

## *The effects of cardiovascular risk factors on cognitive compromise*

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**W**hile the United States population under the age of 65 has tripled since the beginning of the last century, the number of those over age 65 has increased 11-fold. At present, 1 in 8 Americans (33.2 million) are over age 65, up from 1 in 25 in 1900 (3.1 million). This trend is expected to continue. Projections by the US Census Bureau indicate that the elderly population will more than double between now and the year 2050, to 80 million, when it is estimated that 1 in 5 Americans will be elderly.<sup>1</sup> The prevalence of dementia rises steeply with age, doubling every 4 to 5 years from the age of 60, so that more than one third of individuals over 80 years of age are likely to have dementia.<sup>2</sup> With increased life

*As life expectancy in the United States continues to increase, the projected numbers of elderly people who will develop dementia will grow rapidly. This paper reviews four well-established cardiovascular risk factors (type 2 diabetes, hypertension, cholesterol, and inflammation), for which there is longitudinal epidemiological evidence of increased risk of dementia, Alzheimer's disease, mild cognitive impairment, and cognitive decline. These risk factors are of special interest because of their potential modifiability, which may affect the course of cognitive compromise. Diabetes is the cardiovascular risk factor (CvRF) most consistently associated with cognition. Hypertension in midlife is consistently associated with cognition, but its associations with late-life hypertension are less clear. Total cholesterol is not consistently associated with cognition. Interleukin-6 and C-reactive protein are inflammatory markers relatively consistently associated with cognition. Composites of the CvRFs increase the risk for dementia in a dose-dependent fashion, suggesting a cumulative effect of these factors on neuronal stress. In the relatively few studies that have reported interactions of risk factors, they potentiate each other. The effect of each of these risk factors varies according to apolipoprotein E genotype. It may be that the effect of these risk factors varies according to the presence of the others, and these complex relationships underlie the biological mechanisms of cognitive compromise. This may be crucial for understanding the effects on cognition of drugs and other approaches, such as lifestyle change, for treating these risk factors.*

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# Clinical research

expectancy in the United States, the projected numbers of elderly people who will develop dementia will grow rapidly. There are no cures or preventive measures yet for dementia.

Alzheimer's disease (AD) remains the most common cause of dementia in the elderly. The risk factors for AD, other than age, include female gender, family history, and at least one apolipoprotein E4 (APOE4) allele.<sup>3</sup> In addition, cardiovascular risk factors, established as risk factors for vascular dementia, have also been associated with AD.<sup>4</sup> These risk factors are of special interest because of their potential modifiability so they may affect the course of disease. This paper reviews four well-established cardiovascular risk factors (type 2 diabetes, hypertension, cholesterol, and inflammation), for which there is longitudinal epidemiological evidence of increased risk of dementia, AD, mild cognitive impairment (MCI), and cognitive decline.

No two longitudinal epidemiological studies of dementia have the same methodology, and they each study distinct populations. Studies differ in when the risk factor is measured (eg, midlife vs closer to ascertainment of dementia), in the proportions of people carrying the risk factor, in the proportion of people being treated for the risk factor, the methods by which the risk factor was measured (eg, direct measure, self-report, medical charts), in the confounders accounted for, and of course, in the outcome measures (typically AD, vascular dementia, all cause dementia, MCI, or cognitive decline). For each cardiovascular risk factor, this paper summarizes its relationships with the cognitive outcomes. For each risk factor we tabulate the main results of longitudinal epidemiological studies of dementia, MCI, and cognitive decline, including nonsignificant in addition to significant results. Beyond separate effects of these risk factors, we consider multiple causes that may underlie the development of AD and dementia, by discussing combination effects—involving these risk factors with each other and with other factors—which particularly affect cognitive compromise.

