Blood pressure and neuropsychiatric symptoms in old age

Moonen, J.E.F.

Chapter 1

General introduction

Introduction

Persons aged 80 years and older constitute the fastest growing proportion of the population in western countries, mainly due to an increasing life span and decreasing birth rates.[1] In the Netherlands, the percentage of persons aged over 65 years is expected to rise from 18% in 2015 to about 26% in 2040,[2] of which one third will be aged over 80 years. With increasing age cardiovascular disease increases exponentially, which is the leading cause of death worldwide.[3] The use of preventive cardiovascular treatment, including antihypertensive medication, is highest in persons aged over 80 years[4] of whom about 70% are diagnosed with hypertension.[5] Midlife hypertension has a well-established link with cerebrovascular disease[6] and, consequently, with cognitive decline at old age.[7] Nevertheless, it remains debatable whether hypertension in late life has a similar effect on brain structure and function.[8] The rapid increase in the number of older persons implies an increase in the prevalence of cognitive and psychological dysfunction which, in turn, imposes a substantial burden on patients, caregivers, and healthcare costs.[9] Therefore, there is urgent need for comprehensive insight into the role of late-life blood pressure in the occurrence of cognitive and psychological dysfunction.

Cognitive dysfunction

Cognitive dysfunction has a heterogeneous aetiology and is considered to be a dysfunction in complex attention, learning, memory, language, perceptual-motor skills, social cognition and executive function (including planning, impulse control, and goal-directed behaviour), but greater than expected due to ageing alone.[10] Cognitive dysfunction may progress to dementia, including Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, or Parkinson dementia, at an estimated annual rate of 5-15%.[11] Yet, cognitive dysfunction can remain stable or even be reversible when occurring in the context of a metabolic (e.g. vitamin B12 deficiency) or endocrine condition (e.g. hypothyroidism), medication toxicity, trauma (e.g. contusio cerebri), psychiatric (e.g. depression) or cardiovascular disorder.[12] Restoration of cardiac function after cardiac transplantation for example has been shown to restore cerebral blood flow and reverse cognitive dysfunction.[13] Cognitive dysfunction is also frequently observed in otherwise healthy older persons. In a large community-dwelling sample of persons aged 75 years and over the prevalence of cognitive dysfunction, according to a score below 24 on the Mini-Mental State Examination (the most commonly used screening instrument for cognitive dysfunction) was 18%.[14]

Psychological dysfunction

Cognitive and psychological dysfunction often concur,[15] suggesting a close relation between them, but can also occur independently of each other. Psychological dysfunction includes delusions, hallucinations, agitation, aggression, irritability, disinhibition, or symptoms of mania, anxiety, depression and apathy.[16] In particular, symptoms of apathy occur in vascular related cognitive dysfunction.[17] Furthermore, apathy is a common symptom in several neuropsychiatric diseases in older persons,[18] including depression, and is recently recognised as a distinctive syndrome in its own right in which lack of motivation is the predominant feature.[19] Moreover, apathy is frequently observed in community-dwelling older persons without overt neuropsychiatric diseases,[20] with a reported prevalence ranging from 10-20%.[21-23]

The Apathy Scale[24] and the Geriatric Depression Scale (GDS)-15 [25] are reliable and valid instruments to assess symptoms of apathy and depression in older persons, respectively. In contrast to the GDS-15, the Apathy Scale is not commonly used in research. Factor analyses revealed a subset of three of the GDS-15 items to be a cluster of symptoms that identifies apathy; thus, the GDS-3 Apathy (GDS-3A),[26;27] increases the possibility to investigate determinants of apathy. However, because only limited evidence exists for the discriminatory value of the GDS-3A,[28] it is important to determine the sensitivity, specificity and other epidemiological test characteristics of the GDS-3A for the presence or absence of clinically relevant apathy. The relevance of the validation of measures that assess symptom domains of depression, including the apathy domain,[29] is emphasised by the fact that distinct symptom domains may be differentially related to risk factors, such as blood pressure.[30;31]

