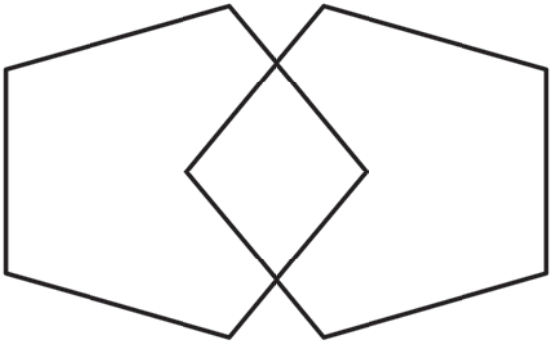
# Determinants of cognitive function in old age

Vliet, P. van

# Chapter 9

## General discussion



## General discussion

This thesis described the study of determinants of cognitive function at old age and was divided into two parts. The first part focused on the reversal of associations of classical risk factors for dementia and mortality with increasing age. We put emphasis on the influence of age on the association between total cholesterol levels and cognitive function and on the influence of structural brain damage on the association between blood pressure and cognitive function. Furthermore, we tried to gain insight in the temporal relation of longitudinal changes of these risk factors with cognitive function, underlying disease, and mortality. The second part of this thesis focused on both phenotypic and genetic variation in apolipoprotein E in relation to cognitive function and on the biological mechanisms behind these relations.
In this chapter the main findings of this thesis are summarized and discussed. Some methodological issues that apply to the studies in this thesis will be addressed, thereby discussing study designs and ways of analyzing. Furthermore, our findings will be evaluated in the light of possible clinical implications and some suggestions for further research are made.

## Main findings

*Traditional metabolic risk factors, cognitive function and mortality in late-life*
In **chapter 1** we give an overview of current literature on the influence of age on the association between total cholesterol levels and cognitive function. Although high cholesterol levels in midlife associate with an increased risk of dementia in late-life, this association attenuates with increasing age. In fact, in old age high cholesterol levels have even been shown to associate with better cognitive function and lower risk of dementia and also with a lower risk of cardiovascular disease. Statin treatment, although shown to be protective for cardiovascular events in old age, has not been shown to decrease the risk of dementia or cognitive impairment in old age, following results from randomized controlled trials. Low cholesterol levels in late-life may reflect underlying disease, thereby explaining the reversal of associations with increasing age.

Also blood pressure has been shown to have age-specific associations with dementia. Hypertension in midlife has clearly been shown to be a risk factor for dementia [1,2], but in late-life hypertension is no longer a risk factor for dementia, and the presence of dementia has even been shown to associate with low blood pressure [3-5]. In **chapter**

**2** we describe that, in a population of patients with memory complaints who were referred to a memory outpatient clinic, high blood pressure associated with better cognitive function in patients with structural brain damage, whereas this association was absent in patients with medium or low structural brain damage. The most likely explanation for these findings is that high blood pressure is needed for maintaining adequate brain perfusion and subsequently adequate brain function, but only in subjects who have functional or structural changes in cerebral vasculature, which has been observed in Alzheimer's disease brains [6-8].

In accordance with the before mentioned results, evidence has accumulated that in late-life, well-known classical risk factors, such as obesity, hypercholesterolemia, and hypertension, are no risk factors for dementia anymore. Moreover, in late-life obesity, high cholesterol levels, and high blood pressure have been associated with lower mortality [9-11], whereas these risk factors impose an increased mortality risk when present in midlife [12-14]. With increasing age, declines in values of these classical risk factors have been observed [15-17], and these declines have been linked to declines in cognitive function and dementia [18-20]. In **chapter 3** and **chapter 4** we used repetitive measurements in late-life of classical risk factors to give better insight in the dynamics of classical risk factors and their relation with changes in cognitive function and with mortality. We showed that declines in global cognitive function preceded declines in total cholesterol levels, HDL cholesterol levels, and blood pressure in following years, and not *vice versa*. Moreover, mortality was associated with larger annual declines in body mass index, total cholesterol levels, HDL cholesterol levels, and blood pressure. Principal component analysis showed clustering in dynamics of the classical risk factors in one component, which strongly associated with cancer mortality, in a profile that is suggestive of an underlying wasting state.

