Role Of Atherosclerosis In Progression Of Alzheimer's Disease: Potential Pathways And Prescription

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Abstract

One of the major issues with worldwide public health is still atherosclerosis, followed by Alzheimer's disease (AD). Growing epidemiologic, clinical and experimental evidence suggests that cerebrovascular atherosclerosis and AD have a reciprocal interaction that impairs brain structure and function, while being formerly viewed as distinct disease entities. While atherosclerosis of the cerebral arteries, which causes hypoperfusion and hypoxia, may cause the amyloid-peptide, a peptide critical to AD pathophysiology, to be synthesised more readily, Through vascular oxidative stress and endothelial dysfunction, amyloid peptide may then encourage the development of atherosclerotic plaques, causing more vascular destruction. There is mounting evidence that AD is significantly influenced by vascular risk factors like hypertension, diabetes mellitus, cardiovascular disease, and cerebrovascular disease. Vascular risk factors could potentially speed up the onset of AD. Vascular disease may have a significant impact on the cause of AD by reducing cerebral blood flow and compromising Aβ-clearance. A possible target to lower the risk of AD by early detection and treatment is atherosclerosis, a significant proxy of vascular pathology.

Keywords: Alzheimer's disease, Atherosclerosis, Amyloid beta peptide, Cerebrovascular disease, Atherosclerotic plaques.

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INTRODUCTION

A persistent neurological illness, Alzheimer's disease identified by amyloid-β (Aβ) accumulation, tau protein phosphorylation and neurofibrillary tangle phosphorylation [1]. AD serves as the main cause of death [2]. AD is the primary typical reason for dementia in the adult people [3]. In AD, unique clusters develop consequently by mutation of amyloid beta peptide and assembly. This group exhibits resistance to internal clearance and produces amyloid plaques, which cause neuronal death, degenerative changes, and loss of brain function [4]. The vascular risk elements, hypertension, diabetes mellitus, cardiovascular and cerebrovascular disorders are identified as contributing factors to AD. Vascular disease contributes remarkably to the AD development as it hindering amyloid beta elimination and reducing cerebral blood flow. Potential targets like atherosclerosis (ATH) were used to lower the risk of AD through prompt detection and therapy [5]. Atherosclerosis, often known as artery hardening, is a crucial factor in the development of dementia. The pathogenesis of dementia has been linked to ATH [6]. The essential basic disease of vascular cognitive impairment is atherosclerosis [3]. Numerous

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tiny atheromatous plaques developed inside the microvasculature of the cerebrovascular atherosclerosis and impeded the micro perfusion. This causes cognitive decline and memory loss [4]. Cerebrovascular Atherosclerosis connected with neurofibrillary tangle (NFT) densities & increased neurotic plaques. In accordance with amyloid cascade theory, aberrant build up of amyloid plaques in various brain regions associated with AD is brought on by an imbalance between amyloid peptide production and clearance [7].

VASCUALR INVOLVEMENT

As ATH is identified by accumulation of cholesterol in artery walls and AD by neuronal death, NFT and amyloid plaque development, both diseases initially seem to clear from one another [8]. The cerebral artery vasculature is primarily linked to the extracellular amyloid deposits in brains of AD patients [9]. Additionally to NFT and amyloid plaques, AD patients exhibit certain levels of cerebral artery obstruction [10]. AD risk is not enhanced in people with coronary or aortic ATH (non-brain ATH). However, it was determined that intracranial atherosclerosis is a significant risk factor for dementia [11]. Thickening of the vascular wall, blood vessel blockage are linked to both AD and ATH. Cerebral artery vasculature and vital arteries in AD and ATH respectively, are primary localizations. The disease-causing pathways can also vary. Vascular deposits in ATH decrease heart performance and pose a considerable risk of circulating and causing a stroke. Brain hypoperfusion linked to the disease in AD on a causal basis. Inadequate oxygen and nutrition supply to the brain is caused by cerebral vascular thickening, which increases the risk of neuronal death. Despite the fact that the location of vascular involvement varies between AD and ATH, the two diseases reflect a spectrum of closely related symptoms [12].

AD & ATH HAVE AN INFLAMMATORY COMPONENT

Inflammatory mechanisms were involved in AD and ATH. Interleukins (IL-1 and IL-6) create the inflammatory marker C-reactive protein (CRP), whose levels are varied in AD and ATH. CRP possesses immune-modulating characteristics and stick with the phosphocholine, a constituent of bacterial cell wall [13]. Immune reactivity of CRP was detected in atheromatous plaques (90%) and in normal specimens (3%). It is well known that in ATH, CRP is upregulated [14]. No confirmation of CRP upregulation in the blood or cerebrospinal fluid (CSF) in AD, but CRP mRNA levels were elevated in the brain notably in the hippocampus which suggested local inflammation in the brain [15].

GENETIC PREDISPOSITION IMPACT OF APOLIPOPROTEIN E (APOE)

A significant risk component for both diseases is the E4 allele at the APOE gene, which codes for apo lipoprotein E. Along with lipid-rich lipoprotein particles that contain insoluble cholesterol, a lipid transport molecule called APOE that circulates in the bloodstream and catabolize components of lipoproteins rich in triglycerides. According to density, LDL (low density lipoprotein), HDL (high density lipoprotein), and VLDL (very low density lipoprotein)) are names given to lipoproteins. Phospholipids, cholesterol esters, and cholesterols with apo lipoproteins on their surfaces make up these [16-19]. The main apo lipoprotein, APOB100, engages the LDL receptor with APOE in order to help cellular absorption. By attaching to LDLR, APOE participates in the transport of cholesterol. Contrarily HDL particles transfer reverse cholesterol from peripheral organs to the liver for release into bile and are primarily composed of APOA1, A2, C and E [20]. The primary Apo lipoprotein in cerebral fluid, APOE, serves a variety of functions, but one of them is likely to drive the transport of cholesterol away from the cell, causing accumulation of cholesterol in lipid-rich intracellular clumps in vascular wall [21]. APOE performs a variety of functions, including tissue healing, immunity, inflammation, and infection. It is not just a cholesterol transporter. The function of proteins in transporting cholesterol and other functions, including infection, immunity, and tissue repair, are impacted by APOE polymorphisms [22,23].