## Type 2 diabetes

Table 1 presents studies examining risks of dementia, MCI, and cognitive decline in patients with type 2 diabetes and demonstrates, relatively consistently, increased risks for each of these outcomes. Type 2 diabetes has been demonstrated to increase risk for dementia in

most,<sup>4-17</sup> but not all,<sup>14,15</sup> prospective epidemiological studies, with the highest odds ratios approaching 3-fold increased risk of dementia for diabetic individuals compared with nondiabetics.<sup>5</sup> Many studies have also shown increased risk for AD and VaD (eg, ref 30). A recent study suggests that type 2 diabetes or impaired fasting glucose might be present in up to 80% of patients with AD.<sup>27</sup> A systematic review of the effect of diabetes on dementia and cognitive decline concludes that these should be considered consequences and disabling manifestations of diabetes.<sup>28</sup> Recently, even prediabetes (defined as glucose >7.8 mmol/L but <11.0 mmol/L) was associated with dementia (HR 1.77; 95% CI 1.02-3.12) and AD (HR 1.98; 1.12-

Reference	Results (95% CI)
<b>Dementia studies</b>	
Schnaider Beerl <sup>5</sup>	OR 2.8 (1.4-5.7)
Brayne <sup>6</sup>	OR 2.6 (0.9-7.8)
Yaffe <sup>7</sup>	OR 2.4 (0.9-6.1)
Ott <sup>8</sup>	RR 1.9 (1.3-2.8)
Leibson <sup>9</sup>	SMR 1.6 (1.3-2.0)
Whitmer <sup>10</sup>	HR 1.5 (1.2-1.8)
Xu <sup>11</sup>	HR 1.5 (1.1-2.1)
Peila <sup>12</sup>	RR 1.5 (1.0-2.2)
Curb <sup>11,13</sup>	RR 1.4 (.97-1.95)
MacKnight <sup>14</sup>	RR 1.3 (0.9-1.7)
Hassing <sup>11,15</sup>	RR 1.2 (0.8-1.7)
<b>MCI studies</b>	
Yaffe <sup>7</sup>	OR 1.8 (1.1-2.8)
Luchsinger <sup>16</sup>	HR 1.5 (1.0-2.3)
Luchsinger <sup>17</sup>	HR 1.4 (1.0-1.9)
<b>Cognitive decline</b>	
Gregg <sup>18</sup>	OR 1.7 (1.3-2.4)
Logroscino <sup>19</sup>	OR 1.3 (1.1-1.6)
Fontbonne <sup>20</sup>	OR >2 for 4 of 9 tests
Knopman <sup>21</sup>	37% to 165% greater rate of cognitive decline in diabetics (depending on the test)
Okereke <sup>22</sup>	Diabetics decline faster; global cognition D-.09 (-.15, -.04)
Hassing <sup>23</sup>	Diabetics decline over twice as fast as non diabetics
Arvanitakis <sup>24</sup>	44% greater rate of cognitive decline in diabetics
Hassing <sup>25</sup>	Diabetics decline twice as fast as nondiabetics
Van den Berg <sup>26</sup>	Diabetes was not associated with cognitive decline

**Table 1.** Risk of dementia, MCI, and cognitive decline in patients with Type 2 diabetes. OR, odds ratio; RR, relative risk; HR, hazard ratio; SMR, standard morbidity ratio; D, difference in rates

3.50).<sup>27</sup> A few epidemiological studies have examined the longitudinal association between diabetes and MCI,<sup>7,19,20</sup> a state of cognitive compromise preceding AD or frank dementia, and all showed significantly increased risk for subjects with diabetes. Impaired fasting glucose, a prediabetic condition, was also associated with MCI.<sup>30</sup> Numerous studies have reported consistently increased risk of cognitive decline in diabetes.<sup>18-26</sup>

Diabetes is a complex metabolic disorder that is closely associated with other risk factors for dementia, such as age, hypertension, and the metabolic syndrome—a clustering of several commonly occurring disorders (including abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) level, and hypertension) that are often associated with diabetes.<sup>31</sup> These risk factors, together with diabetes-specific characteristics (eg, age of onset, glycemic control, use of antidiabetes medications), demographic and socioeconomic factors, and genetic factors, might be important determinants of the increased risk of cognitive decline and dementia in individuals with diabetes.<sup>32,33</sup> Co-occurrence of diabetes and hypertension greatly increases the risk of dementia<sup>34</sup> and of cognitive decline.<sup>35</sup> High systolic blood pressure interacted with borderline diabetes<sup>36</sup> and with frank diabetes<sup>11</sup> multiplying the risk of AD. Diabetes almost doubled the risk of dementia and AD in the Rotterdam study, but diabetics taking insulin were at the highest risk (RR 4.3, 1.7-10.5)<sup>8</sup> suggesting that more severe diabetes increases dementia risk. Consistent with these observations, subjects with longer duration of diabetes<sup>18,19,22</sup> or with diabetes complications<sup>34,35</sup> had steeper cognitive decline.