The results from these studies suggest that late-life declines in classical risk factors are, at least in part, the result of underlying disease, amongst which dementia processes. This gives a plausible explanation for why these classical risk factors have reversed associations with dementia and mortality in old age. For blood pressure however, some other mechanism also seems to play a role in the reversal of associations with cognitive function. We provide support for the theory that high blood pressure in late life may be needed to maintain cognitive function by functioning as a compensatory reaction to overcome the consequences of an aging vasculature.

*Apolipoprotein E variation, cognitive function in late-life, and risk of dementia*
Variation in the *APOE* gene is the strongest genetic risk factor for late onset Alzheimer's disease. Carriers of the ε4-allele are at an increased risk of Alzheimer's disease, whereas ε2-allele carriers might be protected [21-23]. Despite years of research, the exact biological mechanism explaining for this association is unclear. Besides the qualitative variation in the *APOE* gene, quantitative variation in apoE, such as variation in plasma apoE levels, has also been suggested to play a role in the dementia process, although previous studies have shown opposing results [24-28]. In **chapter 5** and **chapter 6** we investigated the association of plasma apoE levels with cognitive function and risk of late onset Alzheimer's disease in two different populations. In **chapter 5** we showed that high plasma apoE levels, when measured at baseline in a population based cohort of 85-year old subjects, associated with worse cognitive function at baseline and during five year follow-up in ε3ε3- and ε3ε4-carriers, but not in ε2ε3 carriers. In **chapter 6** we showed that, using an alternative approach by using a family study design, generally healthy middle-aged offspring with a parental history of Alzheimer's disease had lower plasma apoE levels than offspring without such a history. Although contradicting at first sight, the difference in outcome between the two studies might be explained by the presence of underlying disease in old age. At middle age, higher apoE levels may be protective for late onset Alzheimer's disease, due to the protective effects of apoE on atherosclerosis, oxidative damage, and inflammation [29,30]. In late-life however, high plasma apoE levels may also be the result of decreased clearance, or the result of up regulation of apoE expression as an adaptive response to systemic damage. This way, high apoE levels in late-life may reflect ill health, whereas high apoE levels in midlife could be the mere result of an increased innate expression capacity. In support of this reasoning is that plasma apoE levels are higher in old age compared to middle age, and high plasma apoE levels have been shown to associate with an increased mortality in the 85 year old population [31].

Besides the role of apoE variation in lipid metabolism, lipid peroxidation scavenging, and inflammation regulation, animal studies have pointed in the direction of apoE influencing calcium homeostasis in neuronal cells [32-37]. These studies have shown apoE to increase intracellular calcium levels in an isoform specific (apoE4>apoE3>apoE2) and dose dependent manner by the influx of extracellular calcium. The influx of calcium and the increased intracellular calcium levels resulted in neuronal cell death, which exemplifies the calcium hypothesis of Alzheimer's disease [38]. In our population of 85 year olds, high serum calcium levels have been shown to associate with worse cognitive function [39]. In **chapter 7** we showed that high serum calcium

levels were strongly associated with worse cognitive function in ε3ε4 carriers, to a lesser extent in ε3ε3 carriers, but not in ε2ε3 carriers. These observational findings are suggestive for a similar biological mechanism in humans, as was observed in experimental animal studies. ApoE4 may facilitate calcium influx in neuronal cells stronger than apoE3 and apoE2, which could lead to increased neuronal cell death and subsequent decreased cognitive function. Mechanistically, compared to apoE3 and apoE2, apoE4 could facilitate calcium influx through an increased permeability of neuronal cellular membranes, or an increased beta-amyloid deposition, with subsequent dysregulation of calcium homeostasis.

## Methodological issues on study design and analyses

The data presented in this thesis were derived from a variety of studies with different cross-sectional and longitudinal designs. Generally, data coming from cross-sectional studies are viewed as inferior to data coming from longitudinal studies, because they would not allow drawing conclusions on causality. However, by analyzing the data in different strata in one study and by using a family study design in the other cross-sectional study, we were able to make some remarks on possible causality. The longitudinal data in this thesis provided the opportunity to study temporal relations between changes in classical risk factors and changes in cognitive function.