FAMILIAL DISEASE

Mice with the APOE gene knocked out, in particular were given a diet heavy in fat, generate atherosclerotic plaques comparable to

those observed in ATH in humans. Additionally, ATH develops in mice lacking the APOE binding LDL receptor [24,25]. It is known that well-recognised (albeit uncommon) mutations that are autosomal dominant in AD can lead to familial illness. In numerous instances of genetic AD, mutations in amyloid beta precursor protein, APP gene, which codes the precursor of Aβ peptide, are discovered [26].

BOTH AD & ATH ARE MODULATED BY THE ALZHEIMER PRECURSOR PROTEIN (APP):

While pathologic vascular occlusion distinguishes ATH from AD, cerebral Aβ deposits and neuro fibrillary tangles (NFT) are indicators of AD. The necessity for APOE to bind to Aβ and promote its uptake [27]. Compared to APOE3, APOE4 boosts the synthesis of Aβ and forms an alliance with Aβ toxicity [28,29]. Amyloid beta is connected with macrophages and the cerebrovasculature in AD, particularly in cerebral amyloid angiopathy (CAA). Decreased cerebral blood flow was observed in the brains of AD mice [30] resulting in cerebral vascular disease (CBVD). White-matter lesions, micro infarcts, haemorrhages, microvascular degeneration and cerebral amyloid angiopathy (CAA) are among several CBVD diseases that are seen in 60 to 90 percent AD patients [31]. Amyloid beta has been linked to the movement of macrophages that consume it between blood arteries and neurons [32]. Aβ, APP's hazardous fragments and ATH are also connected [33]. Atherosclerosis damages old people's cognitive deficits and can result in cerebral infarction or stroke [34] patients with stroke had higher serum levels of Aβ [33] and vascular endothelium can be noxiously affected by Aβ [35]. Aortic atherosclerosis resulted from the overexpression of the AD-related mutant APP in mice that were predisposed to developing atherosclerotic lesions and atherosclerotic lesions were dramatically enhanced in mice lacking the APOE gene [36,37].

COMMON RISK FACTORS OF AD & ATH:

1. SMOKING

Smoking for long period of time increases risk for developing AD and ATH [38-40]. Smoking elevates total plasma homocysteine, a standalone risk element for stroke, cognitive decline, AD and various dementias [41-44]. Smoking can hasten the development of atherosclerosis [45] and can result in oxidative stress, connected to excitotoxicity and can kill brain cells [46].

2. MAJOR DEPRESSION

Another risk factor for AD & ATH is major depression. The two disorders are usually linked to late-onset depression. At autopsy, both individuals exhibit more hippocampus disease [47].

3. FUNGAL PATHOGENS

It has been acknowledged that fungus macromolecules shown to be a possible pathophysiological basis for AD and ATH. In some AD patients, hyphae and various-sized fungal cells can be seen inside blood vessels including cappilaries, indicating that fungi can infect the neurovascular system [48,49].

4. AIR POLLUTION

One more environmental element linked to both AD and ATH is air pollution exposure over time. Obesity, metabolic syndromes, CVDs are especially caused by prolonged exposure to airborne pollutants like ozone and particulates [50,51].

INFECTIOUS AGENTS ARE A FACTOR IN AD & ATH:

Chlamydia pneumoniae cultivated from AD brain was used to immunise wild type mice, and these mice acquired amyloid plaques Little, [52]. HSV-1 disease causes a significant improvement in Aβ levels within cells in cultured glial cells as well as neurons; antiviral therapy prevents the development of Aβ [53]. Aβ deposition is a typical aspect of human HIV brain infection [54]. Numerous studies using animal models have shown that an infectious agent that has been injected, such as *Chlamydia pneumoniae*, continues to exist in atherosclerotic plaques and speed up the growth of ATH [55]. Infection with *Chlamydia pneumoniae* increases aortic ATH in LDL receptor mice models [56] and promote the cholesterol-rich foam cell production and increased smooth muscle cell count [57]. Atherogenesis is further accelerated by infections with Porphyromonas gingivalis [58], Helicobacter pylori [59], and Streptococcus mutans [60]. Viruses such as the gamma herpes virus [61], the influenza virus [62], and the

cytomegalovirus cause atherogenesis in ATH-prone animals [63].

Aβ DEPOSTION

According to the theory behind the amyloid cascade, aberrant deposition of Aβ plaques in numerous brain regions causes neurodegeneration in AD [64]. Imbalance between A-peptide synthesis and clearance is significant for AD's neurodegenerative effects [65]. The bulk of Aβ aggregation occurs prior to increasing structural neurodegeneration and cognitive loss, making amyloidosis one of the initial incidents in the neuropathological chain of events that resulted in AD [66]. CAA is caused by Aβ protein that is found in the cerebral blood vessel wall, which raises the risk of cerebral hemorrhage [67]. Solubilized Aβ-peptide injection causes the cerebral and peripheral arteries in Sprague-Dawley rats to become more constricted, resulting in cerebral hypoperfusion, reduced blood flow and enhanced vascular resistance [68]. For both CAA & AD patients, the risk of frequent hemorrhagic strokes and ischemic episodes increases with Aβ aggregation [67].

VASCULAR MORPHOLOGICAL ALTERATIONS IN THE AD & ATH

Structural or cellular modifications inside vesell walls and amyloid accumulation in vessels directly contributes to Artirial stiffness, a pathophysiological process [69]. Additionally, atherosclerosis increases arterial stiffness, a common observation in CVD patients. White matter or cortical infarcts, as well as CAA, can develop in brain as a result of arterial stiffness, it is obvious that it increases the danger of cognitive decline with age [70,71]. Dispersed microvascular networks in the retina and other structural flaws in the cerebral microvansculature have been observed in AD patients [72]. Additionally, AD patients have alterations in the retinal microvasculature, such as twisting of the retinal arteries and constriction of the retinal venules [73].

