Vascular risk factors, cognitve decline, and dementia

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Abstract: Dementia is one of the most important neurological disorders in the elderly. Aging is associated with a large increase in the prevalence and incidence of degenerative (Alzheimer's disease) and vascular dementia, leading to a devastating loss of autonomy. In view of the increasing longevity of populations worldwide, prevention of dementia has turned into a major public health challenge. In the past decade, several vascular risk factors have been found to be associated with vascular dementia but also Alzheimer's disease. Some longitudinal studies, have found significant associations between hypertension, diabetus mellitus, and metabolic syndrome, assessed at middle age, and dementia. Studies assessing the link between hypercholesterolemia, atrial fibrillation, smoking, and dementia have given more conflicting results. Furthermore, some studies have highlighted the possible protective effect of antihypertensive therapy on cognition and some trials are evaluating the effects of statins and treatments for insulin resistance. Vascular risk factors and their treatments are a promising avenue of research for prevention of dementia, and further long-term, placebo-controlled, randomized studies, need to be performed.

Keywords: dementia, hypertension, diabetus mellitus, hypercholesterolemia, metabolic syndrome

Introduction

Dementia is one of the most important neurological disorders in the elderly. As life expectancy increases, the worldwide number of demented patients is projected to grow from 24.3 million in 2001 to 81.1 million in 2040 (Ferri et al 2005). In occidental countries, the most common forms of dementia are Alzheimer's disease (AD) and vascular dementia (Vad), with respective frequencies of 70% and 15% among all dementias (Whitehouse et al 1997). AD is the most common primary neurodegenerative disorder in the elderly. Its neuropathological hallmarks are intraneuronal protein clusters of hyperphosphorylated tau protein (neurofibrillary tangles) and extracellular Aβ protein aggregation. This aggregation is the result of an abnormal amyloid precursor protein (APP) cleavage by β- and γ-secretases and initiates a pathogenic, self-perpetuating cascade ultimately leading to neuronal loss and dementia (Cummings et al 2004). In this context, the prevention of cognitive disorders represents a major challenge in the coming years. The identification of the risk factors for these debilitating conditions must be a priority in order to define the best approach for early prevention.

In the past decade, several vascular risk factors have been found to be associated with not only Vad but also, surprisingly, AD. We propose a review of these epidemiological associations and their underlying pathophysiological mechanisms (apolipoprotein E, hypertension, diabetus mellitus, obesity and metabolic syndrome, hypercholesterolemia, atrial fibrillation, smoking, atherosclerosis). Studies included in this non-systematic review were identified by searches of Medline and were restricted to papers published in English. The search terms were: apolipoprotein E, hypertension, diabetus mellitus, obesity and metabolic syndrome, hypercholesterolemia, atrial fibrillation, smoking, atherosclerosis, heart failure, coronary heart disease AND Alzheimer's

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disease OR dementia OR cognitive decline. Some relevant review articles were taken into account and their bibliographies were screened. Some original case-control, population-based, and intervention studies were included.

Apolipoprotein E genotype and cognitive decline

Numerous genes related to vascular disease have been shown to increase susceptibility for sporadic AD (Panza et al 2004). Among them, apolipoprotein E (Apo E), which occurs in three common alleles (ε2, ε3, ε4), is the best documented. The Apo E protein is one of the major constituents in very low-density lipoproteins and plays a key role in the transport of cholesterol among various cells of the body. The ApoE ε4 allele is known to be associated with coronary artery disease and the development of atherosclerosis (Davignon et al 1988; Eichner et al 2002). This association is presumably related to the higher levels of total cholesterol, low density lipoprotein cholesterol (LDL-C) and apolipoprotein B in subjects homozygous for the APoE ε4 genotype than in those carrying ε2 or ε3.

Epidemiological studies have found an association between the ε4 allele of ApoE and familial and sporadic late-onset AD (Saunders et al 1993). Furthermore, ApoE ε4 is associated with a younger onset of AD in a dose-dependent manner (Blacker et al 1997). Similarly, the Apo E genotype seems to predict the rate of cognitive decline in AD, in a dose-dependent relationship with the ApoE ε4 allele (Martins et al 2005). Mechanisms which could explain the effects of ApoE on the brain of AD subjects are still unclear. They include isoform specific toxicity, ApoE ε4- mediated amyloid aggregation, ApoE ε4- mediated tau hyperphosphorylation, and isoform-driven ApoE concentration changes (Panza et al 2006). ApoE could also modulate the distribution and metabolism of cholesterol in neuronal membranes in an isoform-dependent manner, which may be relevant to Apo E-related pathogenic effects and the development of AD (Yanasigawa 2002).

Hypertension and cognitive decline

The relationship between cognitive function and blood pressure has been the subject of numerous conflicts in the literature. The results of epidemiological studies vary with the methodology used. Cross-sectional studies have found not only positive (Starr et al 1993; Seux et al 1998) but also negative (Farmer et al 1987; Scherr et al 1991) correlations between arterial hypertension and cognitive impairment. Longitudinal studies are more informative since they evaluate the effect of "chronic" hypertension on cognitive function.

Most of them indicate a positive relationship between the presence of hypertension in midlife and the onset of cognitive decline 15–20 years later (Table 1). Skoog et al (1996) have demonstrated that blood pressure values measured at 70 years old were higher in patients developing dementia between the ages of 79 and 85 years than in non-demented subjects. Conversely, in the years preceding the onset of dementia, their blood pressures became identical to or less than those of patients who did not develop dementia. Others studies have observed a similar decrease in blood pressure in patients with AD (Hanon et al 2005b; Verghese et al 2003). Guo et al (1996) reported that blood pressure was lower in individuals over 75 years old with AD compared to patients without dementia and that blood pressure levels decreased with increasing severity of dementia. The reason for the decrease in blood pressure in patients with dementia has not been fully clarified. Whether the blood pressure decline is a cause or an effect of AD is not known. Physical inactivity in those afflicted by advancing mental deterioration as well as body mass and metabolic changes may all play a role. Finally, a recent study including 700 patients with AD found a significant association between hypertension and increased cognitive decline over a 6-month period (odds ratio [OR] = 1.6 [95% CI = 1.0–2.7]) (Bellew et al 2004).

To conclude, the connection between blood pressure and cognitive functions is more complex than a simple linear relationship. Chronic hypertension predisposes to cognitive decline and the development of dementia, but a decrease in blood pressure can be observed in the late interval preceding the onset of dementia and afterward.

The role of lowering blood pressure for the prevention of cognitive decline and dementia is of central importance and has been assessed in both non-randomized studies and several randomized clinical trials.

Non-randomized studies have yielded divergent results concerning the effect of antihypertensive drugs on cognitive functions. A negative effect of antihypertensive drugs on cognitive functions was suspected (Heckbert et al 1997; Maxwell et al 1999). Instead, Guo et al (1999) have shown a significant reduction in the risk of dementia as a result of antihypertensive treatment (relative risk [RR] of 0.7, 95% CI = 0.6–1.0). In the HOPE study (Starr et al 1996), cognitive improvement was seen in subjects treated with diuretics or angiotensin converting enzyme inhibitors who had the greatest drop in blood pressure. Moreover, in the EVA cohort (Tzourio et al 1999), the risk of cognitive decline after 4 years of follow up was significantly lower in hypertensive subjects who received treatment compared to untreated

Table 1 Blood pressure (BP) and cognitive decline or dementia. Longitudinal studies

