HDL from an Alzheimer’s disease perspective

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Purpose of review
We review current knowledge regarding HDL and Alzheimer’s disease, focusing on HDL’s vasoprotective functions and potential as a biomarker and therapeutic target for the vascular contributions of Alzheimer’s disease.

Recent findings
Many epidemiological studies have observed that circulating HDL levels associate with decreased Alzheimer’s disease risk. However, it is now understood that the functions of HDL may be more informative than levels of HDL cholesterol (HDL-C). Animal model studies demonstrate that HDL protects against memory deficits, neuroinflammation, and cerebral amyloid angiopathy (CAA). In-vitro studies using state-of-the-art 3D models of the human blood–brain barrier (BBB) confirm that HDL reduces vascular $A\beta$ accumulation and attenuates $A\beta$-induced endothelial inflammation. Although HDL-based therapeutics have not been tested in clinical trials for Alzheimer’s disease, several HDL formulations are in advanced phase clinical trials for coronary artery disease and atherosclerosis and could be leveraged toward Alzheimer’s disease.

Summary
Evidence from human studies, animal models, and bioengineered arteries supports the hypothesis that HDL protects against cerebrovascular dysfunction in Alzheimer’s disease. Assays of HDL functions relevant to Alzheimer’s disease may be desirable biomarkers of cerebrovascular health. HDL-based therapeutics may also be of interest for Alzheimer’s disease, using stand-alone or combination therapy approaches.

Keywords
Alzheimer’s disease, blood–brain barrier, cerebral amyloid angiopathy, cerebrovasculature, dementia, HDL

INTRODUCTION
Alzheimer’s disease is the leading cause of senile dementia with over 44 million affected persons and an economic burden of over $600 billion [1]. Beyond the beta-amyloid (Aβ) plaques and neurofibrillary tangles that define Alzheimer’s disease, 60–90% of Alzheimer’s disease brains have evidence of cerebral vessel disease [2]. No effective disease-modifying drugs for Alzheimer’s disease exist despite decades of promising research [3]. This may be, in part, to the complex interplay of amyloid and tau disorders, neuroinflammation and cerebrovascular compromise, and significant challenges in defining and staging Alzheimer’s disease. Studies in humans, animals, and in-vitro models support the hypothesis that circulating HDL, which have established vasoprotective properties, may also provide resilience to cerebrovascular dysfunction in Alzheimer’s disease. In this review, we synthesize these data toward a rationale to develop HDL functional assays as potential biomarkers of cerebrovascular health and to consider clinical trials that evaluate HDL-based therapies for Alzheimer’s disease.

THE CEREBROVASCUKATURE AND ITS RELATIONSHIP WITH ALZHEIMER’S DISEASE
Despite constituting only 2% of total body mass, the brain consumes approximately 20% of total cardiac output [4]. The brain’s high metabolic activity and lack of glucose stores requires extensive vasculization to enable oxygen and glucose influx, maintain ion balance, and remove neurotoxic waste products.
Cerebrovascular dysfunction is commonly observed in Alzheimer’s disease patients.

Higher plasma HDL levels are often associated with a lower risk of dementia.

HDL can protect mice from CAA, memory deficits, and neuroinflammation.

HDL protects against CAA and Ab-induced inflammation in 3D artery models.

HDL-based biomarkers may identify Alzheimer’s disease subjects with vascular dysfunction.

Repurposing existing HDL therapies for Alzheimer’s disease is promising because of positive safety data.

Most dementia cases exhibit vascular disorders that may underlie compromised cerebrovascular function [6]. Histopathological evidence for cerebrovascular dysfunction in Alzheimer’s disease includes arteriole and precapillary deformities [7], reduced vascular density [8,9], increased vessel tortuosity [9], and vessel remnants that lack endothelial cells [10–12]. Large-scale autopsy studies by the National Alzheimer’s Coordinating Center and the Religious Orders Study and Rush Memory and Aging Project found a greater burden of macroinfarcts and microinfarcts, atherosclerosis, arteriosclerosis, and cerebral amyloid angiopathy (CAA) in Alzheimer’s disease compared with other neurodegenerative diseases [6], and increased Alzheimer’s disease risk in cases with infarcts and more severe atherosclerosis or arteriosclerosis [13], respectively.