HIGH DENSITY LIPOPROTEIN (HDL) FUNCTION IN AD

HDL actions described by apo lipoproteins, which are connected to HDL, dramatically alter the risk of AD [74,75]. All three APOE isoforms are preferentially linked to HDL, but APOE4 is associated with LDL and VLDL, lipoproteins that are highly connected with cardiovascular illnesses and AD [76,77]. Through a number of mechanisms, most notably APP trafficking/processing and Aβ production/clearance pathways, HDL/APOs have an impact on amyloid pathology [78-80]. In the brain, APP processing, Aβ production, Aβ aggregation, intracellular and extracellular Aβ breakdown and Aβ clearance via blood brain barrier (BBB) and lymphatic routes are all said to be APOE-dependent processes [81]. The reduction of CAA by APOE-enriched HDL particles suggests that peripheral APOE has anti-vascular Aβ-depositional effects [82]. In either tau pathology or cerebral amyloid pathology, APOE is a key player. Other HDL-connected substances, besides APOs, contribute to the anti-inflammatory and antioxidant characterristics of HDL. Paraoxonase 1 (PON1), is a significant HDL-linked enzyme in plasma that is essential for preventing the atherogenic imapct of oxidative consequences on the vasculature [83]. It is well recognised that HDL works to promote vasoprotective activities, which deteriorate with ageing [84,85]. A high concentration of HDL/APOA-I in the peripheral has the power of dissolving arterial plaques, which are mostly made of collagen, cholesterol and fat. On cerebral vascular protein accumulation, HDL or its major protein costituent, APOE in CNS are anticipated to have comparable effects. There is strong evidence that HDL develop BBB function to protect against AD. In support of its involvement in cerebrovascular resilience, HDL improves vascular function and speeds up the removal of Aβ from the brain [82,86]. The integrity and function of the cerebral vascular system are known to be compromised by CAA. Inhibiting endothelial apoptosis and repairing cerebral endothelial damage are two important functions of HDL that are driven by APOA-I [87].

ROLE OF HDL IN THE TREATMENT OF ATHEROSCLEROSIS

Higher non high-density lipoprotein (HDL) and decreased HDL volumes are the vital risk elements for the growth of vascular atherosclerosis [88]. According to experimental data, the HDL particle has a considerable impact on the mobilisation of fat from the

artery wall and has anti-inflammatory and antioxidant properties. The modulation of HDL, its related protein apolipoprotein A-I, and their synthetic imitators led to lesion shrinkage and lesion stabilisation in animal models of hyper-cholesterolemia and atherosclerosis regardless of non-HDL levels. Entrapment of LDL in the arterial wall, its subsequent oxidative alteration, and the stimulation of proinflam-matory gene expression that results in inflammatory cell recruitment, infiltration, and activation are key factors in the development of atherosclerosis, a complex condition [89,90]. This mechanism interacts with HDL at several locations, and these interactions may offer therapeutic goals to stop, sustain or even enhance the relapse of atherosclerosis. Reverse cholesterol transfer or the mobilisation of free cholesterol from the artery wall to the steroid producing tissues and liver is a key physiological role of HDL [91]. Apolipoprotein A-I clears the artery wall of oxidation-seeding compounds [92]. The HDL contains the enzymes paraoxonase and acetyl hydrolase, which prevent LDL from being oxidised [93,94]. Since LDL oxidation can be inhibited, this anti-inflammatory and anti-atherogenic impact is revealed [92]. In addition to delaying the onset of atherosclerosis, HDL has a remarkable impact on plaque vulnerability [95]. Plaque lipid content is decreased by HDL-mediated cholesterol efflux. As a result of HDL-conciliated suppression of lipid oxidation and related inflammatory processes, the amount and activity of plaque macrophages were reduced. The harmful consequences of lipid oxidation are scavenged by HDL-related phospholipids, which prevents the death of smooth muscle [96,97] feeding or practically balancing the atherosclerotic plaques Apolipoprotein A-1 proven to improve smooth muscle content and reduce cholesterol and macrophage levels in plaques in animl stuides. All of these traits enable HDL to alter the composition of the plaque, prevent rupture, and lessen the frequency of acute cardiovascular events [98-100].

REFERENCES

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science (New York, N.Y.),* 297(5580), 353–356. doi:10.1126/science.1072994

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., and Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement.* 3,186–191. doi: 10.1016/j.jalz.2007.04.381

Yarchoan, M., Xie, S. X., Kling, M. A., Toledo, J. B., Wolk, D. A., Lee, E. B., Van Deerlin, V., Lee, V. M., Trojanowski, J. Q., & Arnold, S. E. (2012). Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. *Brain : a journal of neurology,*135(Pt12),3749–3756. doi:10.1093/brain/aws271

Yuan, J., Wen, G., Li, Y., & Liu, C. (2013). The occurrence of cerebrovascular atherosclerosis in Alzheimer's disease patients. *Clinical interventions in aging,* 8, 581–584. doi:10.2147/CIA.S44160

Xie, B., Shi, X., Xing, Y., & Tang, Y. (2020). Association between atherosclerosis and Alzheimer's disease: A systematic review and meta-analysis. *Brain and behavior*, 10(4), e01601. doi:10.1002/brb3.1601

Iadecola C. (2013). The pathobiology of vascular dementia. *Neuron,* 80(4), 844–866. doi:10.1016/j.neuron.2013.10.008

Beach, T. G., Wilson, J. R., Sue, L. I., Newell, A., Poston, M., Cisneros, R., Pandya, Y., Esh, C., Connor, D. J., Sabbagh, M., Walker, D. G., & Roher, A. E. (2007). Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. *Acta neuropathologica*,113(1),13–21. doi:10.1007/s00401-006-0136-y

Iadecola C. (2004). Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nature reviews. Neuroscience*, 5(5), 347–360. doi:10.1038/nrn1387

Vagnucci, A. H., Jr, & Li, W. W. (2003). Alzheimer's disease and angiogenesis. *Lancet (London, England),* 361(9357),605–608.doi:10.1016/S0140-6736(03)12 52 1-4

Roher, A. E., Esh, C., Kokjohn, T. A., Kalback, W., Luehrs, D. C., Seward, J. D., Sue, L. I., & Beach, T. G. (2003). Circle of willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arteriosclerosis, thrombosis, and vascular biology*, 23(11), 2055–2062. doi:10.1161 /01.ATV.0000095973.42032.44.

