Table S1 The current research progress of specific statin drugs in dementia

Type	Clinic study	Vivo study	Vitro study	PMID
Simvastatin	An association of dementia or cognitive impairment was significantly higher in the patients who were on statin therapy compared to the patients who were not on a statin			28611866
	Simvastatin ameliorated the memory deficits in clinical AD patients	Simvastatin ameliorated the memory deficits in animal model of AD. Simvastatin could reduce the mRNA expression of inflammatory cytokines and mediators, suppress the apoptosis of neural stem cells and improve the survival rate of neurons		28528185
	The use of statins may benefit all AD patients with potentially greater therapeutic efficacy in those homozygous for ApoE4			28212683
	Simvastatin was associated with lower Alzheimer disease risk for white women, Hispanic women, Hispanic men, and black women			27942728
		Treatment of rats with simvastatin ameliorated L-methionine-induced behavioral, neurochemical, and histological changes in a manner comparable to cilostazol. Simvastatin may be regarded as a potential therapeutic strategy for the treatment of VaD		27544235
	Two Asian patients who developed cognitive deficits after starting simvastatin. A 32-year-old man and a 54-year-old woman developed different but clear cognitive deficits that reversed after stopping simvastatin. The possibility of new-onset cognitive dysfunction and the deterioration of existing cognitive deficits should be considered when prescribing simvastatin to patients			27048383
		Lipid metabolism represents a potential target for therapeutic intervention in HD. Modifying cholesterol or ketone levels acutely in the brain can partially rescue synaptic alterations, and the KD can prevent weight loss and improve some behavioral abnormalities		27031732
		SV-treatment in $A\beta1_{-42}$-mice exerts dose-dependent neuroprotection and neurotoxicity by reducing FPP to enhance the phosphorylation of NR2B and Akt		26757191
	There is good evidence that statins given in late life to people at risk of vascular disease do not prevent cognitive decline or dementia			26727124
	Due to the low quality of the body of evidence in this review, it is difficult to draw conclusions about the effectiveness of any pharmacological intervention for cognitive decline in people with Down syndrome			26513128
	LDL-L from hypercholesterolaemic, AD and AD-plus patients are inflammatory to HMVECs	In vivo intervention with statins reduces the damaging effects of LDL-L on HMVECs		26399707
			Differential dose-dependent effects of simvastatin on HIF-1α and BACE in cultured Alzheimer's disease cybrid cells	26228060
		The results indicate that the simvastatin-treatment in $A\beta_{25-35}$-mice via reduction of FPP can protect neurogenesis through α7nAChR-cascading PI3K-Akt and increasing BDNF, which may improve spatial cognitive function		26051402
		The administration of simvastatin decreased oxidative stress in plasma		25698600
		The potent benefits of simvastatin on endothelial- and smooth muscle cell-mediated vasomotor responses, endothelial NO synthesis and in preserving capillary integrity. Simvastatin could be indicated in the treatment of cerebrovascular dysfunction associated with VaD and AD		25564230
		The anti-amnesia of simvastatin in $A\beta_{25-35}$-mice depends on its neuroprotection and synaptic plasticity improvement		24289538
		The efficacy of simvastatin on selective AD features in a complex model of the disease, likely reflecting the challenges faced by recent clinical trials in assessing statin efficacy		23954171
		Simvastatin and, possibly, other brain penetrant statins bear high therapeutic promise in early AD and in patients with vascular diseases who are at risk of developing AD		22492027
	Simvastatin had no benefit on the progression of symptoms in individuals with mild to moderate AD despite significant lowering of cholesterol			21795660
		Simvastatin could be effective for the prevention of alterations observed in the STZ dementia model		21744242
		Simvastatin treatment enhanced cognition in intact rats, but had no effect in OBX rats. These results are in line with the idea that statins may attenuate (early) age-associated cognitive decline in humans		21384104
		Simvastatin may well have therapeutic potential in the treatment of neurodegenerative diseases involving excitotoxicity and memory impairment, including AD		21224519
	Simvastatin treatment can affect brain cholesterol metabolism within 12 weeks, but did not alter molecular indices of AD pathology during this short-term treatment			20473136
		Activation of Akt as a molecular pathway for augmented hippocampal LTP by simvastatin treatment, and implicate enhancement of hippocampal LTP as a potential cellular mechanism underlying the beneficial effects of simvastatin on cognitive function		20040368