In **chapter 2** we studied cross-sectional data on the association between blood pressure and cognitive function in patients visiting our memory outpatient clinic. By analyzing the association between blood pressure and cognitive function in strata of structural brain damage severity we were able to disentangle the effects of blood pressure on cognitive function from the effects of structural brain damage on cognitive function. This allowed us to formulate a plausible hypothesis on the biological background, but proof of causality must come from longitudinal studies.

The family study design, which was used in **chapter 6** in this thesis, is the exception to the rule that cross-sectional studies do not allow for causal illation. A family study design offers the opportunity to study risk factors years before the onset of the studied disease, and is therefore not hampered by reversed causation caused by underlying disease. Under the assumption that the studied disease is heritable, children from subjects with the disease and children from subjects without the disease are selected, with the disease being absent in the children. This results in a classical case-control design, with a case group containing subjects at increased risk of the disease and a control group containing subjects not at an increased risk of the disease. By comparing levels or occurrence of suspected risk factors between the two groups,

conclusions can be drawn on factors that increase the risk of disease.
The Leiden 85-Plus Study, a prospective population based study, was used in **chapter 3, chapter 4, chapter 6, and chapter 7** in this thesis. In two chapters the longitudinal design of the Leiden 85-Plus Study offered the opportunity to study the effect of late-life changes in classical risk factors on both mortality and changes in cognitive function. In the latter case, the longitudinal design was essential to study whether changes in cognitive function preceded or followed changes in the risk factors. The five year follow-up period was split in two time-frames, and annual changes in classical risk factors and global cognitive function were calculated for each time-frame. This allowed us to make careful conclusions on causality.
Although associations between changes in classical risk factors and mortality could causally only be interpreted in one direction, with mortality being the endpoint of study, it remains questionable whether changes itself would directly lead to mortality or are simply the consequence of underlying disease leading to mortality. To test for co-occurrence and patterns in changes of classical risk factors, which could be suggestive of underlying processes leading to the changes, we performed principal component analysis in **chapter 4**. Principal component analysis is often used to discover and summarize patterns of intercorrelations among a set of variables [40]. By performing principal component analysis the highest correlations of the input variables with one another are grouped, thereby assuming that a common underlying dimension (component) influences each variable separately. The possibility to operationalize the component as a new variable offered the opportunity to test for the influence of components on specific causes of death. This gave further support for speculations on which underlying process may drive the changes in classical risk factors.

## Clinical implications

In this thesis we provide data that suggest that in late-life, classical risk factors of mortality and dementia are subject to change over time, and these changes are associated with cognitive decline and mortality. Declines in body mass index, total cholesterol levels, and blood pressure are shown to associate with an increased mortality risk. This raises the question whether treatment of obesity, hypercholesterolemia, and hypertension in old age may in itself have detrimental effects, since treatment results in declines in these risk factors. However, randomized controlled trials in elderly populations have shown that statin and antihypertensive treatment both decrease mortality risk [41,42]. This strongly suggests that medication

induced declines in classical risk factors represent a different biological mechanism than observational declines. The latter are likely the result of underlying disease, and therefore associate with increased mortality. Question remains whether treatment as a preventive measure is warranted in the general elderly population, or whether treatment should be reserved for specific groups. In the HYVET-study for instance, only subjects with high systolic blood pressure were selected to participate in the study [43]. This selection criterion resulted in a study sample that represented a fairly healthy subgroup of the general population. Whether further reducing classical risk factors by treatment with statins and antihypertensives in subjects who already have low cholesterol levels and low blood pressure is highly questionable, especially when these are the result of strong declines in previous years. Furthermore, although shown to be protective for cardiovascular events and mortality, statin treatment and antihypertensive treatment have not been shown to decrease the risk of dementia and cognitive decline in old age [41,44,45]. Moreover, data presented in this thesis point to a possible beneficial effect of high blood pressure on cognitive function in patients with structural brain damage. This could imply that antihypertensive treatment of patients with structural brain damage may have detrimental effects on cognitive function. Possibly, discontinuation of antihypertensive treatment may be warranted in these patients, in order to improve brain perfusion and subsequently improve brain function. Although tempting, due to the observational character of our study, strong recommendations on the discontinuation of antihypertensive treatment in patients with structural brain damage cannot be made yet. Despite these uncertainties it is clear that there is no evidence for statin and antihypertensive treatment in old age for the prevention of dementia.