Analysis of 7700 multimodality images from the Alzheimer’s Disease Neuroimaging Initiative identified cerebrovascular dysfunction as an early event in Alzheimer’s disease. This study compared cerebral blood flow (CBF) alterations measured with arterial spin labelling MRI to the progression of amyloid, tau, and neurodegeneration (ATN) research framework developed by the National Institute on Aging and Alzheimer’s Association (NIA-AA) to provide a biological definition of Alzheimer’s disease [21].

The cerebrovasculature plays a pivotal role in removing Aβ from the brain through active transport across brain endothelial cells in a process involving various receptors including LDL receptor-related protein (LRP1), p-glycoprotein, and LDLR. Aβ is also cleared from the brain via perivascular drainage in mid-sized and large-sized arteries along smooth muscle cell basement membranes [22]. Disruption of Aβ clearance via cerebrovascular pathways may contribute to CAA [23].

Vascular comorbidities in Alzheimer’s disease

The importance of the vasculature in Alzheimer’s disease is further supported by associations between cardiovascular diseases (CVD) and Alzheimer’s disease risk [24–26]. Genetic variations in human apolipoprotein E (apoE) increase Alzheimer’s disease risk and reduce age of Alzheimer’s disease onset with ApoE-ε4 being detrimental, ApoE-ε3 neutral and ApoE-ε2 protective [27]. In addition to accelerating amyloidogenesis [28], ApoE-ε4 contributes to reduced CBF, CAA, cerebrovascular inflammation, altered neurovascular coupling, BBB leakiness, and reduced cerebrovascular resilience to cardiometabolic risk factors (reviewed in [29,30]). Alzheimer’s disease and CVD also share many cardiometabolic risk factors including age, sex, smoking, blood pressure, physical activity, blood lipids, and type 2 diabetes mellitus (T2DM) [31*,32,33]. Several of these factors have been combined into the Cardiovascular Risk Factors Aging and Dementia risk score, which correlates with executive function, visual perception, and construction, WMH and CSF Aβ and tau in healthy adults [34]. Furthermore, the population-based Rotterdam Study found that an MRI-based cerebral small vessel disease score was associated with greater dementia risk [35] and the Framingham cardiovascular risk profile score predicts conversion from MCI to Alzheimer’s disease within 24 months [36].

HDL AND VASCULAR RESILIENCE

Circulating HDL is best known for its pivotal role in reverse cholesterol transport [37]. Only one-third of the identified 95 proteins on HDL [38] have roles in lipid metabolism [39,40] whereas others...
function in protease inhibition, complement regulation, hemostasis, and inflammation [41]. Known vasoprotective functions of HDL include promoting endothelial nitric oxide (NO) synthase activity, reducing inflammation, and suppressing vascular adhesion molecule expression [42–46]. Importantly, aging and vascular disease can impair these functions [42,47–49].

**MIXED GENETIC EVIDENCE ON HDL AND VASCULAR RESILIENCE**

Mendelian randomization aims to determine the causality of a modifiable risk factor on disease risk by measuring how disease risk changes based on randomly distributed genetic variants that affect the risk factor [50]. Although it is well accepted that high plasma HDL-C levels associate with reduced heart disease mortality [51], Mendelian randomization questions the causality of this relationship. Several groups observe that genetic variants associated with HDL-C do not alter coronary heart disease (CHD), myocardial infarction, or carotid atherosclerosis risk [52–54], although one study found that an allele score based on all known genetic variants associated with HDL-C was significantly associated with CHD risk [52]. Two Mendelian randomization studies also suggest HDL-C levels are not causal for Alzheimer’s disease risk [55,56]. Importantly, these studies address only a causal link between disease risk and elevated HDL-C levels mediated by particular genes; they do not take into account the complex changes to HDL function and composition that can occur in disease and that can be superior predictors of disease risk [47–49,57–62]. Recently, two large genome-wide association studies (GWAS) for Alzheimer’s disease found lipoprotein metabolism and HDL particle gene sets to be significantly associated with Alzheimer’s disease risk. Genes in these sets encode HDL biogenesis proteins and HDL protein components, such as APOE, ABCA1, APOC1, APOM, APOA2, PON1, CLU, LCAT, CETP, and APOAI [63,64].