References	n[a]	Age at baseline (years)	Follow up (years)	Outcomes
Elias 1993	1702	55–88	12–14	Positive correlation between BP and cognitive decline
Launer 1995	3735	50	20–28	Positive correlation between BP and cognitive decline
Yoshikate 1995	828	74	7	Positive correlation between BP and vascular dementia
Skoog 1996	382	70	9–15	Positive correlation between BP and dementia (Alzheimer's and vascular types)
Starr 1997	603	>69	4	Positive correlation between BP and cognitive decline
Kilander 1998a	999	50	20	Positive correlation between BP and cognitive decline
Swan 1998a,b	717	45	25–30	Positive correlation between BP and cognitive decline
Tzourio 1999	1373	59–71	4	Positive correlation between BP and cognitive decline RR = 2.8 (95% CI = 1.6–5.0)
Launer 2000	3703	50	25	Positive correlation between BP and dementia (Alzheimer's and vascular types) RR = 4.8 (95% CI = 2.0–11.0)
Knopman 2001	10963	47–70	6	Positive correlation between BP and cognitive decline
Kivipelto 2001	1449	53	21	Positive correlation between BP and AD OR = 2.1 (95% CI = 1.0–4.3)
Qiu 2003	1270	81	4.7	Positive correlation between pulse pressure and AD OR = 2.1 (95% CI = 1.0–4.3)
Reinprecht 2003	186	68	13	Positive correlation between BP and cognitive decline
Piguet 2003	377	≥75	6	Positive correlation between BP and cognitive decline
Whitmer 2005	8845	40–44	30	Positive correlation between BP and dementia OR = 2.1 (95% CI = 1.0–4.3)
Okumiya 1997	155	78	3	J curve between BP and cognitive decline
Glynn et al 1999	2068	65–102	6	J curve between BP and cognitive decline
Bohannon 2002	4136	65–105	3	J curve between BP and cognitive decline
Guo et al 1997	1736	75–101	3	Negative correlation between BP and cognitive decline
Zhu et al 1998	924	>75	3	Negative correlation between BP and cognitive decline
Verghese et al 2003	488	79	6.7	Negative correlation between BP and AD
Morris et al 2001	634	>65	13	No correlation between BP and AD
Freitag et al 2006	2505	57	5.1	No corrrelation between pulse pressure and AD

[a]n = numbers of subjects at inclusion.
Abbreviations: AD, Alzheimer's disease; OR, odds ratio; BP, blood pressure; RR, relative risk.

hypertensive subjects (1.9 [95% CI = 0.8–4.4] versus 4.3 [95% CI = 2.1–8.8]). Similarly, a study of 1617 elderly African-American subjects followed for 5 years, indicated a significant 38% decrease in cognitive decline in treated hypertensive subjects compared with untreated subjects (OR = 0.62, 95% CI = 0.45–0.84) (Murray et al 2002). Moreover, a recent study found that in a sample of 1241 elderly patients, the odds ratio for AD was 0.58 (95% CI = 0.42–0.81) in treated compared with untreated hypertensive patients (Hanon et al 2006). Lastly, the recent Cache County Study performed in 3,308 people (Mean age 75 years), followed up 3 years, indicated a significant reduction of the risk of AD from 36% (OR = 0.64, 95% CI = 0.41–0.98) (Khatchaturian et al 2006). Moreover, data from the Honolulu Asia Aging Study showed that the duration of antihypertensive therapy also mattered: For each additional year of treatment, there was a reduction in the risk of dementia incidence (hazard ratio [HR] = 0.94, 95% CI = 0.89–0.99) (Peila et al 2006)

By definition, however, observational studies are subject to bias, and randomized, placebo-controlled studies are necessary to investigate the relationship between antihypertensive treatment and cognitive functions.

Six large randomized placebo-controlled trials have evaluated the effects of antihypertensive drugs on cognitive functions. Their results are summarized in Table 2.

In the MRC project (Prince et al 1996), a subgroup of 2584 elderly subjects followed for 54 months showed no difference in neuropsychometric tests in the treated group (Diuretic or β-blocker) compared to the placebo group. In this study, however, the evaluation of cognitive functions was insufficiently detailed and the 54-month follow up period may have been too short to detect a difference between the 2 groups.

In the SHEP study (SHEP Cooperative research group 1991) the incidence of dementia was not statistically different in the group receiving active treatment with diuretic and/or β-blocker (1.6%) compared to the group receiving placebo (1.9%), after 5 years of follow-up, although it was slightly lower in the first group. In this study, however, differential dropout biased the cognitive evaluations and may have obscured the assessment of a preventive effect of treatment on cognitive decline (Di Bari et al 2001).

Table 2 Effect of antihypertensive drugs on cognitive decline or dementia in randomised, placebo-controlled studies

Studies	n[a]	ΔSBP/DBP (active - placebo)	Drugs	Follow up	Outcomes
MRC	2584	−15.8/5 mmHg	BB or Diu	54 months	Non-significant effect on cognitive function
SHEP	4736	−12/4 mmHg	BB ± Diu	4.5 years	Reduction of dementia 16% (non significant)
SYST-EUR	2418	−8.3/3.8 mmHg	CCB ± ACEI ± Diu	2 years	Reduction of dementia 50% (0 to 76%)
SYST-EUR 2 (open follow up)	2902	−7/3.2 mmHg	CCB ± ACEI ± Diu ± others	4 years	Reduction of dementia 55% (24%–73%)
PROGRESS	6105	−9/4 mmHg	ACEI ± Diu	4 years	Reduction of cognitive decline 19% (4%–32%) Reduction of dementia with recurrent stroke: 34% (3%–55%)
HOPE	9297	−3.8/2.8 mmHg	ACEI	4.5 years	Reduction of cognitive decline related to stroke 41% (6%–63%)
SCOPE	4964	−3.2/1.6 mmHg	ARB ± Diu	3.7 years	Reduction of dementia 7% (non significant)

[a]n = numbers of subjects at inclusion.
Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta blockers; CCB, calcium channel blockers; Diu, diuretics.

On the other hand, the Vascular Dementia project included in the SYST-EUR study (Forette et al 1998) demonstrated for the first time a reduction in the incidence of dementia with antihypertensive treatment. The study was conducted over 2 years in patients with isolated systolic hypertension who were at least 60 years old, randomized to receive the active treatment (n = 1238) or placebo (n = 1180). The active treatment was a calcium channel blocker (nitrendipine), possibly combined with an ACE-inhibitor (enalapril) and/or a diuretic (hydrochlorothiazide). The incidence of dementia was reduced by 50% in the active treatment group compared with the placebo group (p = 0.05). These findings were based on only 32 incident cases. Nevertheless, the incidence of AD was reduced as well as the incidence of vascular or mixed dementia.

After the double-blind, placebo-controlled period, all patients withdrawing from double-blind were invited to continue or start the study antihypertensive treatment for a median period of 2 years (SYST-EUR 2) (Forette et al 2002). The incidence of dementia was updated in patients treated since randomisation (4 years) compared to patients who were actively treated only since the end of the double blind period (2 years). After 4 years, there was still a significant difference in blood pressure between the two groups. Compared with the controls, long-term antihypertensive therapy reduced the incidence of dementia by 55% from 7.4 to 3.3 cases per 1000 patient-years (p < 0.001). Both types of dementia (AD and Vad or mixed dementia) were reduced.

Dementia and cognitive decline were secondary outcomes of the placebo-controlled trial PROGRESS (Tzourio et al 2003). Treatment consisted of perindopril possibly combined with indapamide or a matching placebo. After 4 years of follow up, active treatment significantly reduced the risk of cognitive decline by 19% in the whole population. The risk of dementia was reduced by 12% (95% CI = −8% to 28%) in the active treatment-group and significantly by 34% in patients with recurrent stroke. Similarly, in patients receiving the combination therapy, the risk of dementia was significantly reduced by 23% (95% CI = 0%–41%).

Data from the HOPE study (Bosch et al 2002) of 9297 patients with vascular disease or diabetes and an additional vascular risk factor followed over 4.5 years, have demonstrated a significant 41% reduction in cognitive decline associated with stroke in the ACE inhibitor group (ramipril 2.5–10 mg) compared to placebo.