Blood pressure

Hypertension is conventionally defined as a systolic blood pressure over 140 mmHg and/or a diastolic blood pressure over 90 mmHg.[32] Systolic blood pressure increases steadily with ageing, whereas diastolic blood pressure declines after age 50-60 years (Figure 1). This results in a widened pulse pressure at old age, which is defined as the difference between systolic and diastolic blood pressure, reflecting an increase in arterial stiffness.[33]

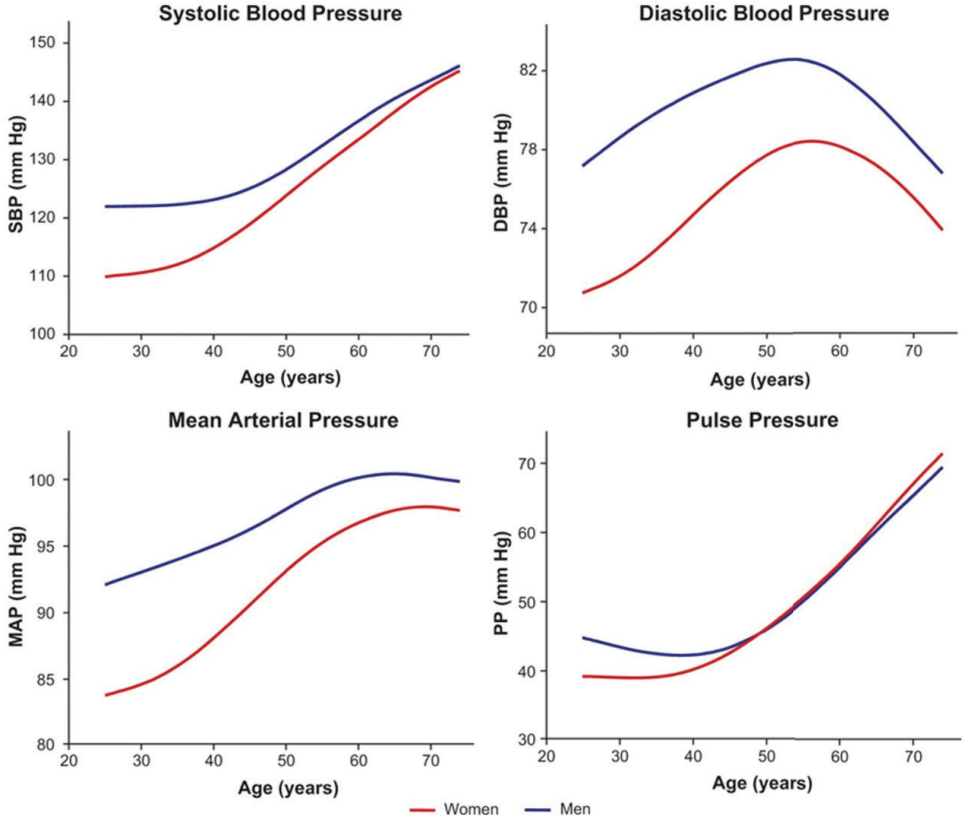

FIGURE 1. Mean blood pressure measures with increasing age for men (blue lines) and women (red lines). Source: *Hypertension* 2012;60(6):1393-1399.[34] http://hyper.ahajournals.org/

Blood pressure risks and ageing

In middle age a higher blood pressure is strongly associated with cerebrovascular disease[6] and, consequently, with cognitive decline at old age.[7] Midlife hypertension may increase the risk of dementia by 60%.[35] Furthermore, a higher blood pressure in community-dwelling older persons without depression (mean age 70-74 years) has been associated with symptoms of apathy according to the GDS-3A [22] or the Apathy Scale.[23] However, the predictive value of a higher blood pressure at old age is still debated and the current paradigm of 'the lower the better' may not apply to blood pressure at old age. There is accumulating observational evidence that older persons with a lower, rather than a higher, blood pressure have an increased risk of cognitive decline[36] and other adverse health outcomes.[37] The age at which the relation between blood pressure and cognitive dysfunction is supposed to change is around 75 years.[38] In persons with cognitive dysfunction and a mean age of 79 years who received antihypertensive treatment, a lower

blood pressure was linked to a greater cognitive decline.[5] In line with these findings, in octogenarians a declining blood pressure during the last decade has been associated with symptoms of depression.[39]

