

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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- 1 Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Chertkow H, Cummings JL, de Leon M, Feldman H, Ganguli M, Hampel H, Scheltens P, Tierney MC, Whitehouse P, Winblad B. Mild cognitive impairment. *Lancet* 2006; **367**: 1262-1270.
- 2 Marc E. *Alzheimer Disease and Other Dementias: A Practical Guide*. Lippincott Williams & Wilkins, Philadelphia, PA, 2007, pp 74-79.
- 3 DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *Lancet Neurol* 2003; **2**: 15-21.
- 4 Forette F, Seux ML, Staessen JA, Thijss L, Birkenhäger WH, Babarskiene MR, Babeau S, Bossini A, Gil-Extermere B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998; **352**: 1347-1351.
- 5 Hanon O, Haulon S, Lenoir H, Seux ML, Rigaud AS, Safar M, Girerd X, Forette F. Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. *Stroke* 2005; **36**: 2193-2197.
- 6 Reitz C, Tang MX, Manly J, Mayeux R, Luchsinger JA. Hypertension and the risk of mild cognitive impairment. *Arch Neurol* 2007; **64**: 1734-1740.
- 7 Luchsinger JA, Reitz C, Patel B, Tang MX, Manly J, Mayeux R. Relation of diabetes to mild cognitive impairment. *Arch Neurol* 2007; **64**: 570-575.
- 8 Matsubayashi K, Okumiya K, Wada T, Osaki Y, Fujisawa M, Doi Y, Ozawa T. Postural dysregulation in systolic blood pressure is associated with worsened scoring on neurobehavioral function tests and leukoaraiosis in the older elderly living in a community. *Stroke* 1997; **28**: 2169-2173.
- 9 Tabara Y, Igase T, Kido T, Ochi N, Miki T, Kohara K. Composition of lower extremity in relation to a high ankle-brachial index. *J Hypertens* 2009; **27**: 167-173.
- 10 Shankle WR, Romney AK, Hara J, Fortier D, Dick MB, Chen JM, Chan T, Sun X. Methods to improve the detection of mild cognitive impairment. *Proc Natl Acad Sci USA* 2005; **102**: 4919-4924.
- 11 Trenkle DL, Shankle WR, Azen SP. Detecting cognitive impairment in primary care: performance assessment of three screening instruments. *J Alzheimers Dis* 2007; **11**: 323-335.
- 12 Cho A, Sugimura M, Nakano S, Yamada T. The Japanese MCI screen for early detection of Alzheimer's disease and related disorders. *Am J Alzheimers Dis Other Demen* 2008; **23**: 162-166.
- 13 Winnicki M, Canali C, Mormino P, Palatini P. Ambulatory blood pressure monitoring editing criteria: is standardization needed? Hypertension and Ambulatory Recording Veneta Study (HARVEST) Group, Italy. *Am J Hypertens* 1997; **10**: 419-427.
- 14 Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S, Imai Y. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens* 2002; **20**: 2183-2189.
- 15 Sugawara J, Hayashi K, Yokoi T, Cortez-Cooper MY, DeVan AE, Anton MA, Tanaka H. Brachial-ankle pulse wave velocity: an index of central arterial stiffness? *J Hum Hypertens* 2005; **19**: 401-406.
- 16 Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359-364.
- 17 DeKosky ST, Ikonomovic MD, Styren SD, Beckett L, Wisniewski S, Bennett DA, Cochran EJ, Kordower JH, Mufson EJ. Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. *Ann Neurol* 2002; **51**: 145-155.
- 18 Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology* 2005; **64**: 834-841.
- 19 Mufson EJ, Chen EY, Cochran EJ, Beckett LA, Bennett DA, Kordower JH. Entorhinal cortex beta-amyloid load in individuals with mild cognitive impairment. *Exp Neurol* 1999; **158**: 469-490.
- 20 Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Berry-Kravis E, Bennett DA. The apolipoprotein E epsilon4 allele and incident Alzheimer's disease in persons with mild cognitive impairment. *Neurocase* 2005; **11**: 3-7.
- 21 Birkenhäger WH, Forette F, Seux ML, Wang JG, Staessen JA. Blood pressure, cognitive functions, and prevention of dementias in older patients with hypertension. *Arch Intern Med* 2001; **161**: 152-156.
- 22 Bellelli G, Pezzini A, Bianchetti A, Trabucchi M. Increased blood pressure variability may be associated with cognitive decline in hypertensive elderly subjects with no dementia. *Arch Intern Med* 2002; **162**: 483-484.
- 23 van Boxtel MP, Henskens LH, Kroon AA, Hofman PA, Gronenschmidt EH, Jolles J, de Leeuw PW. Ambulatory blood pressure, asymptomatic cerebrovascular damage and cognitive function in essential hypertension. *J Hum Hypertens* 2006; **20**: 5-13.