Finally, the SCOPE study (Lithell et al 2003) has evaluated the effect of an angiotensin receptor blocker ± diuretic on the cognitive function of 4964 elderly (70–89 years) hypertensive patients without dementia. After 3.7 years of follow up, no significant difference between the two groups was found for cognitive function and dementia. However, this lack of benefit could probably be attributed to the fact that most patients in the placebo group were treated with other antihypertensive drugs for ethical reasons. Moreover, the cognitive evaluation was based solely on the MMSE (Mini Mental State Examination) which lacks the sensitivity to detect a

slight cognitive decline in subjects without dementia. Lastly, a recent analysis of SCOPE (Skoog et al 2005) has indicated a significant reduction of cognitive decline in the subgroup of subjects with already low cognitive function at baseline (MMSE score between 24 and 28), whereas no benefit was observed in people with normal cognitive function.

Some recent meta-analyses concerning these randomized, placebo-controlled studies were able to give a more complete picture of the effects of antihypertensive treatments on cognition. Some of them have supported a benefit of anti-hypertensive treatments for preventing dementia (Feigin et al 2005; Birkenhager and Staessen 2006) or cognitive disorders (Birns et al 2006).

Alternatively, the Cochrane review concluded that blood pressure reduction resulted in an 11% reduction in the relative risk of dementia in patients with no prior cerebrovascular disease, but this effect was not statistically significant (p = 0.38). Nevertheless, this review takes into account only 3 studies (SCOPE, SHEP, and SYST-EUR) which could minimize the effects of antihypertensive therapy (McGuiness et al 2006).

There are multiple underlying pathophysiological mechanisms that could give an explanation for the association between hypertension and dementia.

Data from histopathological studies indicate a major overlap between vascular lesions and AD (Arregui et al 1982; Victoroff et al 1995; Snowdon et al 1997). By promoting arteriosclerosis and lipohyalinosis of the small vessels, hypertension might be the origin of stroke and/or chronic hypoperfusion of the white matter, thus contributing to the early expression of a still subclinical AD. It has been shown that patients with high midlife systolic blood pressure (SBP) experience cognitive dysfunctions as well as increased volume of white matter hyperintensities in late life (Swan et al 1998a,b). A significant interaction between hypertension, ApoE ε4 allele and white matter lesions has been found (de Leeuw et al 2004). It is also pointed out that the progression of the white matter lesions is highly correlated with cognitive decline. Furthermore, longitudinal studies found an increased risk of AD in people with periventricular white matter lesions (Prinds et al 2004). In this way, a very recent study found that white matter hyperintensities on magnetic resonance imaging scan, were significantly associated with cognitive decline in MCI patients (mean follow-up = 3.8 ± 1.6 years) (Debette et al 2007). Moreover, antihypertensive therapy has been showed to reduce white matter lesions progression in a longitudinal study including patients with a history of stroke (Dufouil et al 2005a). In this way, such presence of cerebral white matter lesions could be an indication for early

neuroprotection. Microcirculation disorders and endothelial dysfunctions are also given as explanations for the cognitive impairment seen in hypertensive subjects. Hypertension is associated with degenerative changes of intracerebral capillaries and arterioles and ADis associated with lesions in the cerebral microvasculature (Perlmutter et al 1991). These vessel changes may compromise the function of the blood-brain barrier, leading to an increased vascular permeability and protein extravasation into the brain parenchyma, resulting in beta-amyloid accumulation (Hardy et al 1986). Likewise, hypertension and beta amyloid act on endothelial cells to produce an excess of free radicals suggesting that oxidative stress is involved in the mechanisms of both vascular disorders and AD. Finally, periods of hypotension, hypoperfusion and hypoxia, observed in hypertensive subjects, might contribute to cognitive deficits in AD patients via reduced cerebral perfusion causing ischemic neuronal lesions in vulnerable areas of the brain.

In summary, hypertension may impair cognitive functions and is related to the occurrence of not only vascular dementia but also AD. Randomized, placebo-controlled trials have demonstrated that blood pressure-reducing agents decrease the incidence of dementia in stroke patients (PROGRESS, HOPE) and in elderly patients with isolated systolic hypertension (SYST-EUR), but this was not found in SCOPE and SHEP.

In this context, the incidence of dementia should be a major outcome measure of future trials comparing different antihypertensive drugs.

Diabetus mellitus and cognitive decline

Type 2 diabetus mellitus (DM) is a common disease in the elderly affecting more than 10% of the elderly population in the US, and its prevalence increases with age (Harris 1998).

A possible relationship between cognitive decline and diabetes has been suggested since the discovery of insulin (Miles and Root 1922). A review of 33 longitudinal studies found that, in patients with type 1 diabetus mellitus, cognitive dysfunction was characterized by a slowing of mental speed and diminished mental flexibility, whereas learning and memory were spared (Brands et al 2005).

Several longitudinal studies have shown a relationship between type 2 DM and accelerated cognitive decline (Allen et al 2004). The results of the Atherosclerosis Risk In Communities study (ARIC) were of particular interest because of an adjustment used for confounding cardiovascular factors (Knopman et al 2001). In this study of 10,963 middle

aged people followed over 6 years, there was a significant association between type 2 DM and decline in sustained attention, psychomotor speed and logical reasoning as well as in verbal learning and recent memory. Moreover, in the same cohort, insulin resistance appeared to be a midlife risk factor for cognitive decline and dementia (Young et al 2006).

A review by Allen et al (2004) put forward several limitations of these large longitudinal studies: Their vulnerability to survivor bias, the importance of confounding factors, their failure to record the duration of DM and the difficulty in choosing and conducting appropriate psychometric tests. More recently, a longitudinal study (Luschinger et al 2007) including 918 participants (mean age = 75.9 years ± 6), with a mean follow-up of 6.1 ± 3.2 years per person, disclosed that DM was related to a higher risk of memory impairment (HR = 1.5; 95% CI = 1.0–2.2; p = 0.02 after adjusting for vascular risk factors). Globally, people with type 2 DM were at increased risk for developing cognitive impairment in comparison with the general population (Allen et al 2004).

Although type 2 DM is a well-established risk factor for stroke (Stegmayer and Asplund 1995), conflicting results have been reported about its association with dementia, especially AD. Cross sectional studies have suggested an association between type 2 DM and dementia (Janson et al 2004), but only longitudinal population-based studies can robustly asses the risk of developing dementia ascribable to DM.

Several studies have been designed with this aim and most of them have been included in a review by Biessels et al (Biessels et al 2006).

Four studies (Table 3) assessed the relationship between DM in midlife and dementia later in life. The Honolulu Asian Study initially failed to find a positive association between DM and Alzheimer Disease (Curb et al 1999). Subsequent follow-up surveys in the same cohort disclosed a different result (Peila et al 2002) which was consistent with neuro-pathological data: DM was associated with an increased risk for total dementia, AD, and VaD. This result was confirmed by the Japanese Adult Health Study (Yamada et al 2003). Similarly, 2 other long-term follow-up studies highlighted the link between DM and dementia (Schnaider Beeri et al 2004; Whitmer et al 2005). Nevertheless, these types of studies are particularly sensitive to survivor bias.

Studies in which DM is assessed late in life show a fairly consistent association between DM and dementia (Table 3) (Ott et al 1999; Luchsinger et al 2001; Hassing et al 2002; MacKnight et al 2002; Arvanitakis et al 2004; Xu et al 2004; Luchsinger et al 2005).

The conclusion of Biessels et al was that, overall, the incidence of dementia was increased by 50%–100% in people with DM relative to those without diabetes. The increased risk included both AD and VaD (Biessels et al 2006). Furthermore, a longitudinal study of 1177 subjects older than 75 years old, followed over 9 years, recently disclosed an association between borderline diabetes and dementia (1.67; 95% CI (1.04–2.67)) and AD (1.77; 95% CI (1.06–2.97)). This was independent of future development of DM, giving a great importance to the link between hyperglycemia and dementia (Xu et al 2007). Similarly, an association was found between glycosylated hemoglobin levels (HbA1c) and the risk of developing memory impairment or dementia in 1938 postmenopausal, osteoporotic women followed over 4 years. For every 1% increase in HbA1c, these women had a greater age-adjusted likelihood of developing mild cognitive impairment or dementia (OR = 1.40; 95% CI = 1.08–1.83) (Yaffe et al 2006).