Blood pressure risks and functional status

The older population is highly heterogeneous even within groups of a similar chronological age, ranging from healthy older persons (i.e. those with a higher functional status) to physically impaired older persons with several comorbidities (i.e. those with a lower functional status).[40] In addition to chronological age, functional status may have an important influence on the relationship between blood pressure and adverse health outcomes. In persons aged 85 years and over with impairment in activities of daily living, a lower blood pressure is associated with an increased risk of stroke[41] and cognitive decline.[36] Furthermore, in older persons who were unable to complete a walking test, i.e. those with a lower functional status, a lower blood pressure was associated with increased mortality risk, whereas the association was inversed among fast walkers.[37] So far, it remains unknown whether functional status also modifies the relationship between blood pressure and the symptoms of apathy and depression at old age.

A large proportion of older persons with lower functional status have widespread vascular damage.[42] Long-lasting hypertension in midlife may damage cerebral vessels, resulting in arterial stiffness and limited ability to adequately regulate cerebral perfusion at old age with varying blood pressure levels. [43] Therefore, it is hypothesized that a higher blood pressure at old age may be required to overcome advanced arterial stiffness and to ensure sufficient cerebral perfusion.[44] This hypothesis raises questions about the desirability of intensive lowering of blood pressure with antihypertensive treatment at old age.

Antihypertensive treatment

Antihypertensive treatment lowers blood pressure via various mechanisms depending on the class of antihypertensive drugs used; these include diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), and beta blockers. Although treatment of hypertension in mid-life prevents cardiovascular morbidity [46] and, consequently, cognitive and psychological dysfunction,[43] its beneficial effects in late life are less clear.[47] In the 2008 HYpertension in the Very Elderly Trial (HYVET; the only available randomised clinical trial on antihypertensive treatment in persons aged 80 years and over: n=3845), the administration of the thiazide-like diuretic indapamide (supplemented, if necessary, by the ACE-inhibitor perindopril) led to a significant reduction in the risk of major cardiovascular events and all-cause mortality, but not to a reduction in incident dementia, when compared with placebo.[48] When the HYVET researchers pooled their data with other placebo-controlled trials of antihypertensive

treatment in older persons, they found a marginally reduced risk of dementia.[48] However, a Cochrane review of randomised trials (including the HYVET) in older persons showed no evidence that antihypertensive treatment reduces the risk of dementia,[49] which is in line with another meta-analysis.[50] Notably, HYVET and the other trials included in these meta-analyses[48-50] generally included participants in good physical and mental condition, resulting in study populations with a higher functional status than average for their age; this limits the generalizability of their findings. A particular concern for clinicians treating lower functioning older persons is that antihypertensive medication will cause orthostatic hypotension.

Orthostatic hypotension

Orthostatic hypotension is defined as a sustained decrease in systolic blood pressure of at least 20 mmHg or a diastolic blood pressure of 10 mmHg within 3 min of standing up.[51] However, the clinical value of this definition is debatable as orthostatic blood measurements have a high within-day and day-to-day variability[52] and because it is a mainly asymptomatic physical finding. Nevertheless, orthostatic hypotension can be accompanied by dizziness[53] and risk of falls.[54] With ageing, the prevalence of orthostatic hypotension increases up to 50% in nursing home residents aged over 80 years.[52]

Orthostatic hypotension develops when compensatory mechanisms fail to maintain a stable blood pressure upon standing. When assuming an upright position, approximately 600 ml of blood shifts down, leading to a decrease in venous blood return to the heart and, consequently, a transient reduction in cardiac output. As a result cardiopulmonary, aortic and carotid baroreceptors are stimulated, leading to an increase in sympathetic outflow, which causes cardiac acceleration and peripheral vasoconstriction.[55] With ageing there is a reduction in the baroreflex sensitivity and an increase in stiffness of the heart and blood vessels.

