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Dyslipidemia and the Risk of Alzheimer's Disease

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Abstract

Whether cholesterol is implicated in the cause of Alzheimer's disease (AD) is still controversial. Several studies that explored the association between lipids and/or lipid-lowering treatment and AD indicate a harmful effect of dyslipidemia on AD risk. The findings are supported by genetic linkage and association studies that have clearly identified several genes involved in cholesterol metabolism or transport as AD susceptibility genes, including apolipoprotein E (*APOE*), apolipoprotein J (*APOJ, CLU*), ATP-binding cassette subfamily A member 7(*ABCA7*), and sortilin-related receptor (*SORL1*). Functional cell biology studies further support a critical involvement of lipid raft cholesterol in the modulation of Aβ precursor protein processing by β-secretase and γ-secretase resulting in altered Aβ production. However, conflicting evidence comes from epidemiological studies showing no or controversial association between dyslipidemia and AD risk, randomized clinical trials observing no beneficial effect of statin therapy, and cell biology studies suggesting that there is little exchange between circulating and brain cholesterol, that increased membrane cholesterol level is protective by inhibiting loss of membrane integrity through amyloid cytotoxicity, and that cellular cholesterol inhibits colocalization of β-secretase 1 and Aβ precursor protein in nonraft membrane domains, thereby increasing generation of plasmin, an Aβ-degrading enzyme. The aim of this article is to provide a comprehensive review of the findings of epidemiological, genetic, and cell biology studies aiming to elucidate the role of cholesterol in the cause of AD.

Keywords

Alzheimer's disease; Cholesterol; High-density lipoprotein; Aβ peptides; Aβ precursor protein; Neurodegeneration; Amyloid

Introduction

Alzheimer's disease (AD) is the commonest cause of dementia and the fourth leading cause of death in Western societies. A clinical hallmark of AD is a progressive loss of cognitive function, in particular the memory domain, ultimately leading to complete dependency and death. The key histopathological hallmarks are extracellular neuritic plaques composed of β-amyloid peptide (Aβ) and intracellular neurofibrillary tangles consisting of an abnormally phosphorylated form of the protein tau.

Worldwide, about 25 million people are affected, and the incidence and costs of AD are predicted to quadruple by 2050 to approximately 80 million cases owing to increasing life

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expectancy.[1–3] These facts underline the role of AD as a major health burden and emphasize the need for identification of risk factors and identification of targets for diagnosis, prevention, and treatment.

Among the search for risk factors, extensive research has been done to explore the role of dyslipidemia in AD. Dyslipidemia is also highly prevalent in Western societies and is a widely recognized vascular risk factor.[4] According to the World Health Organization, it accounts for more than half of the global cases of ischemic heart disease and for more than four million deaths per year.[5] The fact that vascular disease, in turn, is clearly associated with risk of AD[6] and that dyslipidemia can be prevented and controlled in an effective and cost-beneficial manner has spurred interest in determining the association between blood lipid levels and AD risk and the beneficial effects of lipid-lowering intervention in AD. The goal of this article is to comprehensively review the findings of epidemiological, genetic, and cell biology studies aiming to elucidate the role of dyslipidemia in the cause of AD.

Data Collection

The articles were identified by a PubMed (MEDLINE) search, using “cholesterol,” “HDL,” “LDL,” “triglycerides,” “AD,” “dementia,” “statins,” “lipid-lowering agents,” “gene,” and “genetics” as keywords in various combinations. The inclusion criteria were the time period between 1985 and 2012, original articles only, and English language. All suitable articles were evaluated taking into account their internal validity (e.g., population type, dropout rate, diagnostic procedure, confounding control, presence of bias, statistical power) and causal criteria (strength of association and temporality). For epidemiological studies, cross-sectional studies were excluded, as they do not allow conclusions to be drawn regarding causal relationships.

Molecular Evidence for a Role of Lipids in AD

Several notions support the hypothesis that lipids may be directly involved in key pathological changes in AD. First, the brain contains approximately 30% of the total body cholesterol and is thus the cholesterol-richest organ in the body. Cholesterol is an essential component of cell membranes and plays a crucial role in the development and maintenance of neuronal plasticity and function.[7] Neuronal plasticity and function in turn are compromised in AD. Second, all proteins involved in Aβ precursor protein (AβPP) processing leading to generation of Aβ protein are integral membrane proteins, and the Aβ-producing γ-secretase cleavage occurs in the middle of the membrane, suggesting that the lipid environment of the cleavage enzymes influences Aβ production and hence AD pathogenesis.[8] The cleavage of AβPP by α-secretase results in nonamyloidogenic or soluble AβPP. In contrast, cleavage by the membrane associated β-secretase and γ-secretase results in amyloidogenic forms that aggregate as extracellular plaques.