One major modulatory factor in these studies was that DM was frequently associated with co-morbid conditions that are known to play a role in cognitive decline, such as hypertension and hypercholesterolemia. These co-morbid conditions could be important determinants of the increased risk of dementia in people with DM. Several studies provided results adjusted for cardiovascular disease. Two studies reported that adjusting for vascular risks factors did not change the results of univariate analysis (MacKnight et al 2002; Peila et al 2002) for all dementia subtypes. On the other hand, the Kungsholmen study found that systolic hypertension and diabetes combined to modify the relative risk of dementia when considering AD and VaD (Xu et al 2004).

Furthermore, ApoE genotype may be an important confounding factor. Two studies found out that Apo E ε4 genotype combined with DM doubled the relative risk of dementia compared with DM alone (Peila et al 2002; Xu et al 2004). More recently, results of the Framingham Study pointed out that DM did not increase the risk of AD overall. After adjusting for the ApoE ε4 allele or elevated plasma homocysteine levels, however DM appeared as a risk factor for AD (Akomolafe et al 2006). DM, then, was a strong independent risk factor for AD among people at a relatively lower initial risk for developing the disease. In conclusion, longitudinal studies now provide evidence that DM is a risk factor for cognitive decline and dementia (AD and VaD), but the pathophysiological mechanisms underlying this association are still unknown.

Brain autopsy studies may provide information about these underlying mechanisms. First, DM is associated with brain infarcts and pathological changes in the cerebral

Table 3 Risk of incident dementia in patients with Diabetus mellitus in longitudinal studies

Dementia	n[a]	Follow-up (years)	Age[b]	Outcomes
Any dementia				
Peila, 2002	3508	2.9	77	Positive correlation. RR (95% CI) = 1.5 (1.0–2.2)
				Adjusted RR[c] (95% CI) = 1.5 (1.0–2.2)
Whitmer 2005	8845	35	42	Positive correlation. RR (95% CI) = 1.5 (1.2–1.8)
Schneider Berri 2004	10059	35	45	Positive correlation. RR (95% CI) = 2.8 (1.4–5.7)
Ott 1999	6370	2.1	69	Positive correlation. RR (95% CI) = 1.9 (1.3–2.8)
Xu 2004	1301	4.7	81	Positive correlation. RR (95% CI) = 1.5 (1.1–2.1)
				Adjusted RR (95% CI) = 1.5 (1.0–2.1)
Curb 1999	3774	25	53	Non significant correlation. RR (95% CI) = 1.1 (0.7–1.8)
Hassing 2002	702	6	84	Non significant correlation. Adjusted RR (95% CI) = 1.2 (0.8–1.7)
MacKnight 2002	9131	5	74	Non significant correlation. RR (95% CI) = 1.2 (0.9–1.7)
				Adjusted RR (95% CI) = 1.3 (0.9–1.8)
AD				
Peila 2002	3508	2.9	77	Positive correlation. RR (95% CI) = 1.7 (1.0–2.8)
Yamada 2003	1774	30	43	Positive correlation. RR = 4.4
Akomolafe 2006	2210	12.7	70	Positive correlation. Adjusted RR (95% CI) = 2.98 (1.06–8.9)
Ott 1999	6370	2.1	69	Positive correlation. RR (95% CI) = 1.9 (1.2–3.1)
Luchsinger 2001	1799	4.3	76	Positive correlation. RR (95% CI) = 2.4 (1.8–3.2)
				Adjusted RR (95% CI) = 2.0 (1.4–2.9)
Arvanitakis 2004	847	5.5	75	Positive correlation. RR (95% CI) = 1.7 (1.1–2.5)
Xu 2004	1301	4.7	81	No significant correlation. RR (95% CI) = 1.3 (0.8–1.9)
				Adjusted RR (95% CI) = 1.3 (0.9–2.1)
Luchsinger 2005	1786	5.5	76	Positive correlation. RR (95% CI) = 2.4 (1.8–3.2)
				Adjusted RR (95% CI) = 2.0 (1.4–2.9)
Curb 1999	3774	25	53	Non significant correlation. RR (95% CI) = 1.0 (0.5–2)
Hassing 2002	702	6	84	Non significant correlation. Adjusted RR (95% CI) = 0.8 (0.5–1.5)
MacKnight 2002	9131	5	74	Non significant correlation. RR (95% CI) = 1.2 (0.8–1.8)
				Adjusted RR (95% CI) = 1.3 (0.8–2.0)
VaD				
Peila 2002	3508	2.9	77	Positive correlation
				RR (95% CI) = 2.2 (1.1–4.7)
				Adjusted RR (95% CI) = 2.3 (1.1–5.0)
Yamada 2003	1774	30	43	Positive correlation. RR = 1.3 (p = 0.06)
Ott 1999	6370	2.1	69	Positive correlation. RR (95% CI) = 2.0 (1.7–5.6)
Luchsinger, 2001	1799	4.3	76	Positive correlation. RR (95% CI) = 4.2 (2.2–8.3)
				Adjusted RR (95% CI) = 3.4 (1.7–6.9)
Hassing 2002	702	6	84	Positive correlation. Adjusted RR (95% CI) = 2.5 (1.4–4.8)
MacKnight, 2002	9131	5	74	Positive correlation. RR (95% CI) = 2.2 (1.3–3.6)
				Adjusted RR (95% CI) = 2.0 (1.2–3.6)
Xu 2004	1301	4.7	81	Positive correlation. RR (95% CI) = 2.2 (1.1–5.0)
				Adjusted RR (95% CI) = 2.6 (1.2–6.1)
Curb 1999	3774	25	53	Non significant correlation. RR (95% CI) = 1.5 (0.8–2.8)

[a] = numbers of subjects at inclusion.
[b] at baseline.
[c] RR adjusted for vascular risk factors.
Abbreviations: AD, Alzheimer's disease; RR, relative risk; VaD, vascular dementia.

microvasculature including amyloid angiopathy (Peila et al 2002). Furthermore, 216 autopsies from the Honolulu-Asia Aging Study showed that participants with type 2 DM and the ApoE ε4 allele had a higher number of neuritic plaques in the hippocampus and neurofibrillary tangles in the cortex and hippocampus (Peila et al 2002*).

Three main pathological mechanisms are proposed to explain the link between DM and dementia (Biessels et al 2006; Qiu and Folstein 2006).

First, DM may lead to dementia through ischemic cerebrovascular disease. DM, especially in elderly people, often develops in a cluster of vascular risk factors which can constitute the metabolic syndrome, which is already known to be predictor of cerebrovascular disease (Kalmijn et al 2000; Yaffe et al 2004).

Second, hyperglycemia can have a direct toxic effect on neurons by causing oxidative stress and the accumulation of advanced glycation end products, a process which can directly affect brain tissue, and also lead to microvascular changes (Kumari et al 2000). Lastly, insulin and insulin-degrading enzymes could play an important role in amyloid metabolism (Qiu and Folstein 2006*).* Insulin resistance, at least in

the early stages of DM, is associated with compensatory hyperinsulinemia and hyperinsulinemia even in the absence of diabetes and is strongly associated with AD (Luschinger et al 2004). Insulin receptors are distributed with particular abundance in the hippocampus and cortex (Bondy and Cheng 2004). Insulin appears to stimulate amyloid β secretion and inhibits the extracellular degradation of amyloid β (Gasparini and Xu 2003) by competing for insulin degrading enzyme which may be deficient (Qiu and Folstein 2006).

These data offer avenues to the prevention of dementia.