The potential mediating effect of APOE4 genotype and of age in the relationship between diabetes and dementia is less clear. Participants with diabetes and the APOE4 allele had a risk ratio of 5.5 (CI 2.2-13.7) for AD compared with those with neither risk factors in the Honolulu Asia Aging Study,<sup>12</sup> and this was consistent with neuropathological findings. However, borderline diabetes was associated with AD only in non-APOE4 carriers in the Kongsholmen study. The effect of age on the relationships between diabetes and dementia is also difficult to interpret. The relationship between diabetes and dementia in the Framingham study was strongest for participants older than 75<sup>36,54</sup> but diabetes was not associated with accelerated cognitive decline in 85+ years of age participants in another study.<sup>26</sup> This suggests that factors other than CVRFs (ie, age, APOE genotype) inter-

act with diabetes to increase the risk of cognitive compromise.

Several potential mechanisms underlying the association between diabetes and dementia have been proposed:

- Diabetes is associated with micro- and/or macrovascular disease<sup>37</sup> which in turn increase the risk of cognitive decline and dementia<sup>38,39</sup>
- Defective insulin receptor signaling pathway (IRSP) in the central nervous system<sup>40</sup>; the IRSP is associated with vital brain processes including synaptic plasticity,<sup>41-43</sup> neuroprotection, neurodegeneration, survival, growth, energy metabolism, and longevity.<sup>44,45</sup> Insulin receptors (IR) are abundant throughout the brain,<sup>46</sup> and are expressed in especially high abundance in regions that support cognitive function.<sup>47</sup> A $\beta$ , the main component of neuritic plaques, hallmark lesions of AD, decreases insulin affinity and reduces the binding of insulin to its receptor<sup>48</sup> preventing rapid activation of specific kinases required for multiple cellular functions, including long-term potentiation (LTP).<sup>49</sup> Soluble A $\beta$  oligomers were recently shown to significantly lower IR responses to insulin and to cause rapid and substantial loss of neuronal surface IRs.<sup>50</sup> The IR desensitization found in AD brains,<sup>51</sup> hampers the release of A, from the intracellular to the extracellular compartment,<sup>52</sup> which may be a mechanism for its neurotoxicity.<sup>53</sup>
- Advanced glycation end products (AGEs) may have a crucial role in the relationship between diabetes and dementia.<sup>54-57</sup> AGEs, which normally increase with age and faster with diabetes, are the products of naturally occurring reactions between reducing sugars, eg, glucose, and free amine-containing proteins or lipids.<sup>54</sup> AD brains have significantly higher levels of AGEs than normal controls,<sup>58</sup> and in in-vitro studies, AGEs contribute to the formation of amyloid plaques and neurofibrillary tangles.<sup>59,60</sup>

Therefore, treatment for diabetes has the potential for salutary effects on cognitive compromise. In a 24-week randomized double blind trial, metformin, and its resulting improved glycemic control, were associated with improved memory.<sup>61</sup> Rosiglitazone treatment of Tg2576 mice (transgenic mice overexpressing amyloid precursor protein) resulted in better spatial learning and memory abilities and an approximately 25% reduction in A $\beta$ 42 levels.<sup>62</sup> Rosiglitazone therapy resulted in improved memory and selective attention while not affecting glucose levels in a study of 30 AD or MCI nondiabetic subjects during a period of 6 months.<sup>63</sup> A trial with 518 mild-

# Clinical research

-to-moderate AD patients treated with rosiglitazone for 6 months reported significant improvement in cognition only in patients who did not possess an APOE4 allele.<sup>64</sup> It should be noted that these encouraging results must be taken with caution in light of recent studies suggesting increased myocardial infarction and death from cardiovascular causes in rosiglitazone users.<sup>65</sup> Craft et al<sup>66-71</sup> have performed several investigations examining the effect of intravenous insulin in nondiabetic elderly adults with AD. Mild-to-moderate AD patients' immediate and delayed recall were improved in hyperglycemic and hyperinsulinemic conditions compared with a saline control condition. However, normal controls had no change in their cognition.<sup>71</sup> Intranasal insulin administration has recently shown some promising effects on memory.<sup>72,73</sup> Substantially reduced neuritic plaques (NPs), the hallmark lesions of the AD brain, were found in the brains of diabetic subjects who during life received a combination of insulin and another antidiabetic medication.<sup>74</sup> In a recent search of the literature by the Cochrane control trial register, however, no appropriate studies were found for meta-analysis regarding the effect of treatment for type 2 diabetes and degree of metabolic control on the

development of dementia.<sup>75</sup> Recently, the SALSA study reported decreased rates of cognitive decline in diabetic subjects receiving antidiabetic medications (insulin or oral hypoglycemic) compared with untreated diabetic subjects (but see refs 8,16). These studies are provocative and invite systematic investigation of the possible benefits of diabetes medications on cognition, but are not sufficient to draw conclusions.