Although it seems clear that the lipid environment of the cleavage enzymes influences Aβ production, the findings of studies exploring the effect of cholesterol on AD pathogenesis are contradictory. In animal studies, dietary cholesterol accelerates Aβ deposition in the brain, whereas cholesterol-lowering drugs decrease it.[9,10] Other in vitro studies, however, have shown that a high-cholesterol environment results in reduced production of soluble amyloid precursor protein,[11,12] that increased membrane cholesterol level is protective by inhibiting loss of membrane integrity through amyloid cytotoxicity, and that cellular cholesterol inhibits colocalization of β-secretase 1 and AβPP in nonraft membrane domains, thereby increasing generation of plasmin, an Aβ-degrading enzyme.[13] Third, it has been suggested that excess membrane cholesterol may indirectly promote production of neurofibrillary tangles.[14] The notion underlying this hypothesis is that neurofibrillary tangles are composed primarily of hyperphosphorylated tau, and that Aβ can induce tau

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phosphorylation. Consistent with this notion is the observation that injection of $A\beta_{42}$ into rat cortices causes a significant increase in hyperphosphorylation of tau protein.[15] Finally, there is evidence that high concentrations of oxysterols, oxidized derivatives of cholesterol, can provoke neuronal apoptosis and exocytosis.[16,17] Cholesterol oxidation product concentrations increase as a consequence of neuroinflammation associated with brain injury. However, they in turn enhance exocytosis and neurotransmitter release, thereby aggravating excitotoxicity.[17]

The blood–brain barrier prevents direct transport of cholesterol between the peripheral circulation and the CNS. Essentially all the cholesterol used in the brain is synthesized within the CNS. Although astrocytes, glial cells, and neurons can synthesize cholesterol de novo, cholesterol can also be recycled from extracellular locations within the CNS. The biosynthesis of cholesterol is a lengthy process requiring more than 20 reactions, and the rate-limiting step of cholesterol biosynthesis is the catalysis of the formation of mevalonate by 3-hydroxy-3-methylglutaryl coenzyme A reductase, making statins the prominent pharmacological intervention.

Oxysterols, however, are capable of passing through the blood–brain barrier, and over 90% of circulating (24*S*)-hydroxycholesterol originates in the brain. As a consequence, blood concentrations of (24*S*)-hydroxycholesterol reflect CNS cholesterol turnover.[18] Recent data demonstrate that high cholesterol and 27-hydroxycholesterol levels affect memory consolidation in experimental studies, suggesting that this cholesterol metabolite could link peripheral cholesterol to AD pathogenesis.[19] In addition to these cholesterol–24 hydroxylase-associated mechanisms, the exchange of cholesterol between blood and the CNS—and therefore the association between blood cholesterol and brain function—might also be mediated by members of the superfamily of ATP-binding cassette (ABC) membrane transport proteins. These proteins have a channel-like topology and are able to transport various solutes—including ions, drugs, peptides, proteins, sugars, and lipids—across cell membranes by coupling the transport to ATP hydrolysis.

Finally, whether dyslipidemia influences the risk of AD through vascular disease remains unclear. It is clear that both cerebral microvascular and macrovascular disease increase AD risk, but whether dyslipidemia in fact affects risk of cerebrovascular changes remains controversial. Dyslipidemia could be related to dementia risk through being a component of metabolic syndrome. Metabolic syndrome is a multifactorial disorder represented by the co-occurrence of several vascular conditions related to central obesity, including impaired glucose metabolism, dyslipidemia, and high blood pressure. Most of the individual factors and metabolic syndrome as a whole have been repeatedly associated with cognitive decline and dementia.[6,20–23]

Prospective Epidemiological Studies Relating Plasma Cholesterol Levels to AD

The main longitudinal studies on the association between serum lipid levels and development of AD later in life are summarized in Table 1. Most studies explored the effect of total cholesterol levels on AD, but the results of these studies have been inconsistent as have also been the results of studies exploring the effect of HDL, LDL, or triglyceride levels on AD. Closer analysis of the inconsistencies between studies suggests that the discrepancies among them may be accounted for by elements of the study design, specifically a combination of the duration of time between the measurement of lipid level and brain function and the ages at which the measurements were made. In general, it seems that the older the age at which the lipid level is measured and the shorter the interval between lipid level and brain function measurement, the more inconsistent are the study

