntag, W.E., Ramsey, M., Carter, C.S., 2005. Growth hormone and insulin-like growth factor-1 (IGF-1) and their influence on cognitive aging. Ageing Res. Rev. 4, 195–212.
Trejo, J.L., Carro, E., Torres-Aleman, I., 2001. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J. Neurosci. 21, 1628–1634.
Trejo, J.L., Llorens-Martin, M.V., Torres-Aleman, I., 2008. The effects of exercise on spatial learning and anxiety-like behavior are mediated by an IGF-I-dependent mechanism related to hippocampal neurogenesis. Mol. Cell. Neurosci. 37, 402–411.
van Dam, P.S., Aleman, A., de Vries, W.R., Deijen, J.B., van der Veen, E.A., de Haan, E.H., Koppeschaar, H.P., 2000. Growth hormone, insulin-like growth factor I and cognitive function in adults. Growth Horm. IGF Res. 10 (Suppl B), S69–S73.
van Exel, E., Eikelenboom, P., Comijs, H., Deeg, D.J., Stek, M.L., Westendorp, R.G., 2014. Insulin-like growth factor-1 and risk of late-onset Alzheimer's disease: findings from a family study. Neurobiol. Aging 35, e7–10.
Vardy, E.R., Rice, P.J., Bowie, P.C., Holmes, J.D., Grant, P.J., Hooper, N.M., 2007. Increased circulating insulin-like growth factor-1 in late-onset Alzheimer's disease. Journal of Alzheimer's disease. J. Alzheimers Dis. 12, 285–290.
Verghese, J., Annweiler, C., Ayers, E., Barzilai, N., Beauchet, O., Bennett, D.A., Bridenbaugh, S.A., Buchman, A.S., Callisaya, M.L., Camicioli, R., Capistrant, B., Chatterji, S., De Cock, A.M., Ferrucci, L., Giladi, N., Guralnik, J.M., Hausdorff, J.M., Holtzer, R., Kim, K.W., Kowal, P., Kressig, R.W., Lim, J.Y., Lord, S., Meguro, K., Montero-Odasso, M., Muir-Hunter, S.W., Noone, M.L., Rochester, L., Srikanth, V., Wang, C., 2014. Motoric cognitive risk syndrome: Multicountry prevalence and dementia risk. Neurology 83, 718–726.
Voss, M.W., Vivar, C., Kramer, A.F., van Praag, H., 2013. Bridging animal and human models of exercise-induced brain plasticity. Trends Cogn. Sci. 17, 525–544.
Waite, L.M., Grayson, D.A., Piguet, O., Creasey, H., Bennett, H.P., Broe, G.A., 2005. Gait slowing as a predictor of incident dementia: 6-year longitudinal data from the Sydney Older Persons Study. J. Neurol. Sci. 229-230, 89–93.
Watanabe, T., Miyazaki, A., Katagiri, T., Yamamoto, H., Idei, T., Iguchi, T., 2005. Relationship between serum insulin-like growth factor-1 levels and Alzheimer's disease and vascular dementia. J. Am. Geriatr. Soc. 53, 1748–1753.
Westwood, A.J., Beiser, A., Decarli, C., Harris, T.B., Chen, T.C., He, X.M., Roubenoff, R., Pikula, A., Au, R., Braverman, L.E., Wolf, P.A., Vasan, R.S., Seshadri, S., 2014. Insulin-like growth factor-1 and risk of Alzheimer dementia and brain atrophy. Neurology 82, 1613–1619.
Yesavage, J.A., 1988. Geriatric depression scale. Psychopharmacol. Bull. 24, 709–711.

Cigarette Smoking and Cognitive Health in Elderly Japanese

Ryo Hotta, PhD; Takehiko Doi, PhD, PT; Hiroyuki Shimada, PhD, PT; Hyuma Makizako, PhD, PT; Daisuke Yoshida, PhD, PT; Yuya Anan, MS; Kota Tsutsumimoto, MS, PT; Kazuki Uemura, PhD, PT; Hyuntae Park, PhD; Takao Suzuki, PhD, MD

***Objective*: To examine the relationships between smoking status and various domains of cognitive function in community-dwelling elderly subjects. *Methods*: Participants (N = 4348) were asked about smoking status, demographic variables, and lifestyle factors, and underwent multidimensional neurocognitive tests. *Results*: All analyses were conducted separately by sex. Women never smokers exhibited significantly better scores than past and/or current smokers in some neurocognitive tests. Among men, never smokers had significantly higher scores, such as in the Symbol Digit Substitution Test. Multiple linear regression analysis showed that pack-years (history of smoking) were significantly associated with the Symbol Digit Substitution Test in men. *Conclusions*: Smoking status may be associated with a decline in processing speed, and this decline varies by sex.**

***Key words*: smoking; pack-years; cognitive function; elderly**

***Am J Health Behav.* 2015;39(3):294-300**

DOI: http://dx.doi.org/10.5993/AJHB.39.3.1

There are approximately one billion smokers worldwide.[1] Cigarette smoking is associated with various diseases such as ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, and cancer;[2-7] approximately 6 million people die annually of diseases related to cigarette smoking.[1] Moreover, cigarette smoking also appears to be related to neurocognition[8] and constitutes a serious health problem for the elderly.

Smoking increases the risk of Alzheimer's disease.[9] Previous studies suggest that compared to never smokers, smokers in the middle-aged and aged population have poorer cognitive functions such as working memory, attention, executive function, and information-processing speed.[10-14] One study classified smokers into 4 types: *current smokers*, *ever smokers who smoked at least 100 cigarettes in their life*, *former smokers*, and *never smokers*, and reviewed previous studies examining the relationship between dementia and cognitive decline.[15] Current smokers in this study had a higher risk of incident Alzheimer's disease and cognitive decline in comparison with former and never smokers. Additionally, former smokers had a higher rate of cognitive decline than never smokers. These findings indicate that current cigarette smoking behavior, as well as a history of smoking (eg, how long and/or much cigarette smoking), may have an impact on cognitive health.

To examine the effects of smoking in terms of how long and/or how much, many previous studies have measured smoking status using "pack-years" (eg, Glass et al[16]), calculated by multiplying average daily use in packs by the number of years of smoking. Numerous studies used this parameter to investigate the association between smoking and cancer, especially lung cancer; pack-years were found to be related directly to an increased risk for lung cancer.[17] Meanwhile, several studies examined the link between pack-years and cognitive function, and showed that more pack-years correlated with a significantly higher rate of cognitive decline.[16,18] Another study examined the effect of pack-years on changes in global cognitive function in nondemented elderly persons.[19] The investigators found that more cigarette pack-years correlated with a significantly greater cognitive de-

Ryo Hotta, Takehiko Doi, Hiroyuki Shimada, Hyuma Makizako, Daisuke Yoshida, Yuya Anan, and Kota Tsutsumimoto, all from the Department of Functioning Activation, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Aichi, Japan. Kazuki Uemura, Institution of Innovation for Future Society, Nagoya University, Nagoya, Japan. Hyuntae Park and Takao Suzuki, Research Institute, National Center for Geriatrics and Gerontology, Aichi, Japan. Correspondence Dr Hotta; ryo-h@ncgg.go.jp