## Hypertension

The relationships of hypertension with dementia and cognitive decline are less straight forward, as shown in *Table II*. Several longitudinal studies suggest that elevated blood pressure levels or hypertension, both in midlife<sup>10,16,79,81</sup> and closer to dementia ascertainment,<sup>80,88</sup> are associated with increased risk of cognitive decline,<sup>21,85,86</sup> MCI,<sup>84</sup> dementia,<sup>10,78-89</sup> and AD.<sup>34,88</sup> However, some studies do not find these relationships,<sup>34,89,90</sup> or even find that low blood pressure is associated with increased risk<sup>80,82</sup> suggesting the possibility of a U-shaped relationship between blood pressure and cognition. All the studies reporting negative or opposite results measured blood pressure closer to dementia ascer-

Reference	Predictor	Results (95% CI)
<b>Dementia</b>		
Whitmer <sup>10</sup>	HTN in midlife	HR 1.24 (1.04-1.48)
Launer <sup>77</sup>	BP in midlife	OR 4.3 (1.7-10.8) for DBP >95 mm Hg (compared with 80 to 89) and 4.8 (2.0-11.0) for SBP >160 (compared with 110-139)
Kivipelto <sup>78</sup>	BP in midlife	OR 2.8 (1.1-7.2) for SBP >160 mm Hg and 2.3 (1.1-5.1) for DBP >95
Kivipelto <sup>79</sup>	BP in midlife	OR 2.3 (1.0-5.5) for SBP >160 mm Hg
Qiu <sup>80</sup>	BP in late life	OR 1.6 (1.1-2.2) for SBP >180 mm Hg and OR 1.5 (1.0-2.1) for DBP <65
Skooog <sup>81</sup>	BP at the age of 70	Participants developing dementia at the age of 79-85 had higher SBP and DBP 15 years earlier
Ruitenber <sup>82</sup>	BP in late life	RR 0.93 (0.88-0.99) per 10 mm HG SBP and 0.89 (0.79-1.00) per 10 mm HG DBP
Kalmijn <sup>82</sup>	BP in midlife	RR 1.05 (0.91-1.21) for an increase of 1 SD of DBP and RR 1.07 (0.94-1.22) for SBP
Posner <sup>34</sup>	BP in late life	BP was not associated with dementia 7 years later
<b>MCI</b>		
Kivipelto <sup>84</sup>	BP at midlife	OR 1.5 (0.8-2.0) for SBP >160 mm Hg
<b>Cognitive decline</b>		
Tzourio <sup>85</sup>	HTN in late life	OR 2.8 (1.6-5.0) for subjects with a drop > 4 points in the MMSE over 4 years
Knopman <sup>21</sup>	HTN in late life	HTN was associated with greater decline in the digit symbol test but not with delayed recall or letter fluency
Mielke <sup>86</sup>	BP in late life	SBP >160 mm Hg was associated with faster decline in CDR-SOB and MMSE.
Hebert <sup>87</sup>	BP in late life	BP not associated with a 6-year change in global cognitive function
Posner <sup>34</sup>	BP in late life	BP not associated with changes in memory, language, or general cognitive function

**Table II.** Risk of dementia, MCI, and cognitive decline in patients with high blood pressure or a diagnosis of hypertension. OR, odds ratio; RR, relative risk; HR, hazard ratio; CDR-SOB, clinical dementia rating sum of boxes; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension

tainment, suggesting that: i) hypertension is a risk factor for dementia several decades later; and ii) high or low blood pressure are associated with incipient dementia. It has been suggested that the dementing process per se might affect blood pressure<sup>91,92</sup> adding a level of complexity to the directionality of the relationship between hypertension and dementia. In addition, the impact of this risk factor on cognition depends on age. Consistent with the latter, systolic blood pressure >160 at baseline was associated with steeper rates of cognitive decline in 85+ individuals (compared with younger hypertensive or oldest old individuals with lower systolic blood pressure) in the Cache County study.<sup>86</sup>