Apart from these age-related physiological changes, orthostatic hypotension may result from age-associated diseases or medications, such as antihypertensive treatment.[56] For example, beta-blockers may block necessary cardiac accelerations for maintenance of a stable blood pressure upon standing. However, due to lack of data from randomised clinical trials, the relationship between antihypertensive treatment and orthostatic hypotension remains ambiguous.

Cerebral damage

Midlife higher blood pressure is related to cerebral small vessel disease (SVD) at old age.[57] MRI features of cerebral SVD include lacunar infarcts (small subcortical infarcts), microbleeds, white matter hyperintensities, and brain atrophy.[58] SVD is a condition in

which the walls of small cerebral arteries are damaged, with narrowing of the vascular lumen and a failure of vascular mechanisms to maintain a stable cerebral blood flow.[59] The limited observational evidence suggests that, in contrast to midlife higher blood pressure, a late-life lower blood pressure is related to cerebral damage, as it may render the brain vulnerable for cerebral hypoperfusion.[60]

SVD can either be accompanied by cognitive decline, or have few or no symptoms.[61] Besides these overt signs of cerebral damage, information on cerebral microstructural integrity may provide additional information on the relationship between cerebral damage and cognitive function.[62] Diffusion Tensor Imaging (DTI) is an MRI technique that measures the diffusion of water molecules within the brain. This diffusivity is restricted in regions with high organisation (such as in parallel-oriented fibres in white matter tracts), whereas degradation of microstructural integrity is accompanied by an increase in diffusivity rate and/or a decrease in directionality of diffusivity. Changes in DTI parameters are observed not only in lesions visible on conventional MRI, but also in the (surrounding) normal-appearing brain tissue. It remains uncertain whether microstructural integrity is related to cognitive function independently of concomitant SVD.

In conclusion, high blood pressure in midlife may be a major target for the prevention of cognitive and psychological dysfunction in the rapidly ageing western populations. However, the concept 'the lower the better' may not apply for older persons, as observational evidence indicates a link between a *lower* blood pressure and cognitive and psychological dysfunction at old age. Nevertheless, due to the observational design of these studies no definite conclusions can be drawn. Randomised clinical trials in older people are needed to assess the potential benefits of having a higher blood pressure and of discontinuation of antihypertensive treatment.

Aim and outline of this thesis

The general aim of this thesis is to study the relationship between (an increase in) blood pressure and cognitive and psychological symptoms in older persons.

The DANTE Study Leiden

The Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) Study Leiden,[63] a community-based randomised clinical trial with blinded outcome assessment, was initiated to assess whether discontinuation of antihypertensive treatment improves cognitive, psychological and general daily function at 16-weeks follow-up. Between June 2011 and August 2013, a total of 385 patients were enrolled at 128 general practices in and around the city of Leiden, the Netherlands. Patients were eligible when they were 75

years or older, had mild cognitive deficits (according to a Mini Mental State Examination score of 21-27), used antihypertensive treatment, had a systolic blood pressure of 160 mmHg or less, and had no dementia or serious cardiovascular disease. A 3-T nested MRI sub-study was performed in a total of 220 persons at baseline to assess small vessel disease, microstructural integrity and cerebral blood flow. Participants were randomised to continuation or discontinuation of antihypertensive treatment. The primary outcome was change in overall cognitive functioning, and secondary outcomes included changes in memory, psychomotor speed, executive function, symptoms of apathy and depression, and general daily functioning. Furthermore, orthostatic hypotension was assessed at baseline and at follow-up.

The NESDO Study

The Netherlands Study of Depression in Older Persons (NESDO)[64] is an ongoing multi-site naturalistic prospective cohort study which was designed to examine the determinants and course of depressive disorders in older persons. From 2007 to 2010, a total of 510 depressed persons (according to DSM-IV criteria) and non-depressed older persons (≥ 60 years) were recruited from general practices and mental healthcare institutes in five locations throughout the Netherlands. Persons with dementia or insufficient command of the Dutch language were excluded. Analyses were restricted to the 303 persons who met the DSM-IV criteria for major depression, minor depression or dysthymia within the past month, to be able to assess the link between current blood pressure and current depressive symptom domains and symptoms of apathy.