Dolan, H., Crain, B., Troncoso, J., Resnick, S. M., Zonderman, A. B., & Obrien, R. J. (2010). Atherosclerosis, dementia, and Alzheimer disease in the Baltimore Longitudinal Study of Aging cohort. *Annals of neurology*, 68(2), 231–240. doi:10.1002/ana.22055

Roher, A. E., Debbins, J. P., Malek-Ahmadi, M., Chen, K., Pipe, J. G., Maze, S., Belden, C., Maarouf, C. L., Thiyyagura, P., Mo, H., Hunter, J. M., Kokjohn, T. A., Walker, D. G., Kruchowsky, J. C., Belohlavek, M., Sabbagh, M. N., & Beach, T. G. (2012). Cerebral blood flow in Alzheimer's disease. *Vascular health and risk management*, 8, 599–611. doi:10.2147/VHRM.S34874

Black, S., Kushner, I., & Samols, D. (2004). C-reactive Protein. *The Journal of biological chemistry*, 279(47), 48487–48490. doi:10.1074/jbc.R400025200

Reynolds, G. D., & Vance, R. P. (1987). C-reactive protein immunohistochemical localization in normal and atherosclerotic human aortas. *Archives of pathology & laboratory medicine*, 111(3), 265–269.

Yasojima, K., Schwab, C., McGeer, E. G., & McGeer, P. L. (2000). Human neurons generate C-reactive protein and amyloid P: upregulation in Alzheimer's disease.

Brain research, 887(1), 80–89. doi:10.1016/s0006-8993(00)02970-x

Oram, J. F., & Yokoyama, S. (1996). Apolipoprotein-mediated removal of cellular cholesterol and phospholipids. *Journal of lipid research*, 37(12), 2473–2491.

Grundy S. M. (2002). Low-density lipoprotein, non-high-density lipoprotein, and apolipoprotein B as targets of lipid-lowering therapy. *Circulation,* 106(20), 2526–2529. doi:10.1161/01.cir.0000038419.53000.d6

Ohashi, R., Mu, H., Wang, X., Yao, Q., & Chen, C. (2005). Reverse cholesterol transport and cholesterol efflux in atherosclerosis. *QJM: monthly journal of the Association of Physicians*, 98(12), 845–856. doi:10.1093/qjmed/hci136

Rosenson, R. S., Brewer, H. B., Jr, Davidson, W. S., Fayad, Z. A., Fuster, V., Goldstein, J., Hellerstein, M., Jiang, X. C., Phillips, M. C., Rader, D. J., Remaley, A. T., Rothblat, G. H., Tall, A. R., & Yvan-Charvet, L. (2012). Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. Circulation, 125(15), 1905–1919. doi:10.1161/CIRCULATIONAHA.111.066589

Lund-Katz, S., & Phillips, M. C. (2010). High density lipoprotein structure-function and role in reverse cholesterol transport. *Sub-cellular biochemistry*, 51, 183–227. doi:10.1007/978-90-481-8622-8_7

Mahley, R. W., & Ji, Z. S. (1999). Remnant lipoprotein metabolism: key pathways involving cell-surface heparan sulfate proteoglycans and apolipoprotein E. *Journal of lipid research*, 40(1), 1–16

Mahley, R. W., & Rall, S. C., Jr (2000). Apolipoprotein E: far more than a lipid transport protein. *Annual review of genomics and human genetics*, 1, 507–537. doi:10.1146/annurev.genom.1.1.507

Mahley R. W. (1988). Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science (New York, N.Y.),* 240(4852), 622–630. doi:10.1126/science.3283935

Breslow J. L. (1996). Mouse models of atherosclerosis. *Science (New York, N.Y.)*, 272(5262), 685–688. doi:10.1126/science.272.5262.685

Ishibashi, S., Goldstein, J. L., Brown, M. S., Herz, J., & Burns, D. K. (1994). Massive xanthomatosis and atherosclerosis in cholesterol-fed low density lipoprotein receptor-negative mice. *The Journal of clinical investigation*, 93(5), 1885–1893. doi:10.1172/JCI117179

Citron, M., Oltersdorf, T., Haass, C., McConlogue, L., Hung, A. Y., Seubert, P., Vigo-Pelfrey, C., Lieberburg, I., & Selkoe, D. J. (1992). Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production. *Nature*, 360(6405), 672–674. doi:10.1038/360672a0

Tokuda, T., Calero, M., Matsubara, E., Vidal, R., Kumar, A., Permanne, B., Zlokovic, B., Smith, J. D., Ladu, M. J., Rostagno, A., Frangione, B., & Ghiso, J. (2000). Lipidation of apolipoprotein E influences its isoform-specific interaction with Alzheimer's amyloid beta peptides. *The Biochemical journal*, 348 Pt 2(Pt 2), 359–365.