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results. Studies using lipid levels measured in late life are largely inconsistent: whereas some studies reported no effect,[24–28] some reported that high total cholesterol levels or low HDL levels increased risk significantly,[29–31] and further studies reported a significant decline in cholesterol levels before the onset of dementia.[32,33] In contrast, studies that had a long follow-up and were able to explore the effect of midlife lipid levels on late-life cognitive function do in fact suggest harmful effects of high total cholesterol levels and low HDL levels on risk of AD. The fact that only HDL-like lipoproteins are found in CSF and that HDL levels are lowest in *APOE* ε4 carriers and/or people with AD may indicate that this lipoprotein is particularly important.

Evidence from Genetic Studies

The genetic studies on AD performed to date strongly point to a major role for four specific pathways in AD: Aβ metabolism, intracellular trafficking/endocytosis, inflammation, and lipid metabolism. Of the 15 genes that have to date been firmly implicated in the cause and are distributed between these four pathways (*PSEN1, PSEN2, APP, APOE, SORL1, CLU, ABCA7, PICALM, BIN1, CLU, EPHA1, MS4A* cluster, *CR1, CD2AP, CD33*), four (*APOE, CLU, ABCA7*, and *SORL1*) are involved in cholesterol metabolism, providing strong support for the notion that lipids are involved in the cause of AD.

Apolipoprotein E was the very first gene (*APOE*) implicated in the late-onset form of AD and it remains the top-ranked susceptibility gene. It is 3.6 kb long, located on chromosome 1, and encodes a 299 amino acid protein with three common isoforms. Apolipoprotein E is a major constituent of chylomicrons and the most abundant apolipoprotein in the CNS, where it occurs in HDL particles and is involved in cholesterol transfer from the astroglial to the neuronal compartment.[34,35] In addition, apolipoprotein E acts as a pathological chaperone of Aβ, promoting its fibril formation from soluble Aβ by binding interaction between the carboxy-terminal domain of apolipoprotein E and residues 12–28 of full-length Aβ. In general, the ε2 isoform is associated with lower plasma cholesterol level and lower risk of AD, whereas the ε4 allele is associated with higher plasma concentrations of total and LDL cholesterol, a higher risk of atherosclerosis, and higher risk of AD.[36,37] The risks of AD are three and eight times greater in individuals with one or two copies of the ε4 gene, respectively, compared with people homozygous for ε3.[38] In most studies, 40–50% of patients with AD have at least one ε4 allele, compared with 10–15% of healthy controls.[38–40] Individuals who are homozygous for the ε4 allele and live to 80 years of age will almost invariably develop AD, but about 10% of heterozygous ε4 carriers will remain free of AD well into their 80s.[38,41] In addition, the ε4 allele lowers the age at which onset of dementia occurs in a gene-dose-dependent manner by as much as 7–9 years per allele,[40] and is associated with AD endophenotypes including disease progression, brain hypometabolism, amyloid deposition in the parenchyma and vasculature, intraneuronal accumulation of Aβ, and low Aβ42 level in CSF.[42–45] In addition to the *APOE* ε2/3/4 haplotype, a promoter polymorphism is independently associated with AD risk, indicating that not only qualitative differences between the three isoforms but also quantitative variability of apolipoprotein E levels may modulate the risk of AD.[46]

The second gene that was implicated in AD and is associated with lipid metabolism is the sortilin-related receptor containing LDL receptor class A repeats (*SORL1*), which is 177.5 kb long and maps to 11q23.2–q24.2. It is a multifunctional receptor belonging to the family of VPS10 receptors that binds lipoproteins, including apolipoprotein E-containing particles, and mediates their intracellular trafficking. In candidate gene studies on several ethnic groups (including Caucasians, African Americans, Caribbean Hispanics, Israeli Arabs), two specific clusters of single-nucleotide polymorphisms in *SORL1* were identified that are associated with familial and sporadic forms of AD.[47–64] The same alleles have also been