Considering longitudinal studies, strict control of DM seems to be an important goal in order to prevent subsequent dementia. However, the impact of intensive glucose-lowering treatments on the incidence of dementia is still unknown. The ADVANCE study will give some answers, as dementia is being considered as a secondary outcome (Rationale and design of the ADVANCE Study 2001).

In consideration of the underlying pathological mechanisms, researches are being conducted with treatments for insulin resistance such as Rosiglitazone® (Hsueh 2006) and gene therapy targeting insulin degrading enzyme (Qiu and Folstein 2006).

Adiposity, metabolic syndrome and cognitive decline

Obesity affects 25%–30% of adults in industrialised countries (Rennie and Jebb 2005). In the past, studies reported that a low body mass index (BMI) was a risk factor for dementia (White et al 1996). However, these observations were based on cross-sectional studies, and with dementia, previously obese patients may lose up to 50% of their predementia body weight (Wang 2002). As rewieved by Gorospe and Dave (2007) and Gustafson (2006), epidemiological studies of increased BMI as a risk factor for dementia have shown conflicting results. Nevertheless, the studies with statistically significant results had larger sample sizes, longer follow-up periods and younger participants at baseline (Gorospe and Dave 2007). Thus, a 27-year longitudinal, population-based study of 10,276 subjects showed that people with a high BMI had a significant higher risk of dementia (HR = 1.74; 95% CI = 1.35–1.24) after adjusting with vascular comorbidities and socioeconomic status (Whitmer et al 2005). Similarly, a study, that followed participants over 18 years, concluded that for every 1.0 increase in BMI at 70 years old, AD risk increased by 36% after adjusting with vascular confounding factors (Gustafson et al 2003). Two other well-designed and powerful studies found similar results (Kalmijn et al 2000; Rosengreen et al 2005). More recently a 36-year longitudinal study of a large cohort (n = 10,136) found that people who were obese at midlife (BMI > 30) had a 3.10-fold increased risk of AD (HR = 3.10; 95% CI = 2.19–4.38) and a 5-fold increased in risk of Vad (HR = 5.01; 95% CI = 2.98–8.43), while those who were overweight (BMI > 25) had a 2-fold increased risk of AD and Vad (HR = 2.09; 95% CI = 1.69–2.60 for Alzheimer disease and HR = 1.95; 95% CI = 1.29–2.96 for vascular dementia), independent of vascular comorbidities (Whitmer 2007). All these results suggest that an increased BMI is likely to be an important risk factor for dementia, even though there are no published reports that take into account the role of ApoE ε4.

As for DM, excess adiposity could increase the risk of dementia by a vascular pathway (Gustafson 2006). Furthermore, adipose tissue secretes adipocytokines such as leptin which may be involved in neurodegenerative pathways (Benoit et al 2004).

For now, then, an elevated BMI in middle age appears to be an important risk factor for dementia, and the maintenance of a normal weight could be a worthwhile intervention for the prevention of dementia (Gorospe and Dave 2007).

The metabolic syndrome is a cluster of cardiovascular risk factors including obesity. In most studies, it is defined using the National Education Program Third Adult Treatment Panel Guide (Expert Panel 2001). It has been proven to be associated with an increased risk of developing cardiovascular disease (Expert Panel 2001). It is also an independent risk factor for silent brain infarctions on magnetic resonance Imaging in middle age, healthy people (Kwon et al 2006).

Few studies have considered the components of the metabolic syndrome as a whole, whereas several individual components have been linked to risk of developing dementia and cognitive impairment. Furthermore, it is unclear whether the metabolic syndrome has a higher predictive value for the development of dementia than the sum of its individual components (Yaffe 2007).

Some transversal studies have shown a link between metabolic syndrome and cognitive impairment. A population-based study of 959 subjects (range 69 and 78 years old), found that metabolic syndrome was significantly associated with AD (OR = 2.46; 95% CI = 1.27–4.78) (Vanhanen et al 2006). In addition, a cross-sectional study of the 1183 participants of the Longitudinal Aging Study Amsterdam showed that metabolic syndrome was associated to poorer cognitive functioning (Dik et al 2007). Lastly, a very recent case control study, showed that the metabolic syndrome was associated with AD (OR = 3.2, 95% CI = 1.2–8.4, p = 0.02) (Razay et al 2007). This association was strengthened when the hypertension component was excluded.

A few studies with a longitudinal design have been conducted. First, in the Honolulu-Asia Aging study, the long term association between clustered metabolic cardiovascular risk factors in the middle age and the risk of dementia in old age was assessed. Z scores were calculated for 7 cardiovascular risk factors. The z-score sum was higher in subjects with dementia than in subjects without dementia (0.74 versus –0.06 respectively; p = 0.008). Per SD increase in the z-score sum, the risk of dementia was increased by 5% (RR = 1.05, 95% CI = 1.02–1.09). Considering the subtypes of dementia, significance was maintained only for vascular dementia (RR = 1.11, 95% CI = 1.05–1.18) (Kalmijn et al 2000). Furthermore, the Health Aging and Body Composition study assessed the cognitive abilities of 2,949 elderly subjects at baseline, 3 and 5 years by the Modified MMSE, and found that metabolic syndrome was associated with a greater likelihood of cognitive decline (OR = 1.21; 95% CI = 1.03–1.43) (Yaffe et al 2004). Similarly, the Sacramento Area Latino Study of Aging enrolled 1624 elderly Latinos subjects, who were cognitively evaluated yearly over three years by the Modified MMSE and the Delayed Word-List recall from the Spanish – English verbal learning test. Subjects with metabolic syndrome scored lower than those without metabolic syndrome on the Modified MMSE (p = 0.04), but the difference between the two groups on the Delayed Word – List recall was no longer significant (p = 0.18) (Yaffe et al 2007). These two last studies also found that the composite measure of metabolic syndrome was a greater risk for cognitive decline than its individual components.

Thus, metabolic syndrome seems to be a risk factor (Yaffe et al 2007) for cognitive decline, even though further long term prospective studies have to be conducted.

Mechanisms linking metabolic syndrome to cognition remain speculative (Yaffe et al 2007). An association between metabolic syndrome and cognitive decline could be explained by vascular disease. As previously studied in diabetus mellitus, insulin resistance seems to play a key role. This association could also be, a least partly, mediated by inflammation (Yaffe et al 2007). Lastly, central adiposity is a core feature of metabolic syndrome, so adipocytokines could also play a role (Benoit et al 2004).

Cholesterol, statins, and cognitive decline

Several epidemiological studies have assessed the link between cholesterol levels and dementia, especially AD (Panza et al 2006). Cross-sectional studies provided very conflicting results. A Finnish study of 980 people between 69 and 78 years old, found an association between low serum total cholesterol (TC) and AD, independent of ApoE genotype (OR = 0.69; 95% CI = 0.52–0.92, p = 0.011) (Kuusisto et al 1997). Another cross-sectional study of 1449 elderly subjects showed that decreased TC had an inverse association with the incidence of AD, independent of ApoE genotype (RR = 1.6; 95% CI = 1.0–2.7) (Romas et al 1999). The study of Evans et al found that high TC was associated with AD only in the group which lacked an ApoE 4 allele (OR = 1.018; p = 0.027) (Evans et al 2000). Lastly, the three City Study, a population-based cohort of 9,294 subjects selected from electoral rolls, showed that higher TC (>6.20 mmol/L) was associated with increased odds of dementia (p = 0.07) but not AD (Dufouil et al 2005 b).

Several more poverfull longitudinal studies have assessed the increased risk of dementia ascribable to high cholesterol levels. Their results are summarized in the Table 4.