Ji, Z. S., Miranda, R. D., Newhouse, Y. M., Weisgraber, K. H., Huang, Y., & Mahley, R. W. (2002). Apolipoprotein E4 potentiates amyloid beta peptide-induced lysosomal leakage and apoptosis in neuronal cells. *The Journal of biological chemistry*, 277(24), 21821–21828. doi:10.1074/jbc.M112109200

Ye, S., Huang, Y., Müllendorff, K., Dong, L., Giedt, G., Meng, E. C., Cohen, F. E., Kuntz, I. D., Weisgraber, K. H., & Mahley, R. W. (2005). Apolipoprotein (apo) E4 enhances amyloid beta peptide production in cultured neuronal cells: apoE structure as a potential therapeutic target. *Proceedings of the National Academy of Sciences of the United States of America,* 102(51),18700–18705.doi:10.1073/pnas.0508693102

Niwa, K., Kazama, K., Younkin, S. G., Carlson, G. A., & Iadecola, C. (2002). Alterations in cerebral blood flow and glucose utilization in mice overexpressing the amyloid precursor protein. *Neurobiology of disease*, 9(1), 61–68. doi:10.1006/nbdi.2001.0460

Kalaria, R. N., Akinyemi, R., & Ihara, M. (2016). Stroke injury, cognitive impairment and vascular dementia. *Biochimica et biophysica acta,* 1862(5), 915–925. doi:10.1016/j.bbadis.2016.01.015

Zaghi, J., Goldenson, B., Inayathullah, M., Lossinsky, A. S., Masoumi, A., Avagyan, H., Mahanian, M., Bernas, M., Weinand, M., Rosenthal, M. J., Espinosa-Jeffrey, A., de Vellis, J., Teplow, D. B., & Fiala, M. (2009). Alzheimer disease macrophages shuttle amyloid-beta from neurons to vessels, contributing to amyloid angiopathy. *Acta neuropathologica*, 117(2), 111–124. doi:10.1007/s00401-008-0481-0

Lee, P. H., Bang, O. Y., Hwang, E. M., Lee, J. S., Joo, U. S., Mook-Jung, I., & Huh, K. (2005). Circulating beta amyloid protein is elevated in patients with acute ischemic stroke. *Journal of neural transmission* (Vienna, Austria : 1996), 112(10), 1371–1379. doi:10.1007/s00702-004-0274-0

Chui, H. C., Zheng, L., Reed, B. R., Vinters, H. V., & Mack, W. J. (2012). Vascular risk factors and Alzheimer's disease: are these risk factors for plaques and tangles or for concomitant vascular pathology that increases the likelihood of dementia? An evidence-based review. *Alzheimer's research & therapy*, 4(1), 1. doi:10.1186/alzrt98

Thomas, T., Thomas, G., McLendon, C., Sutton, T., & Mullan, M. (1996). beta-Amyloid-mediated vasoactivity and vascular endothelial damage. *Nature*, 380(6570), 168–171. doi:10.1038/380168a0

Li, L., Cao, D., Garber, D. W., Kim, H., & Fukuchi, K. (2003). Association of aortic atherosclerosis with cerebral beta-amyloidosis and learning deficits in a mouse model of Alzheimer's disease. *The American journal of pathology,* 163(6), 2155–2164. doi:10.1016/s0002-9440(10)63572-9

Tibolla, G., Norata, G. D., Meda, C., Arnaboldi, L., Uboldi, P., Piazza, F., Ferrarese, C., Corsini, A., Maggi, A., Vegeto, E., & Catapano, A. L. (2010). Increased atherosclerosis and vascular inflammation in APP transgenic mice with apolipoprotein E deficiency. *Atherosclerosis*, 210(1),78–87. doi:10.1016/j.atherosclerosis.2009. 10.040

Luchsinger, J. A., Reitz, C., Honig, L. S., Tang, M. X., Shea, S., & Mayeux, R. (2005). Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*,65(4),545–551. doi:10.1212/01.wnl.0000172914.08967.dc

Peters, R., Poulter, R., Warner, J., Beckett, N., Burch, L., & Bulpitt, C. (2008). Smoking, dementia and cognitive

decline in the elderly, a systematic review. *BMC geriatrics*, 8, 36. doi:10.1186/1471-2318-8-36

Cataldo, J. K., Prochaska, J. J., & Glantz, S. A. (2010). Cigarette smoking is a risk factor for Alzheimer's Disease: an analysis controlling for tobacco industry affiliation. *Journal of Alzheimer's disease : JAD*, 19(2), 465–480. doi:10.3233/JAD-2010-1240

Bazzano, L. A., He, J., Muntner, P., Vupputuri, S., & Whelton, P. K. (2003). Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Annals of internal medicine,* 138(11), 891–897.doi:10.7326/0003-4819-138-11-200306030-00010

Hankey, G. J., & Eikelboom, J. W. (1999). Homocysteine and vascular disease. *Lancet (London, England)*, 354(9176), 407–413. doi:10.1016/S0140-6736(98)11058-9

Sachdev, P. S., Parslow, R. A., Lux, O., Salonikas, C., Wen, W., Naidoo, D., Christensen, H., & Jorm, A. F. (2005). Relationship of homocysteine, folic acid and vitamin B12 with depression in a middle-aged community sample. *Psychological medicine*, 35(4), 529–538. doi:10.1017/s0033291704003721

Seshadri, S., Wolf, P. A., Beiser, A. S., Selhub, J., Au, R., Jacques, P. F., Yoshita, M., Rosenberg, I. H., D'Agostino, R. B., & DeCarli, C. (2008). Association of plasma total homocysteine levels with subclinical brain injury: cerebral volumes, white matter hyperintensity, and silent brain infarcts at volumetric magnetic resonance imaging in the Framingham Offspring Study. *Archives of neurology*, 65(5), 642–649.doi:10.1001/archneur.65.5.642

Kemp, A. H., & Quintana, D. S. (2013). The relationship between mental and physical health: insights from the study of heart rate variability. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology*, 89(3), 288–296. doi:10.1016/j.ijpsycho.2013.06.018

Ambrose, J. A., & Barua, R. S. (2004). The pathophysiology of cigarette smoking and cardiovascular disease: an update. *Journal of the American College of Cardiology*, 43(10), 1731–1737. doi:10.1016/j.jacc.2003.12.047