Following our results that low plasma apoE levels in midlife may increase the risk of late onset Alzheimer's disease, logical reasoning may point towards beneficial effects of increasing plasma apoE levels. Treatment strategies for humans that are focused on influencing apoE levels have mainly been hypothetical up till now, but some support for these treatments has come forward from animal studies. Most animal studies have focused at influencing intracerebral apoE, instead of systemic apoE. Some beneficial effects have been shown of intrathecal administration of apoE after cerebral ischemia [46]. Other studies have demonstrated improvement in histological and functional outcomes in preclinical models of subarachnoid hemorrhage, multiple sclerosis, and traumatic brain injury after the administration of an apoE-mimetic drug [47]. One small sized pilot clinical trial in a cohort of mild-to-moderate Alzheimer disease subjects showed that administration of probucol for 6 months revealed a concomitant stabilization of symptoms on dementia scales [48]. Probucol is an old cholesterol-lowering drug, which was shown to induce apoE synthesis and secretion

in cortical and hippocampal regions in rats and mice. Given the highly experimental stage at which these trials are performed, it is very questionable whether systemic administration or the stimulation of endogenous apoE production could offer benefit in humans.

## Future research

One of the main findings in this thesis is that high blood pressure could be beneficial for brain function in subjects with structural brain damage, possibly through the maintenance of brain perfusion. However, to clarify the biological mechanism behind this assumption, the effect of variation in blood pressure on cerebral blood flow and cerebral perfusion should be studied in more detail in relation to age and structural brain damage. The final step would be to design trials to study the potential beneficial effects of increasing blood pressure in patient populations with structural brain damage and cognitive impairment, for instance by discontinuing antihypertensive treatment. Designing these trials and selecting patients for these studies should be done with utmost care, since the possible beneficial effect on cognitive function should be weighed against the possible harmful effect on survival and cardiovascular events.

Another intriguing finding of this thesis is that high serum calcium levels were associated with worse cognitive function in ε3ε4 carriers, to a lesser extent in ε3ε3 carriers, but not in ε2ε3 carriers. The negative association between serum calcium levels and cognitive function may explain why treatment with calcium antagonists has been shown to protect against dementia and cognitive decline [49,50], whereas treatment with other antihypertensive medication has not been shown to be beneficial. Following the results in this thesis, it would be interesting to test whether the effect of calcium antagonist treatment is also *APOE* genotype specific. Future pharmacogenetic studies could provide information and ultimately lead to *APOE* genotype specific treatment and prevention regimes.

In conclusion, this thesis clearly shows that classical risk factors of dementia and mortality are subject to change with increasing age. Whereas obesity, hypercholesterolemia, and hypertension are detrimental in midlife, in late-life declines in body mass index, cholesterol levels, and blood pressure, all being likely the result of underlying disease, associate with cognitive decline and mortality. Besides these classical risk factors, plasma apoE levels also seem to be subject to changes with increasing age, supposedly under the influence of underlying disease. In midlife, low plasma apoE levels associate with an increased risk of dementia,

whereas in late-life high plasma apoE levels seem to reflect underlying disease and therefore associate with worse cognitive function. In general, conclusions from studies investigating risk factors of dementia and mortality in middle-aged populations can not be extrapolated to old-aged populations. With increasing age, the prevalence of multi-morbidity strongly increases and this heavily influences the associations of risk factors with dementia and mortality. Whether treatment of classical risk factors in late-life is beneficial or whether treatment effect might be dependent on underlying disease should receive more attention in future research.