Two studies showed an epidemiologic link between high cholesterol level and Vad (Moroney et al 1999; Reitz et al 2004). Nevertheless, the results of studies which have investigated the relationship between cholesterol levels and risk of AD or any dementia are conflicting (Table 4). Globally, when cholesterol level was assessed in the middle age, a positive association with AD was found (Notolka et al 1998; Kivipelto et al 2002) with the exception of the Honolulu Asia aging Study where a cluster of vascular risk factors was considered (Kalmijn et al 2000). On the other hand, when cholesterol levels were considered later in life, the association with AD appeared not to be significant (Tan et al 2003; Reitz et al 2004). Furthermore, very recently, Mielke et al (2005), examined the association between cholesterol level and dementia in a population-based cohort of 70-year-old subjects followed over 18 years. Increasing TC levels at ages 70, 75, and 79 were associated with a reduced risk of dementia between age 79 and 88 (Table 4). The same discrepancy was found for studies investigating the relationship between cholesterol and MCI. In a the study by Solfrizzi et al (Solfrizzi et al 2004b) of 2936 subjects between 65 and 84 years old followed over 3.5 years, multivariate analysis suggested that higher levels of serum TC had a trend for protective effect.Conversly, Kivipelto et al found that elevated serum TC levels (>6.5 mmol/L) in middle age increased the risk for MCI (OR = 2.1; 95% CI = 1.2–3.0) with an average follow-up of 21 years (Kivipelto et al 2001).

These surprising results may be explained by the timing of TC measurements in relation to age and clinical onset of dementia. Indeed, these different findings may be due to the fact that total cholesterol decreases with age

Table 4 Association between cholesterol level and dementiain longitudinal studies

Reference	nª (baseline)	Age at baseline (years)	Follow-up (years)	Outcomes
Notkola 1998	444	40–59	30	Positive correlation between TC and AD RR (95% CI = 3.1(1.2–8.5)
Kivipelto 2002	1449	53	21	Positive correlation between TC and AD RR (95% CI) = 2.8 (1.2–6.7)
Moroney 1999	111	75	7	Positive correlation between LDL-C and AD RR (95% CI) = 3.1 (1.5–6.1)
Kalmijn 2000	8006	52.7	26	Non significant correlation between TC and any dementia RR (95% CI) = 1.10 (0.95–1.26)
Tan 2003	1026	76	8	Non significant correlation between TC and AD RR (95% CI) = 0.97 (0.90–1.05)
Reitz 2004	2820	78	4.8	Non significant between LDL-C and AD RR (95% CI) = 0.48 (0.26–0.86)
Mielke 2005	392	70	18	Negative correlation between TC and any dementia RR (95% CI) = 0.31 (0.11–0.85)

ªn = numbers of subjects at inclusion.

Abbreviations: AD, Alzheimer's disease; LDL-C, LDL-cholesterol; RR, relative risk; TC, total cholesterol.

(Postglione et al 1989) and insufficient nutrition, and that, several years before dementia, blood pressure and BMI begin to decline, possibly as a result of the ongoing AD pathology, suggesting that the same may be true for TC (Panza et al 2006). Decreased cholesterol might be an effect rather than a cause of dementia.

The few studies that have investigated the influence of ApoE genotype on the relationship between plasma lipid levels and dementia risk has given conflicting results (Notolka et al 1998; Evans et al 2000; Kivipelto et al 2002). Nevertheless, TC levels may be influenced by ApoE genotype (Notolka et al 1998; Evans et al 2000).

The pathophysiological mechanisms linking cholesterol metabolism to AD are still unknown (Wolozin 2004; Shobab et al 2005; Panza et al 2006). Cholesterol influences the activity of the enzymes involved in the metabolism of the amyloid precursor protein and in the production of Aβ. Some in vitro studies have shown that a high cholesterol level results in reduced production of soluble amyloid precursor protein (Racchi et al 1997; Simons et al 1998) and that cholesterol modulates α-secretease cleavage of amyloid precursor protein production (Bodovitz and Klein 1996). This implicates the amyloid cascade leading to neuronal death. The mechanism by wich cholesterol affects Aβ production and metabolism is not fully understood, a change in membrane properties has been suggested (Shobab et al 2005). However, cholesterol could have several beneficial effects as well. Cholesterol forms an essential component of cell membranes and has a crucial role in neuronal plasticity (Pfrieger 2003). In addition, in vitro studies have suggested that cholesterol acts as an antioxidant and, therefore, has a protective role in dementia pathogenesis.

The relationship between cholesterol and AD is not clear and at times, is even, contradictory. Epidemiological studies have shown mixed results depending on if TC was assessed in middle age or later in life. A high cholesterol level in middle age seems to be a risk factor for AD, but this positive relationship is not seen in late life (Panza et al 2006). Furthermore, pathophysiological data are also confusing. Given that the timing of exposure may be critical, more studies with long-term follow-up and serial assessments of TC are needed to clarify the causal relationship between cholesterol and dementia. Lastly, some studies have been performed to asses the link between other lipids and cognitive decline. First, the 24S-hydroxycholesterol, an oxidized metabolite of cholesterol which crosses the blood-brain-barrier, reflects brain cholesterol homeostasis more than plasma TC (Shobab et al 2005). During the early stages of AD, 24S-hydroxycholesterol concentrations are high in cerebro- spinal fluid and in peripherical circulation potentially reflecting increased cholesterol turnover in the brain (Lutjohann et al 2000; Papassotiropoulos et al 2000; Kolsh et al 2004). However, in later stages of AD, concentrations of 24S-hydroxycholesterol fall, suggesting that there is a low rate of cholesterol transport as the disease progresses (Kolsh et al 2004). Thus, 24S-hydroxycholesterol might be a biochemical marker of worsening cognitive function in AD. Second, lipoprotein (a) (Lp(a)) is a LDL-like particle. High Lp(a) levels are associated with atherosclerosis (Milionis et al 2000). Some studies provide evidence that higher Lp(a) level could be linked with AD (Mooser et al 2000; Solfrizzi et al 2002a). Nevertheless, larger clinical studies involving MCI patients and longitudinal studies of AD patients are needed to confirm the relationship between Lp(a) concentrations and dementia.

Statins are a first line treatment for hypercholesterolemia and secondary prevention of cardio-vascular disease. A large observational study in three hospitals in the US found that the prevalence of probable AD in the cohort taking statins was 60%–73% (p < 0.001) lower than in the total patient population or when compared with patients taking other medications typically used in the treatment of hypertension or cardio-vascular disease (Wolozin et al 2000). This was confirmed by other cross-sectional studies (Table 5) (Jick et al 2000; Hajjar et al 2002; Zamrini et al 2004; Dufouil et al 2005b). Nevertheless, all these studies were limited by an important indication bias since statins may have been prescribed less frequently in people with dementia. Conversely, the Cache County Study included 5092 elderly subjects, followed over 3 years, and found no association between statin use and subsequent onset of dementia or AD (Zandi et al 2005). However, in a study with longer follow-up (7 years) which included 344 elderly subjects (mean age = 74), statin use was associated with a slight reduction in cognitive decline as assessed by the Modified MMSE (Bernick et al 2005).

On the other hand, 2 large randomized studies do not support a protective effect of statins against dementia. The PROSPER study assessing the benefits of pravastatine versus placebo in 70- to 82-year-old subjects followed over 3 years, did not find any significant effects of this lipid lowering agent on cognitive performance (Shepherd et al 2002). Nevertheless, this result could be explained by an insufficient length of follow-up. Furthermore, cognitive decline was assessed as a secondary endpoint in the Heart Protection Study, which included 20,536 patients, randomized to receive either 40 mg daily of simvastatin or a matching placebo. No statistical difference was found, but dementia was assessed by a phone interview, which may have been an important limitation (Heart Protection Study Collaborative Group 2002).

Interstingly, a recent pilot double blinded study of 63 AD subjects compared atorvastatine versus placebo, and found a beneficial effect of the statin at 6 months as measured by the Alzheimer's Disease Assessment Scale-cognitive Subscale (p < 0.03) and a trend towards a significant benefit at 12 months (p = 0.055) (Sparks et al 2005). In this context longer trials testing statins on AD patients are ongoing.