Rapp, M. A., Schnaider-Beeri, M., Grossman, H. T., Sano, M., Perl, D. P., Purohit, D. P., Gorman, J. M., & Haroutunian, V. (2006). Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. *Archives of general psychiatry,*63(2),161–167. doi:10.1001/archpsyc.63.2.161

Alonso, R., Pisa, D., Rábano, A., & Carrasco, L. (2014). Alzheimer's disease and disseminated mycoses. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology,* 33(7), 1125–1132. doi:10.1007/s10096-013-2045-z

Alonso, R., Pisa, D., Rábano, A., & Carrasco, L. (2014). Alzheimer's disease and disseminated mycoses. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology,* 33(7), 1125–1132. doi:10.1007/s10096-013-2045-z

Wei, Y., Zhang, J. J., Li, Z., Gow, A., Chung, K. F., Hu, M., Sun, Z., Zeng, L., Zhu, T., Jia, G., Li, X., Duarte, M., & Tang, X. (2016). Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: findings from a natural experiment in Beijing. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*, 30(6), 2115–2122. doi:10.1096/fj.201500142

Brook R. D. (2008). Cardiovascular effects of air pollution. *Clinical science (London, England :* 1979), 115(6), 175–187. doi:10.1042/CS20070444

Little, C. S., Hammond, C. J., MacIntyre, A., Balin, B. J., & Appelt, D. M. (2004). Chlamydia pneumoniae induces Alzheimer-like amyloid plaques in brains of BALB/c mice. *Neurobiology of aging*, 25(4), 419–429. doi:10.1016/S0197-4580(03)00127-1

Wozniak, M. A., Itzhaki, R. F., Shipley, S. J., & Dobson, C. B. (2007). Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. *Neuroscience letters,* 429(2-3), 95–100. doi:10.1016/j.neulet.2007.09.077

Green, D. A., Masliah, E., Vinters, H. V., Beizai, P., Moore, D. J., & Achim, C. L. (2005). Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. *AIDS (London, England),* 19(4), 407–411. doi:10.1097/01.aids.0000161770.06158.5c

Moazed, T. C., Kuo, C., Grayston, J. T., & Campbell, L. A. (1997). Murine models of Chlamydia pneumoniae infection and atherosclerosis. *The Journal of infectious diseases*, 175(4), 883–890. doi:10.1086/513986

Liu, L., Hu, H., Ji, H., Murdin, A. D., Pierce, G. N., & Zhong, G. (2000). Chlamydia pneumoniae infection significantly exacerbates aortic atherosclerosis in an LDLR-/- mouse model within six months. *Molecular and cellular biochemistry*, 215(1-2), 123–128. doi:10.1023/a:1026531506202

Coombes, B. K., & Mahony, J. B. (1999). Chlamydia pneumoniae infection of human endothelial cells induces proliferation of smooth muscle cells via an endothelial cell-derived soluble factor(s). *Infection and immunity*, 67(6), 2909–2915. doi:10.1128/IAI.67.6.2909-2915.1999

Miyamoto, T., Yumoto, H., Takahashi, Y., Davey, M., Gibson, F. C., 3rd, & Genco, C. A. (2006). Pathogen-accelerated atherosclerosis occurs early after exposure and can be prevented via immunization. *Infection and immunity*, 74(2), 1376–1380. doi:10.1128/IAI.74.2.1376-1380.2006

Ayada, K., Yokota, K., Hirai, K., Fujimoto, K., Kobayashi, K., Ogawa, H., Hatanaka, K., Hirohata, S., Yoshino, T., Shoenfeld, Y., Matsuura, E., & Oguma, K. (2009). Regulation of cellular immunity prevents Helicobacter pylori-induced atherosclerosis. *Lupus*, 18(13), 1154–1168. doi:10.1177/0961203309106600

Kesavalu, L., Lucas, A. R., Verma, R. K., Liu, L., Dai, E., Sampson, E., & Progulske-Fox, A. (2012). Increased atherogenesis during Streptococcus mutans infection in ApoE-null mice. *Journal of dental research*, 91(3), 255–260. doi:10.1177/0022034511435101

Alber, D. G., Powell, K. L., Vallance, P., Goodwin, D. A., & Grahame-Clarke, C. (2000). Herpesvirus infection accelerates atherosclerosis in the apolipoprotein E-deficient mouse. *Circulation,* 102(7), 779–785. doi:10.1161/01.cir.102.7.779

Naghavi, M., Wyde, P., Litovsky, S., Madjid, M., Akhtar, A., Naguib, S., Siadaty, M. S., Sanati, S., & Casscells, W. (2003). Influenza infection exerts prominent inflammatory and thrombotic effects on the atherosclerotic plaques of apolipoprotein E-deficient

mice. *Circulation*, 107(5), 762–768. doi:10.1161/01.cir.0000048190.68071.2b

Hsich, E., Zhou, Y. F., Paigen, B., Johnson, T. M., Burnett, M. S., & Epstein, S. E. (2001). Cytomegalovirus infection increases development of atherosclerosis in Apolipoprotein-E knockout mice. *Atherosclerosis*, 156(1), 23–28. doi:10.1016/s0021-9150(00)00608-0

Hardy, J. A., & Higgins, G. A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science (New York, N.Y.),*256(5054),184–185.doi:10.1126/science.1566067

Patterson, B. W., Elbert, D. L., Mawuenyega, K. G., Kasten, T., Ovod, V., Ma, S., Xiong, C., Chott, R., Yarasheski, K., Sigurdson, W., Zhang, L., Goate, A., Benzinger, T., Morris, J. C., Holtzman, D., & Bateman, R. J. (2015). Age and amyloid effects on human central nervous system amyloid-beta kinetics. *Annals of neurology*, 78(3), 439–453. doi:10.1002/ana.24454