## References


1. Launer, LJ, Ross, GW, Petrovitch, H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging. 2000; 21:49-55.
2. Kivipelto, M, Helkala, EL, Laakso, MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001; 322:1447-1451.
3. Qiu, C, Winblad, B, and Fratiglioni, L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005; 4:487-499.
4. Guo, Z, Viitanen, M, Fratiglioni, L, et al. Low blood pressure and dementia in elderly people: the Kungsholmen project. BMJ. 1996; 312:805-808.
5. Morris, MC, Scherr, PA, Hebert, LE, et al. The cross-sectional association between blood pressure and Alzheimer's disease in a biracial community population of older persons. J Gerontol A Biol Sci Med Sci. 2000; 55:M130-M136.
6. Kitaguchi, H, Ihara, M, Saiki, H, et al. Capillary beds are decreased in Alzheimer's disease, but not in Binswanger's disease. Neurosci Lett. 2007; 417:128-131.
7. Jeynes, B and Provias, J. The possible role of capillary cerebral amyloid angiopathy in Alzheimer lesion development: a regional comparison. Acta Neuropathol. 2006; 112:417-427.
8. Stopa, EG, Butala, P, Salloway, S, et al. Cerebral cortical arteriolar angiopathy, vascular beta-amyloid, smooth muscle actin, Braak stage, and APOE genotype. Stroke. 2008; 39:814-821.
9. Grabowski, DC and Ellis, JE. High body mass index does not predict mortality in older people: analysis of the Longitudinal Study of Aging. J Am Geriatr Soc. 2001; 49:968-979.
10. Weverling-Rijnsburger, AW, Blauw, GJ, Lagaay, AM, et al. Total cholesterol and risk of mortality in the oldest old. Lancet. 1997; 350:1119-1123.
11. Boshuizen, HC, Izaks, GJ, van Buuren, S, et al. Blood pressure and mortality in elderly people aged 85 and older: community based study. BMJ. 1998; 316:1780-1784.
12. Calle, EE, Thun, MJ, Petrelli, JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999; 341:1097-1105.
13. Stamler, J, Wentworth, D, and Neaton, JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA. 1986; 256:2823-2828.
14. Goldberg, RJ, Larson, M, and Levy, D. Factors associated with survival to 75 years of age in middle-aged men and women. The Framingham Study. Arch Intern Med. 1996; 156:505-509.
15. Stevens, J, Cai, J, Pamuk, ER, et al. The effect of age on the association between body-mass index and mortality. N Engl J Med. 1998; 338:1-7.
16. Solomon, A, Kareholt, I, Ngandu, T, et al. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. Neurology. 2007; 68:751-756.
17. Lernfelt, B and Svanborg, A. Change in blood pressure in the age interval 70-90. Late blood pressure peak related to longer survival. Blood Press. 2002; 11:206-212.
18. Cronin-Stubbs, D, Beckett, LA, Scherr, PA, et al. Weight loss in people with Alzheimer's disease: a prospective population based analysis. BMJ. 1997; 314:178-179.
19. Stewart, R, White, LR, Xue, QL, et al. Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol. 2007; 64:103-107.