		Simvastatin therapy blunted TBI-induced increases in A beta, reduced hippocampal tissue damage and microglial activation, and improved behavioral outcome		19798641
		Low-dose simvastatin treatment in aged APP mice largely salvages cerebrovascular function and has benefits on several AD landmarks		19524673
			Simvastatin reduced expression of apolipoprotein E in astrocytes (P<0.01). Furthermore, both statins reduced expression of microtubule-associated protein tau in astrocytes (P<0.01), while both statins increased its expression in neuroblastoma cells (P<0.01). In SK-N-SH cells, simvastatin significantly increased cyclin-dependent kinase 5 and glycogen synthase kinase 3beta expression, while pravastatin increased amyloid precursor protein expression	19461118
		Simvastatin use improved selected measures of cognitive function without significantly changing CSF Abeta42 or total tau levels		18376061
			Simvastatin induces a partial blockade of retinoblastoma protein phosphorylation and inhibition of cyclin E/cyclin-dependent kinase (CDK) 2 activity associated with increased levels of the CDK inhibitors p21(Cip1) and p27(kip1). These effects of SIM on AD lymphoblasts are dependent on inhibition of the proteasome-mediated degradation of p21 and p27 proteins. The antiproliferative effect of this natural statin may provide a therapeutic approach for AD disease	17928568
	Simvastatin is associated with a strong reduction in the incidence of dementia and Parkinson's disease			17640385
		The effects of simvastatin on learning and memory are independent of amyloid beta protein levels. The mechanisms by which simvastatin exerts its beneficial effects may be related to modulation of signaling pathways in memory formation		17192930
	Simvastatin treatment may favor the non-amyloidogenic pathway of APP processing			15785028
	Simvastatin acts directly on the processing of APP by inhibiting both the alpha- and the beta-secretase pathways			12714796
	The greater reduction of plasma concentrations of 24S-hydroxycholesterol compared with cholesterol indicates that simvastatin in a dosage of 80 mg/d reduces cholesterol turnover in the brain. The present results might describe a possible mechanism of how long-term treatment with statins could reduce the incidence of Alzheimer disease			11843691
		Guinea pigs treated with high doses of simvastatin showed a strong and reversible reduction of cerebral Abeta42 and Abeta40 levels in the cerebrospinal fluid and brain homogenate	The widely used cholesterol-lowering drugs simvastatin and lovastatin reduce intracellular and extracellular levels of Abeta42 and Abeta40 peptides in primary cultures of hippocampal neurons and mixed cortical neurons	11296263
Pravastatin	Pravastatin was associated with reduced Alzheimer disease risk for white women only (HR, 0.82, 95% CI, 0.70–0.95)			27942728
	In this population-based sample, elderly participants treated with statins and untreated controls performed similarly in all tested cognitive areas			20413854
	Pravastatin treatment in old age did not affect cognitive decline during a 3 year follow-up period			19653027
			Pravastatin had a similar but attenuated effect on ABCA1 in astrocytes (–54%, P<0.001) and neuroblastoma cells (–70%, P<0.001). Pravastatin increased amyloid precursor protein expression	19461118
	In AD, one cross-sectional analysis found 73% lower AD rates in pravastatin recipients (P<0.001)			15110128
	Patients having Apolipoprotein E4 (ApoE4) had higher low-density lipoprotein levels and lower Abeta 40 levels in plasma, suggesting ApoE4 seems to influence plasma Abeta levels via cholesterol metabolism			14550919
Atorvastatin		The resultant data suggest that the anti-apoptotic effect of AV could be partially mediated by the pro-inflammatory protein p38 MAPK and the anti-apoptotic protein Bcl-2 in the rat carotid artery. Atorvastatin can therefore be considered a target drug in the prevention or development of atherosclerotic events		28498386
		The administration of atorvastatin ameliorated the cognitive deficits, involved the pathway of reducing farnesyl pyrophosphate	depressed the inflammatory responses, improved the long-term potentiation impairment, and prevents Aβ25-35- induced neurotoxicity in cultured hippocampal neurons. These protective functions of ATV	26846170
	Administration of atorvastatin corrected dyslipidemia in association with a reduction in inflammatory markers			26666876
		Atorvastatin may be promising for the treatment of cognitive sequelae associated with Chronic cerebral hypoperfusion		26485403
		Atorvastatin might attenuate the damage of nerve cells and improve learning and memory ability by inhibiting inflammatory response in the progression of AD		23386786