- 24 Nagai M, Hoshida S, Ishikawa J, Shimada K, Kario K. Ambulatory blood pressure as an independent determinant of brain atrophy and cognitive function in elderly hypertension. *J Hypertens* 2008; **26**: 1636-1641.
- 25 Kario K, Pickering TG, Matsuo T, Hoshida S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001; **38**: 852-857.
- 26 Harada T, Murata T, Omori M, Takahashi T, Kosaka H, Wada Y, Yoshida H. Abnormal nocturnal blood pressure fall in senile-onset depression with subcortical silent cerebral infarction. *Neuropsychobiology* 2003; **47**: 187-191.
- 27 Luckhaus C, Flübb MO, Wittsack HJ, Grass-Kapanke B, Jännér M, Khalili-Amiri R, Friedrich W, Suprian T, Gaebel W, Mödder U, Cohen M. Detection of changed regional cerebral blood flow in mild cognitive impairment and early Alzheimer's dementia by perfusion-weighted magnetic resonance imaging. *Neuroimage* 2008; **40**: 495-503.
- 28 Caroli A, Testa C, Geroldi C, Nobili F, Barnden LR, Guerra UP, Bonetti M, Frisoni GB. Cerebral perfusion correlates of conversion to Alzheimer's disease in amnestic mild cognitive impairment. *J Neural* 2007; **254**: 1698-1707.
- 29 Sander D, Winbeck K, Klingelhöfer J, Conrad B. Extent of cerebral white matter lesions is related to changes of circadian blood pressure rhythmicity. *Arch Neurol* 2000; **57**: 1302-1307.
- 30 Kario K, Matsuo T, Kobayashi H, Imaia M, Matsuo M, Shimada K. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. *Hypertension* 1996; **27**: 130-135.
- 31 Smith EE, Egorova S, Blacker D, Killiany RJ, Muzikansky A, Dickerson BC, Tanzi RE, Albert MS, Greenberg SM, Guttmann CR. Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Arch Neurol* 2008; **65**: 94-100.
- 32 Lopez OL, Jagust WJ, Duberg C, Becker JT, DeKosky ST, Fitzpatrick A, Breitner J, Lyketsos C, Jones B, Kawas C, Carlson M, Kuller LH. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. *Arch Neurol* 2003; **60**: 1394-1399.
- 33 Zanetti M, Ballabio C, Abbate C, Cutaia C, Vergani C, Bergamaschini L. Mild cognitive impairment subtleties and vascular dementia in community-dwelling elderly people: a 3-year follow-up study. *J Am Geriatr Soc* 2006; **54**: 580-586.
- 34 Cicconetti P, Morelli S, Ottaviani L, Chiarotti F, De Serra C, De Marzio P, Costarella M, Sgrecchia A, Ciotti V, Marigliano V. Blunted nocturnal fall in blood pressure and left ventricular mass in elderly individuals with recently diagnosed isolated systhypertension. *Am J Hypertens* 2003; **16**: 900-905.
- 35 Moretti R, Torre P, Antonello RM, Manganaro D, Vilotti C, Pizzolato G. Risk factors for vascular dementia: hypotension as a key point. *Vasc Health Risk Manag* 2008; **4**: 395-402.
- 36 Grassi G, Seravalle G, Quarti-Trevano F, Dell'Oro R, Bombelli M, Cuspidi C, Facchetti R, Bolla G, Mancia G. Adrenergic, metabolic, and reflex abnormalities in reverse and extreme dipper hypertensives. *Hypertension* 2008; **52**: 925-931.
- 37 Takakuwa H, Shimizu K, Izumiya Y, Kato T, Nakaya I, Yokoyama H, Kobayashi K, Ise T. Dietary sodium restriction restores nocturnal reduction of blood pressure in patients with primary aldosteronism. *Hypertens Res* 2002; **25**: 737-742.
- 38 Uzu T, Takeji M, Yamauchi A, Kimura G. Circadian rhythm and postural change in natriuresis in non-dipper type of essential hypertension. *J Hum Hypertens* 2001; **15**: 323-327.
- 39 Higashi Y, Oshima T, Ozono R, Nakano Y, Matsuura H, Kambe M, Kajiyama G. Nocturnal decline in blood pressure is attenuated by NaCl loading in salt-sensitive patients with essential hypertension: noninvasive 24-h ambulatory blood pressure monitoring. *Hypertension* 1997; **30**: 163-167.
- 40 Kario K, Eguchi K, Nakagawa Y, Motai K, Shimada K. Relationship between extreme dippers and orthostatic hypertension in elderly hypertensive patients. *Hypertension* 1998; **31**: 77-82.
- 41 Kidd PM. Alzheimer's disease, amnestic mild cognitive impairment, and age-associated memory impairment. *Altern Med Rev* 2008; **13**: 85-115.