**EPIDEMIOLOGICAL EVIDENCE FOR A PROTECTIVE EFFECT OF HDL ON ALZHEIMER’S DISEASE**

Several studies show that Alzheimer’s disease risk is attenuated by higher levels of HDL cholesterol (HDL-C) or apoA-I, the major protein component of HDL [65]. Cross-sectional studies showed serum apoA-I and HDL-C levels are significantly lower in Alzheimer’s disease patients and inversely correlated with Mini Mental State Examination (MMSE) scores [66,67]. A role for HDL in Aβ clearance is suggested by positive correlations between plasma apoA-I and Aβ40 in CAA patients [68], and an inverse correlation between plasma HDL-C and brain amyloid burden in cognitively normal people on PET [69]. In people without dementia, positive associations have been found between HDL-C levels and working memory [70,71], MMSE scores [70], and verbal learning scores [71]. The prospective Honolulu-Aging study followed 929 Japanese-American men and found that the highest quartile of plasma apoA-I at baseline correlated with the lowest risk of dementia 16 years later [72]. Similarly, those with the highest baseline HDL-C in a cohort of 1130 elderly people in New York followed for a median of 4 years had reduced Alzheimer’s disease risk [73] and higher baseline HDL-C in the Baltimore Longitudinal Study of Aging protected against cognitive impairment and brain volume reductions 20 years later [74**].

However, other cross-sectional studies including the Framingham study of 1100 elderly participants [75] and a small cohort of Spanish nonagenarians [76] and prospective studies including the Adult Changes in Thought study and two studies in cognitively normal elderly women [77–80] found no relationship between HDL-C and cognitive impairment. Baseline age and follow-up length may explain these inconsistencies [72,78]. Indeed, the above studies with follow-up times greater than 10 years found significant associations between HDL-C levels and Alzheimer’s disease risk [72,74**] whereas others with less than 10 years of follow-up did not [78,80]. Furthermore, those measuring baseline HDL-C levels at middle age all found significant associations with Alzheimer’s disease risk [67,71,72] whereas those with baseline measures in subjects at least 70 years old did not [79,80]. HDL may, therefore, exert its greatest influence on Alzheimer’s disease risk at mid-life.

The mechanisms by which HDL influences Alzheimer’s disease risk remain unknown. Many HDL-associated proteins, such as apoA-I, apoJ, apoE, apoC-III, apoD, and apoA-IV are present within the brain parenchyma, cerebrospinal fluid (CSF), and cerebrovascular intima of leptomeningeal arteries [81–84]. Except for apoE, the CSF levels of these proteins correlate moderately with their respective levels in plasma, suggesting transport or diffusion from the periphery to the brain. Although it has been reported that HDL can be transported through human brain microvascular endothelial cells via scavenger receptor (SR)-B1 [85] and CSF lipoproteins are similar in density to plasma HDL [86], there is currently no evidence that HDL enters the brain as an intact particle in vivo. Therefore, HDL might indirectly influence brain health as a circulating...
factor primarily acting from the cerebrovascular lumen and intima (Fig. 1).

**VASOPROTECTIVE FUNCTIONS OF HDL IN ALZHEIMER’S DISEASE ANIMAL MODELS**

Studies in mice genetically engineered to develop amyloid have explored how HDL levels affect Alzheimer’s disease-relevant outcomes. Genetic ablation of apoA-I worsened memory deficits and increased CAA in APP/PS1 mice, a common Alzheimer’s disease model [87], without altering parenchymal Aβ plaque load [87,88]. Conversely, APP/PS1 mice with transgenic apoA-I overexpression exhibited attenuated memory deficits, CAA, and neuroinflammation [89]. Treatment of Alzheimer’s disease mice with HDL-based therapeutics resulted in similar improvements [90–93].