Yau, W. W., Tudorascu, D. L., McDade, E. M., Ikonomovic, S., James, J. A., Minhas, D., Mowrey, W., Sheu, L. K., Snitz, B. E., Weissfeld, L., Gianaros, P. J., Aizenstein, H. J., Price, J. C., Mathis, C. A., Lopez, O. L., & Klunk, W. E. (2015). Longitudinal assessment of neuroimaging and clinical markers in autosomal dominant Alzheimer's disease: a prospective cohort study. *The Lancet. Neurology*, 14(8), 804–813. doi:10.1016/S1474-4422(15)00135-

Kalaria, R. N., Akinyemi, R., & Ihara, M. (2012). Does vascular pathology contribute to Alzheimer changes?. *Journal of the neurological sciences*, 322(1-2), 141–147. doi:10.1016/j.jns.2012.07.032

Suo, Z., Humphrey, J., Kundtz, A., Sethi, F., Placzek, A., Crawford, F., & Mullan, M. (1998). Soluble Alzheimers beta-amyloid constricts the cerebral vasculature in vivo. *Neuroscience letters,* 257(2), 77–80. doi:10.1016/s0304-3940(98)00814-3

Hughes, T. M., Kuller, L. H., Barinas-Mitchell, E. J., Mackey, R. H., McDade, E. M., Klunk, W. E., Aizenstein, H. J., Cohen, A. D., Snitz, B. E., Mathis, C. A., Dekosky, S. T., & Lopez, O. L. (2013). Pulse wave velocity is associated with β-amyloid deposition in the brains of very elderly adults. Neurology, 81(19), 1711–1718. doi:10.1212/01.wnl.0000435301.64776.37

Hughes, T. M., Craft, S., & Lopez, O. L. (2015). Review of 'the potential role of arterial stiffness in the pathogenesis of Alzheimer's disease'. *Neurodegenerative disease management,* 5(2), 121–135. doi:10.2217/nmt.14.53

.Henry-Feugeas, M. C., Roy, C., Baron, G., & Schouman-Claeys, E. (2009). Leukoaraiosis and pulse-wave encephalopathy: observations with phase-contrast MRI in mild cognitive impairment. *Journal of neuroradiology = Journal de neuroradiologie*, 36(4), 212–218. doi:10.1016/j.neurad.2009.01.003

Williams, M. A., McGowan, A. J., Cardwell, C. R., Cheung, C. Y., Craig, D., Passmore, P., Silvestri, G., Maxwell, A. P., & McKay, G. J. (2015). Retinal microvascular network attenuation in Alzheimer's disease. *Alzheimer's & dementia (Amsterdam, Netherlands*), 1(2), 229–235. doi:10.1016/j.dadm.2015.04.001

Cheung, C. Y., Ong, Y. T., Ikram, M. K., Ong, S. Y., Li, X., Hilal, S., Catindig, J. A., Venketasubramanian, N., Yap, P., Seow, D., Chen, C. P., & Wong, T. Y. (2014). Microvascular network alterations in the retina of patients with Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association,* 10(2), 135–142. doi:10.1016/j.jalz.2013.06.009

Hottman, D. A., Chernick, D., Cheng, S., Wang, Z., & Li, L. (2014). HDL and cognition in neurodegenerative disorders. *Neurobiology of disease*, 72 Pt A, 22–36. doi:10.1016/j.nbd.2014.07.015

Button, E. B., Robert, J., Caffrey, T. M., Fan, J., Zhao, W., & Wellington, C. L. (2019). HDL from an Alzheimer's disease perspective. *Current opinion in lipidology*, 30(3), 224–234. doi:10.1097/MOL.0000000000000604

Castelli W. P. (1988). Cholesterol and lipids in the risk of coronary artery disease--the Framingham Heart Study. *The Canadian journal of cardiology*, 4 Suppl A, 5A–10A.

Wingo, T. S., Cutler, D. J., Wingo, A. P., Le, N. A., Rabinovici, G. D., Miller, B. L., Lah, J. J., & Levey, A. I. (2019). Association of Early-Onset Alzheimer Disease With Elevated Low-Density Lipoprotein Cholesterol Levels and Rare Genetic Coding Variants of APOB. *JAMA neurology*, 76(7), 809–817. doi:10.1001/jamaneurol.2019.0648

Yamazaki, Y., Zhao, N., Caulfield, T. R., Liu, C. C., & Bu, G. (2019). Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. *Nature reviews. Neurology*, 15(9), 501–518. doi:10.1038/s41582-019-0228-7

Huynh, T. V., Davis, A. A., Ulrich, J. D., & Holtzman, D. M. (2017). Apolipoprotein E and Alzheimer's disease: the influence of apolipoprotein E on amyloid-β and other amyloidogenic proteins. *Journal of lipid research*, 58(5), 824–836. doi:10.1194/jlr.R075481

Huang, Y., & Mahley, R. W. (2014). Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. *Neurobiology of disease*, 72 Pt A, 3–12. doi:10.1016/j.nbd.2014.08.025

Huynh, T. V., Wang, C., Tran, A. C., Tabor, G. T., Mahan, T. E., Francis, C. M., Finn, M. B., Spellman, R., Manis, M., Tanzi, R. E., Ulrich, J. D., & Holtzman, D. M. (2019). Lack of hepatic apoE does not influence early Aβ deposition: observations from a new APOE knock-in model. *Molecular neurodegeneration*, 14(1), 37. doi:10.1186/s13024-019-0337-1

Robert, J., Button, E. B., Martin, E. M., McAlary, L., Gidden, Z., Gilmour, M., Boyce, G., Caffrey, T. M., Agbay, A., Clark, A., Silverman, J. M., Cashman, N. R., & Wellington, C. L. (2020). Cerebrovascular amyloid Angiopathy in bioengineered vessels is reduced by high-density lipoprotein particles enriched in Apolipoprotein E. *Molecular neurodegeneration*, 15(1), 23. doi:10.1186/s13024-020-00366-8