The PROMODE Study

In the Proactive Management of Depression in the Elderly (PROMODE) Study,[65] the GDS-3A and the Apathy Scale were assessed as part of a neuropsychological evaluation, which allowed us to examine the diagnostic accuracy of the GDS-3A compared to the Apathy Scale. PROMODE was designed to investigate the (cost-) effectiveness of a stepped-care intervention programme compared to usual care among older persons with depressive symptoms. From April 2007 until July 2008, persons (aged ≥ 75 years) without current treatment for depression or a diagnosis of dementia and with a Mini-Mental State Examination score of at least 19, were recruited from general practices in the Netherlands. For a total of 1118 participants, data were available on the GDS-3A and the Apathy scale.[21]

Brief description of chapters

- The first chapters explore the link between blood pressure and psychological symptoms in older persons. **Chapter 2** describes the relationship between blood pressure and depressive symptom domains and symptoms of apathy among depressed older persons, using baseline data of the NESDO Study. In **chapter 3** we evaluate whether the association between blood pressure and symptoms of apathy and depression in older persons depends on the level of functional status, using baseline data of the DANTE Study.
- **Chapter 4** investigates how accurately the Geriatric Depression Scale-3A discriminates between the presence and absence of apathy, compared to the Apathy Scale, in the DANTE Study and the PROMODE Study.
- **Chapter 5** presents the main findings of the DANTE Study Leiden, i.e. the effect of discontinuation of antihypertensive treatment on cognitive, psychological and general daily functioning in older persons.
- **Chapter 6** elaborates on the main findings in Chapter 5 and describes the effect of discontinuation of antihypertensive treatment on orthostatic hypotension.
- In **Chapter 7** and **Chapter 8** the focus is on cross-sectional results from the DANTE MRI sub-study. Chapter 7 presents the relationship between blood pressure, and conventional features of small vessel disease and cerebral microstructural integrity. Chapter 8 analyses the effect of features of small vessel disease and cerebral microstructural integrity on cognitive and psychological function.
- Finally, in **Chapter 9** we provide a summary of the main findings and in **Chapter 10** we discuss the main findings of this thesis in the context of current knowledge, propose pathophysiological explanations, address its limitations and strengths, present recommendations for future research and give implications for clinical practice.

References

1. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. *Lancet*. 2009;374(9696):1196-1208.
2. Centraal Bureau voor de Statistiek (CBS); www.cbs.nl
3. Mendis S, Davis S, Norrving B. Organizational update: the world health organization global status report on noncommunicable diseases 2014; one more landmark step in the combat against stroke and vascular disease. *Stroke*. 2015;46(5):e121-e122.
4. Charlesworth CJ, Smit E, Lee DS, Alramadhan F, Odden MC. Polypharmacy Among Adults Aged 65 Years and Older in the United States: 1988-2010. *J Gerontol A Biol Sci Med Sci*. 2015;70(8):989-995.
5. Mossello E, Pieraccioli M, Nesti N et al. Effects of Low Blood Pressure in Cognitively Impaired Elderly Patients Treated With Antihypertensive Drugs. *JAMA Intern Med*. 2015.
6. Strandgaard S, Paulson OB. Cerebrovascular consequences of hypertension. *Lancet*. 1994;344(8921):519-521.
7. Joas E, Backman K, Gustafson D et al. Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. *Hypertension*. 2012;59(4):796-801.
8. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005;4(8):487-499.
9. Prince MJ, Wu F, Guo Y et al. The burden of disease in older people and implications for health policy and practice. *Lancet*. 2015;385(9967):549-562.
10. Winblad B, Palmer K, Kivipelto M et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256(3):240-246.
11. Farias ST, Mungas D, Reed BR, Harvey D, DeCarli C. Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. *Arch Neurol*. 2009;66(9):1151-1157.
12. Baker JM, Salinas J, Berkowitz AL. Clinical Reasoning: A 56-year-old man with cognitive impairment and difficulty tying his necktie. *Neurology*. 2015;85(15):e116-e122.
13. Gruhn N, Larsen FS, Boesgaard S et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke*. 2001;32(11):2530-2533.
14. Rait G, Fletcher A, Smeeth L et al. Prevalence of cognitive impairment: results from the MRC trial of assessment and management of older people in the community. *Age Ageing*. 2005;34(3):242-248.
15. Vinkers DJ, Gussekloo J, Stek ML, Westendorp RGJ, van der Mast RC. Temporal relation between depression and cognitive impairment in old age: prospective population based study. *British Medical Journal*. 2004;329(7471):881-883.
16. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-2314.
17. Ishii N, Nishihara Y, Imamura T. Why do frontal lobe symptoms predominate in vascular dementia with lacunes? *Neurology*. 1986;36(3):340-345.
18. van Reekum R, Stuss DT, Ostrander L. Apathy: why care? *J Neuropsychiatry Clin Neurosci*. 2005;17(1):7-19.
19. Robert P, Onyike CU, Leentjens AF et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry*. 2009;24(2):98-104.
20. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *Int Psychogeriatr*. 2010;22(3):426-436.
21. Groeneweg-Koolhoven I, De Waal MW, van der Weele GM, Gussekloo J, van der Mast RC. Quality of life in community-dwelling older persons with apathy. *Am J Geriatr Psychiatry*. 2014;22(2):186-194.
22. Ligthart SA, Richard E, Fransen NL et al. Association of vascular factors with apathy in community-dwelling elderly individuals. *Arch Gen Psychiatry*. 2012;69(6):636-642.
23. Yao H, Takashima Y, Mori T et al. Hypertension and white matter lesions are independently associated with apathetic behavior in healthy elderly subjects: the Sefuri brain MRI study. *Hypertens Res*. 2009;32(7):586-590.

24. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992;4(2):134-139.
25. D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, detection and management of depression in elderly primary care attenders. I: The acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. *Fam Pract*. 1994;11(3):260-266.
26. Adams KB. Depressive symptoms, depletion, or developmental change? Withdrawal, apathy, and lack of vigor in the Geriatric Depression Scale. *Gerontologist*. 2001;41(6):768-777.
27. Adams KB, Matto HC, Sanders S. Confirmatory factor analysis of the geriatric depression scale. *Gerontologist*. 2004;44(6):818-826.
28. van der Mast RC, Vinkers DJ, Stek ML et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry*. 2008;23(3):266-271.
29. Hegeman JM, Wardenaar KJ, Comijs HC, Waal de MWM, Kok RM, Mast van RC. Symptom dimensions and subscales of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in older persons. *article in press*. 2012.
30. Jorm AF. Association of hypotension with positive and negative affect and depressive symptoms in the elderly. *Br J Psychiatry*. 2001;178():553-555.
31. Kim BS, Bae JN, Cho MJ. Depressive symptoms in elderly adults with hypotension: different associations with positive and negative affect. *J Affect Disord*. 2010;127(1-3):359-364.
32. Fields LE, Burt VL, Cutler JA, Hughes J, Roccella EJ, Sorlie P. The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension*. 2004;44(4):398-404.
33. Mitchell GF, Lacourciere Y, Ouellet JP et al. Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. *Circulation*. 2003;108(13):1592-1598.
34. Cheng S, Xanthakis V, Sullivan LM, Vasan RS. Blood pressure tracking over the adult life course: patterns and correlates in the Framingham heart study. *Hypertension*. 2012;60(6):1393-1399.
35. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10(9):819-828.
36. Sabayan B, Oleksik AM, Maier AB et al. High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85-plus Study. *J Am Geriatr Soc*. 2012;60(11):2014-2019.
37. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. *Arch Intern Med*. 2012;172(15):1162-1168.
38. Euser SM, van Bemmel T, Schram MT et al. The Effect of Age on the Association Between Blood Pressure and Cognitive Function Later in Life. *Journal of the American Geriatrics Society*. 2009;57(7):1232-1237.
39. Siennicki-Lantz A, Andre-Petersson L, Elmstahl S. Decreasing blood pressure over time is the strongest predictor of depressive symptoms in octogenarian men. *Am J Geriatr Psychiatry*. 2013;21(9):863-871.
40. Baune BT, Schmidt WP, Roesler A, Berger K. Functional consequences of subcortical white matter lesions and MRI-defined brain infarct in an elderly general population. *J Geriatr Psychiatry Neurol*. 2009;22(4):266-273.
41. Sabayan B, van VP, de Ruijter W, Gussekloo J, de Craen AJ, Westendorp RG. High blood pressure, physical and cognitive function, and risk of stroke in the oldest old: the Leiden 85-plus Study. *Stroke*. 2013;44(1):15-20.
42. Brunner EJ, Shipley MJ, Witte DR et al. Arterial stiffness, physical function, and functional limitation: the Whitehall II Study. *Hypertension*. 2011;57(5):1003-1009.
43. Iadecola C, Davisson RL. Hypertension and cerebrovascular dysfunction. *Cell Metab*. 2008;7(6):476-484.
44. Birns J, Markus H, Kalra L. Blood pressure reduction for vascular risk - Is there a price to be paid? *Stroke*. 2005;36(6):1308-1313.
45. Sabayan B, Westendorp RG. Blood pressure control and cognitive impairment--why low is not always better. *JAMA Intern Med*. 2015;175(4):586-587.
46. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. *Blood Press*. 2014;23(1):3-16.