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associated with various AD endophenotypes, including age of onset of AD, abstract reasoning, white matter lesions, hippocampal atrophy, $A\beta_{42}$ CSF measures and full-length-*SORL1* expression in brain, further validating the role of this gene in AD.[65–68] Of note, in 2011, also the *SORL1* homologue *SORCS1* was firmly implicated as a risk gene for AD by demonstrating genetic association between *SORCS1* and AD, and by showing that *SORCS1* also alters processing of AβPP and thereby accumulation of Aβ.[69] In functional cell biology analyses, *SORL1* modulates trafficking of AβPP from the cell surface to the Golgi endoplasmic reticulum complex, and underexpression of *SORL1* leads to overexpression of Aβ and an increased risk of AD.[70]

Recent major genome-wide association studies on AD identified two additional lipid-related genes, which are currently ranked third and fourth in the AlzGene database. Clusterin (*CLU*) is located on chromosome arm 8p21-p12, is 36.3 kb long, and encodes the second major apolipoprotein in the CNS (apolipoprotein J). It has several functional similarities with apolipoprotein E: it is involved in reverse cholesterol transport as a constituent of HDL particles,[71] and additive to apolipoprotein E, it also acts as an Aβ chaperone, regulating the conversion of Aβ to insoluble forms as well as its toxicity, thereby promoting amyloid plaque formation.[72] Moreover, it may be involved in the transport of Aβ across the blood–brain barrier and in its uptake by glial cells and brain macrophages.[73] These effects are influenced by the molar ratios of apolipoprotein J and Aβ and by the aggregation state of the latter.[74,75]

The second gene implicated by the recent major genome-wide association studies is the integral transmembrane ABC transporter ABCA7, which belongs to the ABC family of proteins that mediate the biogenesis of HDL with cellular lipid and helical apolipoproteins.[76] Members of this protein family bind apolipoprotein A–I and function in apolipoprotein-mediated phospholipid and cholesterol efflux from cells and via the blood–brain barrier, providing a possible link between blood cholesterol levels and AD.[77] In addition, variants in *ABCA7* may also affect the transport and thereby metabolism of other important proteins through the cell membrane and within the cell. For example, *ABCA7* is highly expressed in the brain and is involved in the processing of amyloid precursor protein.[77] Finally, ABCA7 plays a role in host defense through an effect on phagocytosis by macrophages of apoptotic cells.[76]

Several additional lipid-related genes have been explored in AD with inconsistent results (http://www.alzgene.org). In interpretation of these findings, it is important to keep in mind that for most genes the markers investigated do not capture the entire genetic variation, and that the sample size of most studies performed was clearly too small to detect loci with modest effect sizes.

Evidence from Randomized Controlled Trials

The main effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, also known as statins, is to lower LDL cholesterol levels by hindering cholesterol synthesis in the liver although they also slightly increase HDL levels by 3–13%. As a group, statins are thought to prevent cardiovascular disease by improving endothelial function, reducing inflammatory responses, maintaining stability of atherosclerotic plaques, and preventing the formation of thrombi,[78] even in those with normal cholesterol levels. These pleiotropic effects of statins have led to interest in exploring their effect on noncardiovascular conditions, including AD. Several well-performed, population-based observational studies show a protective effect of statin therapy against the risk of AD and dementia, even after adjustment for demographic and vascular confounders, whereas a few studies failed to show this effect.[79–92] However, these data did not translate to controlled randomized trials, most

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of which have found no benefit.[93–99] There are several explanations for these significant differences between observational studies and clinical trials. First, as stated above, statins largely target LDL and they do not have a strong enough effect on HDL levels (which in turn seem to be more strongly associated with AD) to reduce dementia risk. Second, treatment trials tend to be short term and include patients with advanced disease who are typically older, whereas observational cohort studies normally include a wider age range of people with normal cognition to more-advanced disease and are usually longer in duration. Statins are not regenerative medicines and are unable to restore the lost function of an end-organ tissue to the function before vascular disease was present. By analogy, if dementia results from long-term vascular disease, then statins might be unable to benefit subjects once overt dementia is apparent. The window of opportunity for statins might require treatment beginning at midlife, when statin treatment can function as a protective factor rather than as a treatment for subjects with dementia. Consistent with this notion, Li et al.[88] reported greater benefits from statin therapy for those younger than 80 years, as did a previous study,[83] and in one of the smaller trials of atorvastatin, Sparkes et al.[97] noted that in an earlier stage of progression, higher starting cholesterol level and *APOE* ε 4 status could modify the effects of statin on change in cognitive function in patients with AD. A third explanation for the differences between epidemiological studies on statins and the findings of randomized controlled trials could be confounding by indication. People with dementia are likely to be denied statins, reflecting a trend to be less aggressive in their medical care including the treatment of vascular risk factors. Finally, it also remains possible that the conceptualization of the pathophysiology of AD is incomplete.