Another reason for differences among results is the effect of use of antihypertensive medication. For example, in the Honolulu Asia Aging Study, the association between high blood pressure and AD was strongest among those who were never treated for hypertension,<sup>77</sup> while in the Kungsholmen Study low diastolic blood pressure was associated with incident AD and dementia, particularly in persons who used antihypertensive medication.<sup>80</sup> Antihypertensive medication has been shown to be associated with reduced incidence of AD,<sup>77,93,94</sup> and with reduced rates of cognitive decline<sup>95</sup> in additional longitudinal studies. The effect of antihypertensive use on risk of dementia was particularly pronounced in APOE4 carriers in one study<sup>96</sup> and in men with longer duration of hypertensive medication use in another.<sup>97</sup> Low diastolic blood pressure had a synergistic effect with APOE4 to significantly increase the risk of AD, but antihypertensive medication counteracted the deleterious effect of high systolic blood pressure in subjects with the APOE4 allele.<sup>98</sup> Six placebo-controlled antihypertensive trials had dementia or cognitive decline as their secondary outcomes.<sup>99-104</sup> Reduced risk of incident dementia was found in one study<sup>102</sup>; other studies found reduced cognitive decline or dementia risk only in post hoc analysis. In a meta-analysis combining these data, the combined hazard ratio favored treatment (HR 0.87, CI 0.76-1.00).

Cerebrovascular disease resulting from hypertension is one major reason for increased risk of dementia and cognitive decline in hypertensive subjects.<sup>105,106</sup> Additionally, direct relationships of hypertension with AD neuropathology have been found. Elevated systolic and diastolic blood pressure in midlife was associated with a greater number of NPs and neurofibrillary tangles (NFTs), respectively.<sup>107</sup> Similarly, hypertension was associated with increased extent of NPs and NFTs in non-

demented, middle-aged individuals.<sup>108</sup> Hypertension may cause changes in vessel walls which may lead to hypoperfusion,<sup>109</sup> ischemia,<sup>110</sup> or hypoxia of the brain,<sup>111,112</sup> all of which have been related to the development of AD pathology.<sup>110-112</sup> An association between high blood pressure and hippocampal atrophy was only found in individuals not treated for hypertension,<sup>113</sup> and lower NPs and NFTs were found in the brains of subjects who were taking antihypertensive medication<sup>114</sup> and who did not have cerebrovascular disease, suggesting that hypertension medication may have an effect on AD neuropathology. The studies described in this section suggest that the interpretation of results of associations of hypertension with cognition has to be cautious and should take into consideration antihypertensive medication use, APOE genotype, subjects' age, and the presence of other CVRFs.

## Hypercholesterolemia

Similarly to the relationships between hypertension and cognitive compromise, most of the studies found total cholesterol measured in midlife to be a significant predictor of subsequent dementia,<sup>104,79</sup> MCI,<sup>83</sup> or cognitive decline<sup>84</sup> (Table III). Total cholesterol in midlife was also associated with AD in some studies<sup>84,123</sup> and especially with concomitant hypertension. Studies assessing cholesterol levels later in life have been less consistent in their ability to show a predictive effect for later cognitive decline. Several studies did not find a relationship between cholesterol and dementia<sup>116,117</sup> or even found an inverse association.<sup>118</sup> Cholesterol was not associated with AD in several studies.<sup>124-126</sup> The two studies examining MCI as an outcome did not find an association with cholesterol.

The question of association between cholesterol and AD is of particular interest because APOE is the principal cholesterol carrier protein in the brain,<sup>127</sup> the APOE-4 allele is a marker of both increased risk of AD and increased plasma cholesterol concentration. Nonetheless, very few studies report having examined the interactions of cholesterol, APOE genotype, and AD or dementia risk. High cholesterol in late life was associated with higher AD risk in APOE4 noncarriers only,<sup>128</sup> but this association was found only in APOE4 carriers in another study.<sup>129</sup> Moderate decrease in cholesterol from midlife to late life was associated with more impaired cognitive status, especially in APOE4 carriers.<sup>115</sup>