		Atorvastatin and pitavastatin reduced the level of oxidative stress, as revealed by the presence of 4-HNE and AGE, in AD mouse brains, and that treatment with statins improves insulin signaling and LDL-R/ApoE systems. The beneficial effects of these statins may be associated with direct pleiotropic effects on AD mouse brains, indirect effects through improving the serum adiponectin/leptin balance, or both		23336815
		Atorvastatin have high potential for a preventative approach in patients at risk of AD		22732109
	Atorvastatin increased regional CBF in persons at risk for AD			22175654
		Treatment with atorvastatin or pitavastatin ameliorated the activation of MMP-9		21955601
		Atorvastatin (80 mg/d for 14.5 months) treatment resulted in an up-regulation of the inducible isoform of haem oxygenase (HO-1), an enzyme with significant neuroprotective activity. Atorvastatin selectively increased HO-1 in the parietal cortex but not cerebellum		21767440
			Atorvastatin and pitavastatin can maintain the number of PCs and their synaptic networks in the AD cerebellum	21419111
		Atorvastatin (80 mg/day for 14.5 months) significantly reduced lipoperoxidation, protein oxidation and nitration, and increased GSH levels in parietal cortex of aged beagles. This effect was specific for brain because it was not paralleled by a concomitant reduction in all these parameters in serum. In addition, atorvastatin slightly reduced the formation of cholesterol oxidation products in cortex but increased the 7-ketocholesterol/total cholesterol ratio in serum. We also found that increased oxidative damage in the parietal cortex was associated with poorer learning (visual discrimination task)		21193043
		Early treatment with both atorvastatin and pitavastatin prevented subsequent worsening of cognitive function and the amyloidogenic process, probably due to pleiotrophic effects, suggesting a therapeutic potential for Alzheimer's disease		21112317
		Atorvastatin could inhibit tau hyperphosphorylation and decrease Abeta generation		20819569
	Statin therapy as a treatment for mild to moderate Alzheimer disease, atorvastatin was not associated with significant clinical benefit over 72 weeks			20200346
		Both Atorvastatin as well as Pitavastatin attenuated L-Methionine induced endothelial dysfunction associated memory deficits		18691432
	Cholesterol lowering with atorvastatin produces no significant change in CRP levels in treating AD patients who participated in ADCLT (AD cholesterol lowering trial)			16945213
	Atorvastatin therapy may be of benefit in the treatment of mild-to-moderately affected AD patients, but the level of benefit produced may be predicated on earlier treatment, an individual's apolipoprotein E genotype or whether the patient exhibits elevated cholesterol levels			16866904
	Atorvastatin produced change in the slope of deterioration on the MMSE. Accordingly, atorvastatin therapy may be an effective treatment and may slow the progression of AD among mild-to-moderately affected patients			15974900
	Atorvastatin treatment may be of some clinical benefit and could be established as an effective therapy for Alzheimer disease if the current findings are substantiated by a much larger multicenter trial			15883262
Fluvastatin		Fluvastatin significantly prevented memory impairment induced by Abeta. The beneficial effects of fluvastatin might be explained by the preservation of neurons through a significant decrease in Abeta accumulation and oxidative stress		18425343
Lovastatin			Our recent studies revealed a neuronal protective effect of lovastatin (LOV) from N-methyl-d-aspartic acid (NMDA) excitotoxicity	25770969
		The neuro-restorative and -protective effect of lovastatin may be attributed to the regulation of Akt- and p38-mediated signaling pathway together with improvement of muscarinic/NMDA receptor functions.		20219644
		Lovastatin administration can reduce alpha-syn aggregation and associated neuropathology and support the possibility that treatment with cholesterol-lowering agents may be beneficial for patients with PD and/or DLB		19944097
			Lovastatin is neuroprotective in TNF-R1(-/-) neurons, while protection is completely absent in TNF-R2(-/-) neurons. Furthermore, lovastatin-mediated neuroprotection led to an increase in PKB/Akt and NF-kappaB phosphorylation, whereas inhibition of PKB/Akt activation entirely abolished lovastatin-induced neuroprotection. Thus, lovastatin-induced neuroprotection against glutamate-excitotoxicity via activation of TNF-R2-signaling pathways	18376053
		Lovastatin lowers cholesterol level in both genders, but enhances beta-amyloid production and senile plaque deposition only in brains of female Tg2576 mice		12885571
	Lovastatin may thereby be effective in delaying the onset and/or slowing the progression of AD		Lovastatin reduces Abeta formation	11900994
			Studies *in vitro* have shown that inhibiting cholesterol metabolism with lovastatin, or its active metabolite lovastatin acid, lowers A beta production	11466161