Khalil, A., Fulop, T., & Berrougui, H. (2021). Role of Paraoxonase1 in the Regulation of High-Density Lipoprotein Functionality and in Cardiovascular Protection. *Antioxidants & redox signaling,* 34(3), 191–200. doi:10.1089/ars.2019.7998

Boyce, G., Button, E., Soo, S., & Wellington, C. (2017). The pleiotropic vasoprotective functions of high density lipoproteins (HDL). *Journal of biomedical research*, 32(3), 164–182. Advance online publication. doi:10.7555/JBR.31.20160103

Holzer, M., Trieb, M., Konya, V., Wadsack, C., Heinemann, A., & Marsche, G. (2013). Aging affects high-density lipoprotein composition and function. *Biochimica et*

biophysica acta, 1831(9), 1442–1448. doi:10.1016 /j.bbalip.2013.06.004

Robert, J., Button, E. B., Yuen, B., Gilmour, M., Kang, K., Bahrabadi, A., Stukas, S., Zhao, W., Kulic, I., & Wellington, C. L. (2017). Clearance of beta-amyloid is facilitated by apolipoprotein E and circulating high-density lipoproteins in bioengineered human vessels. *eLife,* 6, e29595. doi:10.7554/eLife.29595

Riwanto, M., & Landmesser, U. (2013). High density lipoproteins and endothelial functions: mechanistic insights and alterations in cardiovascular disease. *Journal of lipid research*, 54(12), 3227–3243. doi:10.1194/jlr.R037762

Price, M. J., & Shah, P. K. (2002). New strategies in managing and preventing atherosclerosis: focus on HDL. *Reviews in cardiovascular medicine*, 3(3), 129–137.

Berliner, J. A., Navab, M., Fogelman, A. M., Frank, J. S., Demer, L. L., Edwards, P. A., Watson, A. D., & Lusis, A. J. (1995). Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. *Circulation*, 91(9), 2488–2496. doi:10.1161/01.cir.91.9.2488

Navab, M., Berliner, J. A., Watson, A. D., Hama, S. Y., Territo, M. C., Lusis, A. J., Shih, D. M., Van Lenten, B. J., Frank, J. S., Demer, L. L., Edwards, P. A., & Fogelman, A. M. (1996). The Yin and Yang of oxidation in the development of the fatty streak. A review based on the 1994 George Lyman Duff Memorial Lecture. *Arteriosclerosis, thrombosis, and vascular biology*, 16(7), 831–842. doi:10.1161/01.atv.16.7.831

91. Hill, S. A., & McQueen, M. J. (1997). Reverse cholesterol transport--a review of the process and its clinical implications. *Clinical biochemistry*, 30(7), 517–525. doi:10.1016/s0009-9120(97)00098-2

Navab, M., Hama, S. Y., Anantharamaiah, G. M., Hassan, K., Hough, G. P., Watson, A. D., Reddy, S. T., Sevanian, A., Fonarow, G. C., & Fogelman, A. M. (2000). Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: steps 2 and 3. *Journal of lipid research*, 41(9), 1495–1508

Mackness, M. I., Arrol, S., Abbott, C., & Durrington, P. N. (1993). Protection of low-density lipoprotein against oxidative modification by high-density lipoprotein associated paraoxonase. *Atherosclerosis*, 104(1-2), 129–135. doi:10.1016/0021-9150(93)90183-u

Watson, A. D., Navab, M., Hama, S. Y., Sevanian, A., Prescott, S. M., Stafforini, D. M., McIntyre, T. M., Du, B. N., Fogelman, A. M., & Berliner, J. A. (1995). Effect of platelet activating factor-acetylhydrolase on the formation and action of minimally oxidized low density lipoprotein. *The Journal of clinical investigation*, 95(2), 774–782. doi:10.1172/JCI117726

Shah P. K. (2000). Plaque disruption and thrombosis: potential role of inflammation and infection. *Cardiology in review*, 8(1), 31–39.

Matsuda, Y., Hirata, K., Inoue, N., Suematsu, M., Kawashima, S., Akita, H., & Yokoyama, M. (1993). High density lipoprotein reverses inhibitory effect of oxidized low density lipoprotein on endothelium-dependent arterial relaxation. *Circulation research,* 72(5), 1103–1109. doi:10.1161/01.res.72.5.1103

Nilsson, J., Dahlgren, B., Ares, M., Westman, J., Hultgårdh Nilsson, A., Cercek, B., & Shah, P. K. (1998). Lipoprotein-like phospholipid particles inhibit the smooth muscle cell cytotoxicity of lysophosphatidylcholine and platelet-activating factor. *Arteriosclerosis, thrombosis, and vascular biology,* 18(1), 13–19. doi:10.1161/01.atv.18.1.13

Shah, P. K., Nilsson, J., Kaul, S., Fishbein, M. C., Ageland, H., Hamsten, A., Johansson, J., Karpe, F., & Cercek, B. (1998). Effects of recombinant apolipoprotein A-I(Milano) on aortic atherosclerosis in apolipoprotein E-deficient mice. *Circulation,* 97(8), 780–785. doi:10.1161/01.cir.97.8.780

Rong, J. X., Li, J., Reis, E. D., Choudhury, R. P., Dansky, H. M., Elmalem, V. I., Fallon, J. T., Breslow, J. L., & Fisher, E. A. (2001). Elevating high-density lipoprotein cholesterol in apolipoprotein E-deficient mice remodels advanced atherosclerotic lesions by decreasing macrophage and increasing smooth muscle cell content. *Circulation*, 104(20), 2447–2452. doi:10.1161/hc4501.098952

Shah, P. K., Yano, J., Reyes, O., Chyu, K. Y., Kaul, S., Bisgaier, C. L., Drake, S., & Cercek, B. (2001). High-dose recombinant apolipoprotein A-I(milano) mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein e-deficient mice. Potential implications for acute plaque stabilization. *Circulation,* 103(25), 3047–3050. doi:10.1161/hc2501.092494