Although these studies have contributed toward understanding how HDL may protect from cerebrovascular dysfunction in Alzheimer’s disease, they may have only modest translational value because of differences in the distribution of circulating lipoproteins between rodents and humans. In mice, circulating lipids are mainly carried by HDL whereas in humans they are mainly carried by LDL [94]. These differences are, in part, governed by the activity of cholesterol ester transfer protein (CETP). CETP facilitates exchange of cholesteryl esters and triglycerides between lipoprotein subclasses and high CETP activity associated with lowered HDL-C levels [95]. However, mice and rats do not express CETP, which may partly underlie their high HDL-C levels [96]. Mice genetically engineered to express human CETP have a moderate dose-dependent reduction of HDL in the presence of both murine, and human apoA-I, but no change in other lipoprotein pools [96,97]. In addition, the murine and human APOE genes are substantially different [98] and extensive efforts have been made to develop

![Image of HDL functions in Alzheimer's disease](image-url)
targeted replacement or transgenic mice expressing each humanAPOE isoform [99–105], yet, these models may still under-report cerebrovascular compromise because of the high levels of circulating HDL. To our knowledge, there has not been a concerted effort to produce an animal model combining expression of human apoE, apoA-I, CETP, APP, and tau to improve the predictive power of murine models with respect to the vascular contributions to Alzheimer’s disease.

**MECHANISTIC STUDIES OF HDL-MEDIATED VASOPROTECTION IN IN-VITRO MODELS**

Developing human-based vascular models that retain anatomical and physiological similarities to humans are, therefore, highly desirable to overcome the difficulties of translating research from mice to humans. Many BBB studies have been performed using two dimensional (2D) cell culture of human brain endothelial cells from primary, immortalized, or pluripotent stem cell sources [106–114]. However, as cells behave differently in 3D compared with 2D environments [115], 3D BBB models are considered superior. Trans-well systems offer highly reproducible models for permeability assays [116,117] but lack complex cell–cell and cell–matrix interactions. Multicellular spheroids of human primary brain endothelial cells, pericytes, and astrocytes spontaneously self-organize into a BBB-like structure [118,119] but are not perfusible. Several ‘organ-on-a-chip’ approaches have been developed to overcome these barriers, beginning with microfluidic
models culturing primary murine neurons and glia cells with human cerebral endothelial cells [120]. Completely human-based systems have also been developed using iPSC-derived endothelial cells, primary pericytes, and astrocytes [121]. Maoz et al. [122] developed an innovative microfluidic system linking a BBB chip to a brain chip, however, this model lacks anatomical connections between cells of the neural vascular unit. Our group developed a 3D bioengineered human vessel model using a scaffold-directed dynamic pulsatile flow bioreactor system, populated with primary human endothelial cells, smooth muscle cells, and astrocytes [123,124]. These engineered tissues display histological features of native peripheral and cerebral arteries and can be used to model CAA and vascular inflammation. This model can also be used to interrogate four beneficial functions of HDL on cerebral vessels, namely preventing Aβ-induced endothelium activation, reducing Aβ vascular accumulation, maintaining Aβ in a soluble state, and inducing endothelial NO secretion [123,124,125] (Fig. 1).

CONSIDERATIONS TO EVALUATE HDL AS A POTENTIAL THERAPEUTIC AGENT FOR THE VASCULAR CONTRIBUTIONS TO ALZHEIMER’S DISEASE

The human, animal, and in-vitro studies discussed above provide support for HDL-based therapeutic approaches to protect or repair the BBB. Several HDL-based therapeutics for CVD have advanced to clinical trials and have both safety and efficacy data (Table 1). The recombinant apoA-I protein CER-001 [126–128], apoA-I mimetics, such as D-4F [129,130] and L-4F [131], the plasma-derived apoA-I formulation CSL-112 [132], and autologous administration of patient-derived apoA-I [133] were all well tolerated in phase I clinical trials for acute coronary syndrome or stable CHD. Although development of many of these agents was halted because of failure to meet primary outcomes of reduced atherosclerosis [126–128] or improved HDL function [131], CSL-112 and autologous apoA-I administration have shown promise and are undergoing phase III trials (NCT03473223, NCT03135184).