# Clinical research

Biochemical and cell biology studies suggest that altered cholesterol metabolism in neurons may underlie pathological processes of AD. Both the generation and clearance of A $\beta$  are regulated by cholesterol. A polymorphism of CYP46, a gene playing a major role in hydroxylation of cholesterol and thereby mediating its removal from the brain, was associated with increased A $\beta$  load in brain tissue. It was also associated with increased A $\beta$  peptides and phosphorylated tau protein in cerebrospinal fluid (CSF).<sup>130</sup> Consistent with this observation, cholesterol was higher with increasing certainty of AD neuropathological diagnosis.<sup>131,132</sup> However, high cholesterol was not associated with increased neuritic plaques in the neocortex or hippocampus,<sup>133</sup> or with A $\beta$  levels in CSF.<sup>134</sup> Since cholesterol increases atherosclerosis which in turn is associated with dysregulation of cerebral blood flow and hypoperfusion, the effects of cholesterol on dementia risk might not depend only on A $\beta$  mechanisms but also on vascular mechanisms.<sup>135</sup>

Because of some epidemiological studies suggesting an increased risk of dementia in individuals with elevated cholesterol, and because of the biological plausibility underlying this relationship, the protective effect of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), among the most widely prescribed cholesterol-lowering medications, was postulated.<sup>136</sup> Prospective epidemiological studies are inconsistent but not contradictory in their results, with several finding that statin use is associated with decreased risk of AD and dementia<sup>137-138</sup> and others finding no associations.<sup>140,141</sup> A Cochrane review con-

cluded that there is no conclusive evidence to recommend statins to reduce the risk of AD,<sup>142</sup> but that there is a growing body of biological and epidemiological evidence suggesting that lowering cholesterol might retard the pathogenesis of AD.

## Inflammation

Blood elevations of inflammatory markers, specifically C-reactive protein (CRP) and interleukin-6 (IL-6), have been shown to be risk factors for dementia (*Table IV*). Combination of high levels of several inflammatory markers in the Conselice Study of Brain Aging<sup>144</sup> was associated with increasing hazard ratios for dementia, and specifically high CRP/IL-6 ratios (HR=1.6, 1.03-2.4). As shown in *Table IV*, high levels of inflammatory markers are also consistently associated with greater rates of cognitive decline. Of interest are the results of the Health, Aging and Body Composition (ABC) study, in which subjects with the metabolic syndrome and high levels of inflammatory markers (IL-6 and CRP) had significantly higher rates of cognitive decline than subjects with the metabolic syndrome but low levels of blood markers of inflammation.<sup>150</sup> The effect of higher IL-6 levels on global and memory function decline was stronger in APOE4 carriers than in non-carriers in the Leiden 85+ study,<sup>151</sup> and was associated with steeper global cognitive decline only in APOE4 carriers in the Rotterdam study.<sup>152</sup> These observations again suggest that interpretation of relationships between inflammation and cognitive compromise have to be cautious and take into consideration of other factors.

Reference	Predictor	Results (95% CI)
Kivipelto <sup>79</sup>	Midlife	OR 1.89 (1.02-3.49) for TC>251 mg/dL
Whitmer <sup>10</sup>	Midlife	HR 1.42 (1.22-1.66) for TC $\geq$ 240 mg/dL
Kalmijn <sup>83</sup>	Midlife	RR 1.10 (0.95-1.26) for an increase of 1SD of TC
Stewart <sup>116</sup>	Midlife	No associations with baseline TC but increased risk for men with greater declines in TC
Li <sup>117</sup>	Late life	HR 1.16 (0.81-1.67) for highest 3 TC quartiles compared with lowest
Mielke <sup>118</sup>	Late life	HR 0.31 (0.11-0.85) for highest TC quartiles compared with lowest
<b>MCI</b>		
Kivipelto <sup>22</sup>	Midlife	OR 1.9 (1.2-3.0) for TC $\geq$ 6.5 mmol/L
Reitz <sup>119</sup>	Late life	TC was not associated with incident MCI
Solfrizzi <sup>28</sup>	Late life	TC was not associated with incident MCI
<b>Cognitive decline</b>		
Solomon <sup>115</sup>	Midlife	OR 1.8 (1.1-3.0) for midlife to late life TC decrease of more than 0.5 mmol/L
Yaffe <sup>121</sup>	Late life	OR 1.77 (1.06-2.97) for highest TC quartile compared with lowest
Knopman <sup>21</sup>	Late life	Hyperlipidemia was not associated with decline in delayed recall, digit symbol, or letter fluency
Reitz <sup>122</sup>	Late life	TC was not associated with decline in memory, visuospatial, or language abilities