Conclusions

In summary, the current evidence from epidemiological, animal, cell biology, and genetic studies supports a possible involvement of cholesterol in the development of dementia and AD, suggesting dyslipidemia as one of the modifiable risk factors to be targeted by therapeutic interventions which are already widely available.

However, the mechanisms through which dyslipidemia exerts its effect are still unclear. First, although it is clear that dyslipidemia induces vascular disease, also alterations in brain cholesterol homeostasis have been linked to the main pathological features of AD, in particular Aβ. Brain cholesterol and serum cholesterol, however, are separate pools whose interaction has not been fully characterized. Second, dyslipidemia could be related to dementia risk through being a component of metabolic syndrome. Metabolic syndrome is a multifactorial disorder represented by the co-occurrence of several vascular conditions related to central obesity, including impaired glucose metabolism, dyslipidemia, and high blood pressure. Each individual factor and metabolic syndrome as a whole have been repeatedly associated with cognitive decline and dementia.[6,20–23] Third, the available data relating the various lipid types (LDL cholesterol, HDL cholesterol, triglycerides) to AD are still insufficient. The fact that only HDL-like lipoproteins are found in CSF and that HDL levels are lowest in *APOE* ε4 carriers and/or people with AD may indicate that this lipoprotein is particularly important. However, these findings need to be confirmed. Fourth, association and linkage studies exploring the role of cholesterol-metabolism-related genes in AD have clearly implicated *APOE, CLU, ABCA7*, and *SORL1*. The results for other cholesterol-related genes are inconsistent, but most of the studies that have been performed were underpowered and/or did not cover the complete genetic variation in the gene. Thus, it is possible that studies with larger sample sizes would pick up additional disease-related variants. Finally, it is clear that AD is a complex disease with multiple risk factors involved. To properly characterize the association of different risk factors with dementia/AD and to pinpoint the critical etiological pathways in which they are involved, early identification of the disease process (before its clinical expression) and long-term studies with multiple time

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points are needed. Monotherapy is not likely to be sufficiently effective in a complex disease, and a more detailed risk profile can provide clues for a better multitargeted interventional strategy.

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Table 1

Longitudinal observational studies relating lipid levels to the risk of dementia

Study	Cohort	Population size/follow-up time	Diagnostic criteria	Findings
Kuusisto et al.[100]	Kuopio	*n* = 980 (46 AD) Age range: 66–75 years Follow-up: 3.5 years	DSM-IIIR	Low total cholesterol levels associated with increased AD risk
Notkola et al.[30]	Seven Countries Study (Finland)	*n* = 444 men (47 dementia, 27 AD) Baseline age: 40–59 years Follow-up: 15–25 years	DSM-IIIR	High total cholesterol levels associated with increased AD risk
Moroney et al.[101]	WHICAP	*n* = 987 (126 AD) Mean age: 73 years Follow-up: 2.5 years	NINCDS-ADRDA	Low total cholesterol levels associated with increased AD risk
Romas et al.[26]	WHICAP	*N* = 1,449 Age: 75.8 ± 6.4 years Cross-sectional study	NINCDS-ADRDA	No association
Kalmijn et al.[102]	HAAS	*n* = 3,734 men (251 dementia, 82 AD, 73 VaD) Mean baseline age: 53 years Mean follow-up: 25 years	DSM-IIIR, NINCDS-ADRDA	Triglyceride levels positively associated with AD risk
Kivipelto et al.[103]	CAIDE Study	*n* = 1,449 (57 dementia, 48 AD) Mean baseline age: 50 years Mean follow-up: 21 years	DSM-IV, NINCDS-ADRDA	Midlife high total cholesterol levels associated with increased AD risk
Tan et al.[27]	Framingham Study	*n* =1,026 subjects who had undergone biennial evaluation for cardiovascular risk factors since 1950 and who were alive and free of stroke and dementia at examination cycle 20 (1988–1989); 77 developed AD afterwards	DSM-IV, NINCDS-ADRDA	No association
Reitz et al.[104]	WHICAP	*n* = 1,168 (119 AD, 54 VaD) Mean age: 78.4 years Follow-up: 4.8 years	DSM-IIIR, NINCDS-ADRDA	Higher total cholesterol levels associated with decreased AD risk. Higher LDL cholesterol and non-HDL-cholesterol levels associated with increased VaD risk
Dufouil et al.[90]	Three-City Study	*n* = 9,294 Age: 74.2 ± 5.5 years Cross-sectional analyses	DSM-IV, NINCDS-ADRDA	Hyperlipidemia associated with increased risk of non-AD dementia, lipid-lowering treatment associated with decreased dementia risk
Whitmer et al.[31]	Kaiser Permanente Medical Care Program of Northern California	*n* = 8,845 (721 dementia) Baseline age: 40–44 years Mean follow-up: 27 years	ICD-9-CM	Positive association
Li et al.[24]	ACT Study	*n* = 2,141 (152 AD) Mean age: 74.9 years Follow-up: 5.6 years	DSM-IV, NINCDS-ADRDA	No association