Indirect HDL-based therapeutics include the apoA-I transcription up-regulator RVX-208, the lecithin-cholesterol acyltransferase (LCAT) recombinant protein ACP-501, niacin, and CETP inhibitors (Table 1). RVX-208 lacked efficacy against atherosclerosis and caused a dose-dependent increase in liver transaminase levels [134,135]. ACP-501 was well tolerated in stable CHD patients [136] and is undergoing a phase II trial evaluating its effects on apolipoprotein B metabolism in CVD patients (NCT03773172). Early trials suggested niacin treatment could reduce cardiovascular events and atherosclerosis [137], however, two large randomized control trials (RCT) were terminated because of lack of efficacy [138,139]. Several trials for CETP inhibitors were terminated early because of futility or safety issues including increased mortality in the case of torcetrapib [140–142]. However, the most recent phase III trial of the potent CETP inhibitor anacetrapib had no adverse effects and reduced major coronary events [143]. CETP inhibitors may be especially useful for repurposing for Alzheimer’s disease as certain CETP polymorphisms are associated with Alzheimer’s disease risk and memory decline, particularly in APOE4 carriers [144–146].

Evaluation of HDL-based therapeutics on Alzheimer’s disease-relevant outcomes in animal models

Although no HDL-based therapeutic strategies have been tested for Alzheimer’s disease in clinical trials, several preclinical studies have been performed in Alzheimer’s disease mice. Intravenous administration of reconstituted HDL reduced soluble brain Aβ levels in APP/PS1 mice [90] as well as in SAMP8 mice [90], where it also reduced microgliosis and memory deficits [91]. APP23 mice treated intravenously with recombinant apoA-I Milano had reduced microgliosis, Aβ deposition, and CAA [93]. Oral D-4F treatment improved memory, Aβ deposition, microgliosis, astrogliosis, and other markers of inflammation in APPswe/PS1ΔE9 mice [92]. Outside the context of Alzheimer’s disease, D-4F treatment after middle cerebral artery occlusion reduced neuroinflammation and white matter damage [147] and D-4F improved cognition and reduced brain arteriole inflammation in atherosclerotic mice [148].

Additional lipid-modifying therapeutics for the prevention and treatment of dementia

Lipid-modifying approaches not directly targeting HDL may also be of interest for Alzheimer’s disease (Table 1). Statins inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase to block cholesterol synthesis and subtly increase the HDL:LDL ratio [149]. Meta-analyses suggest statin use lowers dementia risk in prospective trials [150–152] but not in two large RCTs [150,153]. Retrospective cohort studies on niacin found higher intake during young adulthood improved some measures of cognitive function 25 years later [154], and older adults with higher intake had reduced risk of
Alzheimer’s disease and cognitive decline over 6 years of follow-up [155], however, these studies lacked direct measurement of blood niacin levels.

Drugs targeting ATP-binding cassette A1 (ABCA1), such as liver-x-receptor (LXR) and retinoid-x-receptor (RXR) agonists, are another potential indirect HDL-based therapy as the rate-limiting step of HDL biogenesis involves ABCA1-mediated efflux [156–158]. Direct LXR and RXR agonists increase plasma HDL-C levels [159–162], central nervous system (CNS) apoE lipidation, and cognitive function in Alzheimer’s disease animal models (reviewed in [163]). Significant hepatotoxic and systemic side effects have hampered clinical development of direct LXR/RXR agonists [164–166], although new, LXR-independent ABCA1 modulators may avoid these liabilities [167]. The first ABCA1-targeting compound to reach clinical trials was the RXR agonist bexarotene, which in a phase I trial raised CSF apoE levels but had poor bioavailability [168] (Table 1).

LEVERAGING HDL AS A POTENTIAL THERAPEUTIC TO PROTECT AND REPAIR THE CEREBROVASCULARATURE IN ALZHEIMER’S DISEASE

The considerable evidence for the safety of several HDL-based therapeutics in clinical trials suggest these agents could be potentially repurposed for Alzheimer’s disease. Specifically, HDL may be of interest to prevent CAA and Alzheimer’s disease-related neuroinflammation based on its effects in mouse models [87,89,92,93,169] and 3D bioengineered human arteries [123**,124**,125]. HDL may also be developed as a carrier for drugs and microRNAs to overcome the issue of BBB penetration in drug delivery. Already, a reconstituted HDL carrying an Aβ-targeting drug has been shown to enter Alzheimer’s disease mouse brains, reduce amyloidosis, and improve memory [170].