**Table III.** Risk of dementia, MCI, and cognitive decline in patients with high total cholesterol (TC). OR, odds ratio, RR, relative risk, HR, hazard ratio

These longitudinal studies are consistent with the in vitro and in vivo studies of neurobiological mechanisms associated with cognitive function, suggesting a potential role of inflammation in the development of cognitive compromise. Several lines of evidence support the importance of inflammation in the pathogenesis of cognitive impairment and AD. Acute-phase proteins, cytokines, chemokines, and their receptors are upregulated in brains of AD patients.<sup>153</sup> The abundance of activated microglia, the primary neuronal immune surveillance cell, is a relatively early pathogenic event in patients with AD.<sup>154</sup> Proinflammatory cytokines augment amyloid precursor protein (APP),<sup>155,156</sup> and in turn, A $\beta$  induces further release of cytokines.<sup>157</sup> In addition, gene polymorphisms of several inflammatory mediators have been associated with increased risk of AD.<sup>158</sup>

Based on the epidemiological and biological evidence, nonsteroidal anti-inflammatory drugs (NSAIDs) are potential candidate drugs for treatment of AD. However, except for a clinical trial with indomethacin in which beneficial results were found,<sup>159</sup> trials with NSAIDs show

either nonsignificant beneficial trends<sup>160</sup> or no benefits.<sup>161-164</sup> The failure of these trials might have been for methodological reasons (short follow-up period, inadequate time of intervention, or insufficient dosing). Examination of anti-inflammation drugs with mechanisms other than cyclooxygenase inhibition is warranted.

## Conclusions

The relationships of the four reviewed cardiovascular risk factors with dementia and cognitive decline are complex. Diabetes seems to be the risk factor with the most consistent associations. Composites of the risk factors seem to increase in a dose-dependent fashion the risk for dementia,<sup>2,3,97</sup> suggesting an accumulating effect of these factors on neuronal stress. In the relatively few studies that have reported interactions of risk factors, they potentiate each other rather than simply accumulating deleterious effects. Moreover, the effect of each of the risk factors discussed in this review seem to depend on APOE genotype. If the underlying biological mechanism

Study	Predictor	Results (95% CI)
<b>Dementia</b>		
HAAS <sup>143</sup>	CRP	OR 2.7 (1.7-4.7) for highest quartile compared with lowest
Conselice Study of Brain Aging <sup>144</sup>	CRP	HR 1.63 (1.10-2.39)
	ACT	HR 1.62 (1.10-2.38)
	IL-6	No association
Rotterdam Study <sup>145</sup>	CRP	RR 1.12 (0.99-1.25)
	IL-6	RR 1.28 (1.06-1.55)
	ACT	RR 1.49 (1.23-1.81)
<b>Cognitive decline</b>		
Helsinki Aging Study <sup>146</sup>	CRP	RR 2.32 (1.01-5.46) for CRP>5 mg/L decline
Mac Arthur Studies of Successful Aging <sup>147</sup>	IL-6	OR 2.03 (1.30-3.19) for upper tertile of IL-6.
Health ABC Study <sup>148</sup>	CRP, IL-6	RR 1.66 (1.19-2.32) for high CRP and IL-6, and the metabolic syndrome
	TNF $\alpha$	No association
Longitudinal Aging Study Amsterdam <sup>149</sup>	ACT	Decline in MMSE but not with other cognitive tests
	CRP, IL-6	No associations
Leiden 85+ Study <sup>150</sup>	IL-6	Decline in memory
	CRP, ACT	No associations
Rotterdam Study <sup>145</sup>	IL-6	Decline in memory in APOE4
	CRP, ACT	No associations
Edinburgh Artery Study <sup>152</sup>	IL-6	Decline in information processing
	Fibrinogen	Decline in nonverbal reasoning
	ICAM-1	Decline in nonverbal reasoning and global cognition

**Table IV.** Risk of dementia, MCI, and cognitive decline in patients with high inflammatory marker levels. CRP, C-reactive protein; IL-6, Interleukin 6; TNF $\alpha$ ; Tumor necrosis factor  $\alpha$ ; ACT-alpha-1-antichymotrypsin; ICAM-1-intercellular adhesion molecule-1 \*Subjects with metabolic syndrome and high CRP or IL-6 had the highest risk