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Study	Cohort	Population size/follow-up time	Diagnostic criteria	Findings
Mainous et al.[25]	NHEFS	*n* = 6,558 Baseline age: 40–74 years Follow-up: 20 years	ICD-9	No association
Mielke et al.[105]	Göteborg	*n* = 382 (93 dementia) Baseline age: 70 years Follow-up: 18 years	DSM-IIIR, NINCDS-ADRDA	High total cholesterol levels associated with reduced risk of dementia
Kivipelto et al.[29]	CAIDE Study	*n* = 1,449 (61 dementia, 48 AD) Mean baseline age: 50 years Mean follow-up: 21 years	DSM-IV, NINCDS-ADRDA	Midlife high total cholesterol levels associated with increased AD risk
Hayden et al.[106]	Cache County Study	*n* = 3,264 (185 dementia) Mean age: 73.7 years Follow-up: 3.2 years	DSM-IIIR, NINCDS-ADRDA	High total cholesterol levels associated with increased AD risk
Stewart et al.[32]	HAAS	1,027 Japanese American men (56 AD) Mean age: 80.2 years Follow-up: 26 years	DSM-IIIR, NINCDS-ADRDA	Decline in cholesterol levels in men at least 15 years before diagnosis of dementia
Solomon et al.[107]	Kaiser Permanente Northern California Medical Group	*N* = 9,844 Age at study entry: 40–45 years Follow-up: 3 decades	ICD-9	Midlife serum total cholesterol levels associated with increased risk of AD and VaD
Reitz et al.[108]	WHICAP	*n* = 1,130 (101 AD) Mean age: 75.7 years Follow-up: 4 years	DSM-IIIR, NINCDS-ADRDA	High HDL levels associated with reduced AD risk
Beydoun et al.[33]	BLSA	*n* = 1,604 (259 dementia, 182 AD) Mean age: 57.6 years Follow-up: 25 years	DSM-IIIR, NINCDS-ADRDA	Decline in total cholesterol levels associated with increased dementia risk
Solfrizzi et al.[109]	ILSA	*n* = 2,097 Age: 72.9 ± 5.6 years Follow-up: 3.5 years	DSM-IIIR, NINCDS-ADRDA	Metabolic syndrome associated with higher risk of VaD
Reynolds et al.[110]	Swedish Adoption Twin Study of Aging	*N* = 819 twins Age: 50–96 years Follow-up: 16 years	DSM-IV, NINCDS-ADRDA	In women but not men, higher HDL cholesterol and lower triglyceride levels predict better maintenance of cognitive abilities
Mielke et al.[28]	Prospective Population Study of Women	*N* = 1,462 women without dementia Age: 38–60 years Follow-up: 32 years	DSM-IIIR, NINCDS-ADRDA	Midlife cholesterol level is not associated with increased risk of AD

AD Alzheimer's disease, *BLSA* Baltimore Longitudinal Study of Aging, *DSM-IIIR Diagnostic and Statistical Manual of Mental Disorders*, third edition, text revision, *DSM-IV Diagnostic and Statistical Manual of Mental Disorders* fourth edition, *HAAS* Honolulu-Asia Aging Study, *ICD-9* International Classification of Diseases, *ICD-9-CM* International Classification of Diseases, ninth revision, clinical modification, *ILSA* Italian Longitudinal Study on Ageing, *NHEFS* National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study *NINCDS-ADRDA* National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association, *VaD* vascular disease, *WHICAP* Washington Heights–Inwood Columbia Aging Project