HDL AS A POTENTIAL PREDICTIVE BIOMARKER FOR VASCULAR COMPROMISE IN ALZHEIMER’S DISEASE

Biomarker research for Alzheimer’s disease has rapidly progressed in recent years with the development of imaging techniques to visualize Aβ and tau deposits in living people and breakthroughs in fluid biomarker sensitivity and specificity [171]. As HDL can be isolated from the blood of Alzheimer’s disease patients and assayed in-vitro, it may be possible to develop HDL-based assays that specifically report on cerebrovascular health, particularly if they correlate with cerebrovascular disorders, such as a CAA, microinfarcts, or WMH. Again, there is currently no evidence that HDL can enter the brain parenchyma as an intact particle in vivo, instead HDL circulating in the lumen of cerebral vessels is proposed to impact brain health through effects on vessel health. It is well understood that HDL composition and function is altered by aging and in T2DM, and CAD patients [47–49,57–60]. Reduced cholesterol efflux and anti-inflammatory activity have also been observed in HDL from Alzheimer’s disease subjects [172,173]. Such changes to HDL function, or to other Alzheimer’s disease-relevant functions including modifying CAA, attenuating Aβ-induced endothelial activation, maintaining Aβ solubility, and promoting NO secretion [123**,124**,125], have the potential to act as predictive or prognostic biomarkers for Alzheimer’s disease.

Predictive biomarkers are used to stratify patient populations into subpopulations that would benefit from certain therapeutic strategies [174]. HDL functional assays reporting on cerebrovascular dysfunction could, therefore, act as predictive biomarkers for Alzheimer’s disease patients who may benefit from vascular-specific therapies. Whether HDL functions can predict risk, progression, or resolution of amyloid-related imaging abnormalities (ARIa) resulting from vascular Aβ clearance in response to anti-Aβ immunotherapies may also be interesting to evaluate [175]. HDL functional assays may also work as prognostic biomarkers. Diagnosing Alzheimer’s disease before unrepairable neurodegeneration occurs is a major obstacle in treating the disease. Prognostic biomarkers that can predict a patient’s progression into Alzheimer’s disease earlier than existing biomarkers could be a solution [171]. As vascular dysfunction occurs early in Alzheimer’s disease [14*,20*,21,176], biomarkers indicating cerebrovascular dysfunction have considerable potential in predicting cognitive decline. It is, therefore, important to evaluate longitudinal changes to HDL function to determine if HDL-based measurements could improve prognostic precision for Alzheimer’s disease’s vascular components.

It is less clear whether levels of HDL-associated proteins may become Alzheimer’s disease biomarkers. Circulating apoA-I levels are negatively associated with risk of future dementia in many [72,73,74**] but not all [77–80] studies. Furthermore, although a panel including serum apoA-I was shown to have high sensitivity and specificity for MCI [177,178], there were no HDL-associated protein hits in a nontargeted proteomic analysis employed to develop a multiprotein Alzheimer’s disease biomarker panel [179]. Early work investigating HDL-associated protein levels and
cerebrovascular dysfunction found that serum apoA-I levels are significantly lower in Alzheimer’s disease, MCI, and control subjects with severe CBF impairments [178]. Other studies found that the levels of HDL particles containing apoE and lacking apoJ predict greater WMH volume in normal and MCI subjects [180], and that plasma apoJ levels are higher in subjects with CAA-related intracerebral hemorrhages compared with Alzheimer’s disease subjects [68].

CONCLUSION
A growing body of evidence in humans, mice, and 3D in-vitro models supports a role for HDL in cerebrovascular resilience. As various HDL formulations have already been developed and tested in clinical trials for CVD, repurposing those with attractive safety profiles may offer a novel strategy for preventing or treating the cerebrovascular disorder associated with Alzheimer’s disease. Assays of HDL function could also act as biomarkers for cerebrovascular disorder in Alzheimer’s disease, which could assist in stratifying Alzheimer’s disease patients for more specific therapeutic interventions and providing a wider window for treating patients before irreversible neurodegeneration occurs.

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Conflicts of interest
There are no conflicts of interest.

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