# Clinical research

depends on multiple risk factors for its full expression, the apparent effect of a single risk factor would depend on whether the others were present. This may be crucial for understanding the effects on cognition of drugs treating these risk factors. Thus, these considerations may pro-

foundly affect the results of clinical trials and at least partially explain why epidemiological associations are seldom reflected in clinical trials. Epidemiological indications of interactions might suggest subgroups to target in interventional studies. □

## **Los efectos de los factores de riesgo cardiovascular en el compromiso cognitivo**

*Dado que la expectativa de vida en los Estados Unidos continúa incrementándose, el número proyectado de personas de edad avanzada que desarrollarán demencia crecerá rápidamente. Este artículo revisa cuatro factores de riesgo cardiovascular bien establecidos (diabetes tipo 2, hipertensión, colesterol e inflamación), para los cuales existen evidencias epidemiológicas longitudinales de un riesgo aumentado de demencia, Enfermedad de Alzheimer, deterioro cognitivo leve y decaimiento cognitivo. Estos factores de riesgo son de especial interés ya que son potencialmente modificables, lo que puede influir en la evolución del compromiso cognitivo. La diabetes es el factor de riesgo cardiovascular (FRCv) que se asocia con mayor consistencia con la cognición. La hipertensión en la edad media de la vida está asociada consistentemente con la cognición, pero las asociaciones de esta última con la hipertensión de las etapas tardías de la vida son menos claras. El colesterol total no está asociado consistentemente con la cognición. La interleukina 6 y la proteína C reactiva son marcadores inflamatorios con una asociación relativamente consistente con la cognición. Una combinación de los FRCv aumenta el riesgo para demencia de manera dosis-dependiente, lo que sugiere un efecto acumulativo de estos factores de estrés neuronal. En los relativamente pocos estudios que han dado cuenta de las interacciones entre los factores de riesgo, estos se potencian unos con otros. El efecto de cada uno de los factores de riesgo varía de acuerdo con el genotipo para la apolipoproteína E. Puede ser que el efecto de estos factores de riesgo se modifique según la presencia de los otros, y estas complejas relaciones estén a la base de los mecanismos biológicos del compromiso cognitivo. Para el tratamiento de los factores de riesgo puede ser crucial comprender los efectos que tienen en la cognición los fármacos y otras intervenciones, como el cambio de estilo de vida.*

## **Les effets des facteurs de risque cardiovasculaire sur le déficit cognitif**

*L'espérance de vie continuant à augmenter aux États-Unis, le nombre de sujets âgés qui développeront une démence est appelé à augmenter rapidement. Cet article examine quatre facteurs de risque cardiovasculaire bien connus (diabète de type 2, hypertension, cholestérol et inflammation) qui ont montré lors d'études épidémiologiques longitudinales qu'ils présentaient un risque accru de démence, de maladie d'Alzheimer, de déficit cognitif léger et de déclin cognitif. Ces facteurs de risque sont très intéressants car ils peuvent être modifiés, ce qui pourrait influencer l'évolution du déclin cognitif. Le diabète est le facteur de risque cardiovasculaire (FRCv) le plus régulièrement associé à la cognition. L'hypertension des sujets d'âge moyen semble liée aux capacités cognitives, ce qui apparaît moins important chez les sujets plus âgés. Le cholestérol total n'est pas corrélé à la cognition alors que les marqueurs de l'inflammation interleukine-6 et protéine-réactive C le seraient relativement. Les FRCv augmenteraient le risque de démence de façon dose-dépendante, avec un potentiel effet cumulatif sur le stress neuronal. Dans les relativement rares études qui ont rapporté des interactions des facteurs de risque, ces derniers semblaient se potentialiser les uns les autres. Par ailleurs, l'effet de chacun d'entre eux varierait selon le génotype de l'apolipoprotéine E. L'effet de ces facteurs de risque pourrait varier en fonction de la présence des autres et ces relations complexes sous-tendent les mécanismes biologiques du déficit cognitif. Leur étude apparaît cruciale pour la compréhension des effets des médicaments et d'autres approches thérapeutiques (modification du style de vie) sur la cognition, afin de traiter ces facteurs de risque.*



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