All studies concerning statins and cognitive decline have a pathophysiological rationale. Statins inhibits HMG-CoA reductase, a key enzyme in the synthesis of cholesterol. Even though statins could be protective due to their cholesterol-lowering effects, and their reduction of atherosclerotic plaque formation, it has been suggested that statins could have a more specific effect. Indeed, simvastatin has been shown to reduce the levels of Aβ 42 and Aβ 40 in vitro and in the brain of guinea pigs (Fassbender et al 2001). Moreover statins show a broad range of functions, such antioxidant activity, immunomodulation and regulation of inflammatory processes which could prevent neuronal death.

The relationship between cholesterol and dementia varies, depending on when the cholesterol is measured over the life course. Midlife high cholesterol level appears to be a risk factor for dementia, especially AD. Statins and AD are an attractive avenue of research, considering the putative preventive or curative role of statins. Further long-term, placebo controlled trials need to be conducted.

Atrial fibrillation and cognitive decline

Recently, there has been increasing evidence that AF may contribute to the development of cognitive dysfunction. Most of the data have been provided by observational studies.

First, in the Rotterdam study of 6584 subjects, a positive association was found between AF and dementia (OR = 2.3, 95% CI = 1.4–3.7) or impaired cognitive functions (OR = 1.7, 95% CI = 1.2–2.5). The strongest association was found not for Vad but rather for AD with cerebrovascular disease (OR = 4.1, 95% CI = 1.7–9.7). An association was also present between AF and "pure" AD (OR = 1.8; 95% CI = 1.7–9.7) (Ott et al 1997).

Similarly, other cross-sectional studies have shown that AF is associated with cognitive dysfunction, independent of stroke or other cardiovascular risk factors. For example, a study by Kilander et al of 952 men between 69 and 75 years old found that the 44 men with AF had poorer cognitive functions when compared to those without AF as assessed by the MMSE and the Trail making test, independent of stroke (Kilander et al 1998b). This was confirmed by a case-control study, which provided a complete cognitive assessment (O'Connell et al 1998) and another cross-sectional study (Sabatini et al 2000).

Very recent longitudinal studies have assessed the link between AF and dementia. First, a community-based cohort study (Miyasaka et al 2007) enroled 2837 subjects (mean age 71 ± 15 years) who were diagnosed with AF for the first time and followed them for a median timeof 4.6 years, found a high Kaplan-Meier cumulative rate of dementia: 22.5 per 1000 person-years whereas in the general population, the incidence of dementia was 6.8 per 1000 person-years (Edland et al 2002).

Similarly, the impact of AF on the conversion to dementia from a normal cognitive status (n = 431) or mild cognitive

Table 5 Association between statin use and dementia or cognitive decline

Reference	n[a]	Age (years)	Population	Type of study	Outcomes
Jick 2000	1364	>50	General population	Cross sectionnal	Association between statin and decreased risk of AD.
					OR (95% CI) = 0.29 (0.13–0.63)
Hajjar 2002	655	79	Elderly subjects	Cross sectionnal	Association between statin and decreased risk of dementia.
					OR (95% CI) = 0.23 (0.1–0.56)
					Association between statin and decreased risk of AD.
					OR (95% CI) = 0.37 (0.19–0.74)
Zamrini 2004	3397	70	Elderly subjects	Cross sectionnal	Association between statin and decreased risk of AD.
					OR (95% CI) = 0.61 (0.42–0.87)
Dufouil-b 2005	8574	74	General population	Cross sectionnal	Association between statin and decreased risk of AD.
					OR (95% CI) = 0.56 (0.33–0.94)
Bernick 2005	334	74	Elderly subjects	Longitudinal (F up = 7 years)	Association between statin and slower cognitive decline
Masse 2005	342	73.5	AD	Longitudinal (F up = 34 months)	Association between statin use and slower cognitive decline
Zandi 2005	5092	>65	Elderly subjects	Longitudinal (F up = 3 years)	No correlation between statin use and dementia
					OR (95% CI) = 1.19(0.53–2.34)
					No correlation between statin use and AD
Rea 2005	2798	>65 years	Elderly subjects with never use of lipid-lowering agents	Longitudinal (F up = 15,030 person – years)	No correlation between statin use and dementia HR (95% CI) = 1.08 (0.77–1.52)
HPS	20536	40–80	High CV risk	Randomized Controlled trial (F up = 5 years)	No correlation between statin use and cognitive function
PROSPER	5804	70–82	High CV risk	Randomized controlled trial (F up = 3.2 years)	No correlation between statin use and cognitive function

[a]n = numbers of subjects at inclusion.
Abbreviations: AD, Alzheimer's disease; CV, Cardiovascular; F up, follow-up; HR, hazard ratio; OR, odds ratio; VaD, vascular dementia.

impairment (MCI) (n = 180), was studied in elderly patients, followed over an average of 4 and 3 years for subjects with normal cognitive status and MCI, respectively. AF was significantly associated with conversion to dementia (HR = 4.63, 95% CI = 1.72–12.46) in the MCI group, but not in the cognitively normal group (HR = 1.10; 95% CI = 0.40–3.03) (Forti et al 2007).

There are multiple possible mechanisms explaining the association between AF and risk of dementia. Thromboembolic damage and cerebral hypo perfusion due to fluctuations in the cardiac output are involved (Sabatini et al 2000). Cerebrovascular disease is acknowledged to often coexist and overlap with AD and silent micro infarcts may markedly contribute to AD development (Kalaria 2002). Therefore, it is possible that the brain damage as

a result of AF plays a significant role in the onset of AD because it brings neuronal function below a threshold where clinical symptoms begin to appear. Furthermore, experimental studies emphasises that ischemic insults or cerebrovascular insufficiency lead to increased expression of amyloid precursor protein which leads to the formation of classic AD neurodegenerative lesions (Kalaria 2000; de la Torre 2006).

To conclude, there is some evidence that AF could be associated with AD. But there are not enough longitudinal studies. Anticoagulation is the gold standard for treatment of AF in order to prevent stroke. Nevertheless, the ability of anticoagulation therapy to prevent or postpone dementia in cases of AD has not been studied yet. Aspirin is sometime an alternative therapy for AF when

anticoagulation can not be used. A longitudinal study (Nilsson et al 2003) of 702 elderly people found that those who used high doses aspirin had a significantly lower prevalence of AD than those who did not use aspirin, but Kang et al did not showed any benefit in prevention of cognitive decline for the 6377 women, included in the Women's health study, after a 9.6 years follow-up (Kang et al 2007).

Smoking and cognitive decline

First, results from case-control studies have suggested that smoking could protect against AD (Graves et al 1991) supporting a neuroprotective effect of the nicotine in cigarette smoke. On the other hand, smoking is a risk factor for atherosclerosis, cerebrovascular accidents and could cause vascular dementia (Shinton and Beevers 1989).

Recent prospective studies on cohorts without dementia suggest that smokers have a significantly increased risk of dementia, including AD (Ott et al 1998; Launer et al 1999; Merchant et al 1999). The results of the Honolulu-Asia Aging Study (Tyas et al 2003) are of particular interest because of data collected about the amount of smoking, neuropathologic data and the long follow-up period. The association between midlife smoking and late-life dementia was assessed in 3734 Japanese-American men. Adjusting for age, education, and Apo E genotype, the risk of AD in smokers increased with pack-years of smoking at both medium (OR = 2.18; 95% CI = 1.07–4.69) and heavy (OR = 2.40; 85% CI = 1.16–5.17) smoking levels. Neuropathologic data were available for 218 men and in an autopsied sub-sample, the number of neuritic plaques increased with smoking level.