47. Muller M, Smulders YM, de Leeuw PW, Stehouwer CD. Treatment of hypertension in the oldest old: a critical role for frailty? *Hypertension*. 2014;63(3):433-441.
48. Peters R, Beckett N, Forette F et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurology*. 2008;7(8):683-689.
49. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2009;4):CD004034.
50. Staessen JA, Thijs L, Richart T, Odili AN, Birkenhager WH. Placebo-controlled trials of blood pressure-lowering therapies for primary prevention of dementia. *Hypertension*. 2011;57(2):e6-e7.
51. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology*. 1996;46(5):1470.
52. Ooi WL, Barrett S, Hossain M, Kelley-Gagnon M, Lipsitz LA. Patterns of orthostatic blood pressure change and their clinical correlates in a frail, elderly population. *JAMA*. 1997;277(16):1299-1304.
53. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Hypertension*. 1992;19(6 Pt 1):508-519.
54. Ooi WL, Hossain M, Lipsitz LA. The association between orthostatic hypotension and recurrent falls in nursing home residents. *Am J Med*. 2000;108(2):106-111.
55. Lipsitz LA. Orthostatic hypotension in the elderly. *N Engl J Med*. 1989;321(14):952-957.
56. Luukinen H, Koski K, Laippala P, Kivela SL. Prognosis of diastolic and systolic orthostatic hypotension in older persons. *Arch Intern Med*. 1999;159(3):273-280.
57. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke*. 2008;39(10):2712-2719.
58. Wardlaw JM, Smith EE, Biessels GJ et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822-838.
59. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. *Stroke*. 1997;28(3):652-659.
60. van Dijk EJ, Breteler MM, Schmidt R et al. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. *Hypertension*. 2004;44(5):625-630.
61. Gootjes L, Teipel SJ, Zebuhr Y et al. Regional distribution of white matter hyperintensities in vascular dementia, Alzheimer's disease and healthy aging. *Dement Geriatr Cogn Disord*. 2004;18(2):180-188.
62. Kantarci K, Senjem ML, Avula R et al. Diffusion tensor imaging and cognitive function in older adults with no dementia. *Neurology*. 2011;77(1):26-34.
63. Moonen JE, Foster-Dingley JC, de Ruijter W et al. Effect of Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning-the DANTE Study Leiden: A Randomized Clinical Trial. *JAMA Intern Med*. 2015;175(10):1622-1630.
64. Comijs HC, Van Marwijk HW, van der Mast RC et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Res Notes*. 2011;4(1):524.
65. van der Weele GM, De Waal MW, van den Hout WB et al. Effects of a stepped-care intervention programme among older subjects who screened positive for depressive symptoms in general practice: the PROMODE randomised controlled trial. *Age Ageing*. 2012;41(4):482-488.