20. Qiu, C, von, SE, Winblad, B, et al. Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. Stroke. 2004; 35:1810-1815.
21. Corder, EH, Saunders, AM, Strittmatter, WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993; 261:921-923.
22. Raber, J, Huang, Y, and Ashford, JW. ApoE genotype accounts for the vast majority of AD risk and AD pathology. Neurobiol Aging. 2004; 25:641-650.
23. Corder, EH, Saunders, AM, Risch, NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet. 1994; 7:180-184.
24. Taddei, K, Clarnette, R, Gandy, SE, et al. Increased plasma apolipoprotein E (apoE) levels in Alzheimer's disease. Neurosci Lett. 1997; 223:29-32.
25. Folin, M, Baiguera, S, Conconi, MT, et al. Apolipoprotein E as vascular risk factor in neurodegenerative dementia. Int J Mol Med. 2004; 14:609-613.
26. Slooter, AJ, de Knijff, P, Hofman, A, et al. Serum apolipoprotein E level is not increased in Alzheimer's disease: the Rotterdam study. Neurosci Lett. 1998; 248:21-24.
27. Scacchi, R, Gambina, G, Ruggeri, M, et al. Plasma levels of apolipoprotein E and genetic markers in elderly patients with Alzheimer's disease. Neurosci Lett. 1999; 259:33-36.
28. Siest, G, Bertrand, P, Qin, B, et al. Apolipoprotein E polymorphism and serum concentration in Alzheimer's disease in nine European centres: the ApoEurope study. ApoEurope group. Clin Chem Lab Med. 2000; 38:721-730.
29. Pedersen, WA, Chan, SL, and Mattson, MP. A mechanism for the neuroprotective effect of apolipoprotein E: isoform-specific modification by the lipid peroxidation product 4-hydroxynonenal. J Neurochem. 2000; 74:1426-1433.
30. Jofre-Monseny, L, Minihane, AM, and Rimbach, G. Impact of apoE genotype on oxidative stress, inflammation and disease risk. Mol Nutr Food Res. 2008; 52:131-145.
31. Mooijaart, SP, Berbee, JF, van Heemst, D, et al. ApoE plasma levels and risk of cardiovascular mortality in old age. PLoS Med. 2006; 3:e176.
32. Hartmann, H, Eckert, A, and Muller, WE. Apolipoprotein E and cholesterol affect neuronal calcium signalling: the possible relationship to beta-amyloid neurotoxicity. Biochem Biophys Res Commun. 1994; 200:1185-1192.
33. Wang, XS and Gruenstein, E. Rapid elevation of neuronal cytoplasmic calcium by apolipoprotein E peptide. J Cell Physiol. 1997; 173:73-83.
34. Muller, W, Meske, V, Berlin, K, et al. Apolipoprotein E isoforms increase intracellular Ca2+ differentially through a omega-agatoxin IVa-sensitive Ca2+-channel. Brain Pathol. 1998; 8:641-653.
35. Tolar, M, Keller, JN, Chan, S, et al. Truncated apolipoprotein E (ApoE) causes increased intracellular calcium and may mediate ApoE neurotoxicity. J Neurosci. 1999; 19:7100-7110.
36. Veinbergs, I, Everson, A, Sagara, Y, et al. Neurotoxic effects of apolipoprotein E4 are mediated via dysregulation of calcium homeostasis. J Neurosci Res. 2002; 67:379-387.
37. Qiu, Z, Crutcher, KA, Hyman, BT, et al. ApoE isoforms affect neuronal N-methyl-D-aspartate calcium responses and toxicity via receptor-mediated processes. Neuroscience. 2003; 122:291-303.
38. Khachaturian, ZS. Hypothesis on the regulation of cytosol calcium concentration and the aging brain. Neurobiol Aging. 1987; 8:345-346.

39. Schram, MT, Trompet, S, Kamper, AM, et al. Serum calcium and cognitive function in old age. J Am Geriatr Soc. 2007; 55:1786-1792.

40. Coste, J, Bouee, S, Ecosse, E, et al. Methodological issues in determining the dimensionality of composite health measures using principal component analysis: case illustration and suggestions for practice. Qual Life Res. 2005; 14:641-654.

41. Shepherd, J, Blauw, GJ, Murphy, MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002; 360:1623-1630.

42. Beckett, NS, Peters, R, Fletcher, AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008; 358:1887-1898.

43. Bulpitt, C, Fletcher, A, Beckett, N, et al. Hypertension in the Very Elderly Trial (HYVET): protocol for the main trial. Drugs Aging. 2001; 18:151-164.

44. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002; 360:7-22.

45. 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 Neurol. 2008; 7:683-689.

46. McAdoo, JD, Warner, DS, Goldberg, RN, et al. Intrathecal administration of a novel apoE-derived therapeutic peptide improves outcome following perinatal hypoxic-ischemic injury. Neurosci Lett. 2005; 381:305-308.

47. Laskowitz, DT and Vitek, MP. Apolipoprotein E and neurological disease: therapeutic potential and pharmacogenomic interactions. Pharmacogenomics. 2007; 8:959-969.

48. Poirier, J. Apolipoprotein E represents a potent gene-based therapeutic target for the treatment of sporadic Alzheimer's disease. Alzheimers Dement. 2008; 4:S91-S97.

49. Forette, F, Seux, ML, Staessen, JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet. 1998; 352:1347-1351.

50. Trompet, S, Westendorp, RG, Kamper, AM, et al. Use of calcium antagonists and cognitive decline in old age. The Leiden 85-plus study. Neurobiol Aging. 2008; 29:306-308.