The effects of smoking on global cognitive function in elderly subjects without dementia were also assessed in a multi-center cohort including 9,209 subjects, 65 years old and over, who were followed up 2.3 years (Ott et al 2004). The average yearly decline in MMSE score was compared among groups, adjusting for age, sex, baseline MMSE, education, and stroke. The adjusted decline of former smokers was 0.03 points greater than subjects who never smoked. For current smokers, this decline was 0.13 point greater than subjects who never smoked (p < 0.001), suggesting that smoking may accelerate cognitive decline in elderly people without dementia.

Finally, a recent meta-analysis (Anstey et al 2007), of 19 prospective studies with at least a 12-month follow-up period concluded that smokers at baseline, had risks of 1.79 (95% CI = 1.43–2.23) for incident AD, 1.78 (95% CI = 1.28–2.47) for incident Vad and 1.27 (95% CI = 1.02–1.60) for any dementia, relative to subjects who had never smoked. The authors concluded that elderly smokers have an increased risk of dementia and cognitive decline.

Smoking could affect cognition through various mechanisms. First, chronic tobacco exposure causes atherosclerosis which increase the risk of silent brain infarctions (Cruickshank et al 1989). Smoking may also be linked to AD by mechanisms leading to plaque formation. Smokers may experience greater oxidative stress than non-smokers and increased oxidative stress may cause neuronal degeneration (Markesbery 1997). Nevertheless, these underlying mechanisms are insufficiently understood and require further experimental studies.

Atherosclerosis, coronary artery disease, heart failure, and cognitive decline

Atherosclerosis is believed to be involved in development of dementia and its major subtypes, vascular dementia and AD (de la Torre 2004). The association may be mediated by cerebrovascular disease or result from brain hypo perfusion.

Indeed, there is some epidemiologic evidence for a relation between atherosclerosis and dementia risk. According to a cross-sectional report from the Rotterdam study (Hofman et al 1997), a strong association was found between atherosclerosis and dementia, especially AD (OR = 3.0; 95% CI = 1.5–3.2). Furthermore, a very recent longitudinal study, including 6647 participants in the Rotterdam study with a mean follow-up of 9 years, disclosed that atherosclerosis (common carotid intima media thickness, carotid plaques, peripheral artery disease), predominantly carotid atherosclerosis, was associated with an increased risk for any type of dementia (van Oijen et al 2007). In the same way, a significant relationship between aterial stiffness and cognitive impairment has been showed (Hanon et al 2005a). This association has been recently confirmed in a longitudinal study (Waldstein et al 2008).

These results suggest an independent relationship between atherosclerosis and AD (Casserly and Topol 2004). Indeed, the two diseases share common risks factors and pathophysiological elements. Hypercholesterolemia, oxydative stress and inflammation have emerged as the dominant mechanisms in the development of both atherosclerosis and AD (Steinberg 2002). In the same way, the ε4 allele of the Apo E gene represents a genetic risk factor for atherosclerosis (Wilson et al 1996) and the most important

genetic risk factor for sporadic AD in the general population (Farrer et al 1997). Furthermore, vascular endothelial cells could play a role in the secretion of the precursor substrate of the neurotoxic A beta-protein leading to the destruction of cortical neurons in AD (Vagnucci and Li 2003). Likewise, endothelial lesions in AD have been related to the location and number of senile plaques (Kalaria and Hedera 1996) and it has been reported that beta amyloid could interact with vascular endothelial cells to produce an excess of free radicals (Thomas et al 1996).

Some investigations have shown the importance of inflammation in the pathogenesis of AD (Akiyama et al 2000). Fibrillar Aβ has been shown to directly activate the complement pathway in vitro. Furthermore, all the cytokines and chemokines seem to be upregulated in AD. The migcroglia seems to be the most important cell mediator in the AD brain. Microglia cluster at sites of Aβ deposition and could play a role through the processing of APP and Aβ or in the conversion of nonfibrillar Aβ into amyloid fibrils.

In this way findings from observational studies have supported a treatment benefit of low dose aspirin and non steroidal anti-inflammatory drugs in AD (Etminam et al 2003). However, results from a randomized study of the effects of a selective COX-2 inhibitor on disease progression have been negative (Reines et al 2004).

Moreover, coronary heart disease, one the major complications of atherosclerosis, has been associated with cognitive decline. In the cardiovascular health study cohort, including 3602 subjects followed up 5.4 years, the incidence of dementia was higher in those with prevalent coronary artery disease. The rate of AD was 34.4 per 1000 person-years for subjects with coronary heart disease versus 22.2 per 1000 person-years without coronary heart disease (HR = 1.3; 95% CI = 1.0–1.7) (Newman et al 2005). Furthermore, a recent anatomopathological study disclosed that, coronary artery disease was associated with AD's neuropathological hallmarks in APoE 4 carriers (Beeri et al 2006).

Congestive heart failure may also be an atherosclerosis' complication and is a common medical condition among elderly people (Cowie et al 1997). Some studies have assessed the link between heart failure and cognitive impairment. It has been observed a higher prevalence of heart failure in people with cognitive disorders and the risk of cognitive impairment was 1.96-fold greater in subjects with chronic heart failure (CHF) (OR = 1.96; 95% CI = 1.07–3.58) compared to those without CHF (Cacciatore et al 1998). These results have been confirmed in a large study including 13,635 patients showing an increased prevalence of cognitive disorders among patients with heart failure (Zuccala et al 2001). Particularly, low blood pressure was significantly associated with cognitive impairment in patients with heart failure (Zuccala et al 2001) suggesting the role of low cardiac output in cognitive dysfunction. Furthermore, in a 10-year prospective study, including 650 elderly people, cognitive decline was predicted by various vascular factors including heart failure (RR = 1.8) (Tilvis et al 2004).

Few studies have assessed a putative association between chronic heart failure and dementia.

A recent study addressed prospectively the relationship between heart failure and dementia among 1301 individuals 75 years or older, with cognitive evaluation 3 times over a 9-year period (Qiu et al 2006). Heart failure was associated with a multi-adjusted HR of 1.84 (95% CI: 1.35–2.51) for dementia and 1.80 (95% CI: 1.25–2.61) for AD. In this trial, heart failure and low diastolic blood pressure (<70 mmHG) had an additive effect on the risk for developing dementia (HR = 3.07; 95% CI: 1.64–5.61). The potential biological pathways linking heart failure to cognitive impairment, dementia and AD are still unknown. First, heart failure is a risk factor for multiple cerebral emboli which could lead to cognitive impairment (Pullicino and Hart 2001). Second, low cardiac output may result in decreased cerebral perfusion which could play a part in the neurodegenerative process (Pullicino and Hart 2001). Prospective studies, concerning the effect of cardiac heart failure treatment need to be conducted. In the study by Qiu et al it is suggested that the use of antihypertensive drugs (83% of which were diuretics) could reduce the risk of dementia related to heart failure (Qiu et al 2006) and ACE inhibitors have been suggested to improve cognitive performance in patients with heart failure (Zuccala et al 2005). Nevertheless, some long-term prospective studies have to test this hypothesis

Conclusion

Vascular risk factors may impair cognitive functions and are related to the occurrence of not only Vad but also AD. This level of evidence for these associations is highest for hypertension and DM, especially when these factors are assessed in middle age. Furthermore, a dementia risk score, including age, sex, education, SBP, TC, physical activity and ApoE ε4 genotype, was recently proposed (Kivipelto et al 2006), but should be validated and further refined to increase its predictive value. Considering pathophysiological mechanisms, there are mechanistic studies that provide leads, but do not indicate which of these leads are clinically relevant. Some studies have highlighted the possible protective

effect of antihypertensive therapy on cognition and some trials are assessing the effects of statins and treatments for insulin-resistance. Considering that dementia is a worldwide problem, finding a preventive or curative treatment is a major health concern, and vascular risk factors are a promising avenue of research. Further long-term, placebo-controlled, randomized studies, need to be performed, eg, antihypertensive therapy, statins, glitazones, antithrombotic agents versus placebo to slow down cognitive decline in MCI or AD populations even though in the absence of hypertension, hypercholesterolemia, and diabetus mellitus.

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