alzheimer's
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REVIEW

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

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Abstract

Recent epidemiologic studies have noted that risk factors for atherosclerosis (for example, diabetes mellitus, hypertension, and hyperlipidemia) are associated with increased risk of incident Alzheimer's disease (AD). In this evidence-based review, we frame the proposition as a question: are vascular risk factors also risk factors for plaques and tangles or just for concomitant vascular pathology that increases the likelihood of dementia? To date, no representative, prospective studies with autopsy (evidence level A) show significant positive associations between diabetes mellitus, hypertension, or intracranial atherosclerosis and plaques or tangles. Some prospective, representative, epidemiologic studies (evidence level B) show associations between diabetes, hypertension, hyperlipidemia, and aggregated risk factors with clinically diagnosed incident AD. However, the strength of association diminishes in the following order: vascular dementia (VaD) > AD + VaD > AD. This pattern is arguably more consistent with the hypothesis that atherosclerosis promotes subclinical vascular brain injury, thereby increasing the likelihood of dementia and in some cases making symptoms present earlier. Several autopsy studies from AD brain banks (evidence level C) have observed positive associations between intracranial atherosclerosis and severity of plaques and tangles. However, these studies may reflect selection bias; these associations are not confirmed when cases are drawn from non-dementia settings. We conclude that, at the present time, there is no consistent body of evidence to show that vascular risk factors increase AD pathology.

Framing the question

Neurodegenerative and cerebrovascular diseases are the most common causes of disabling cognitive impairment in late life. Alzheimer's disease (AD), defined by widespread amyloid/neuritic plaques (NPs) and neurofibrillary tangles (NFTs), is the prototypical neurodegenerative disorder. Atherosclerosis leading to cerebral infarction and stroke is the prototypical cerebrovascular disease. Historically, these were considered two common but parallel and independent pathways leading to cognitive decline.

Recently, the concept that risk factors for atherosclerosis are also risk factors for AD has gained traction.
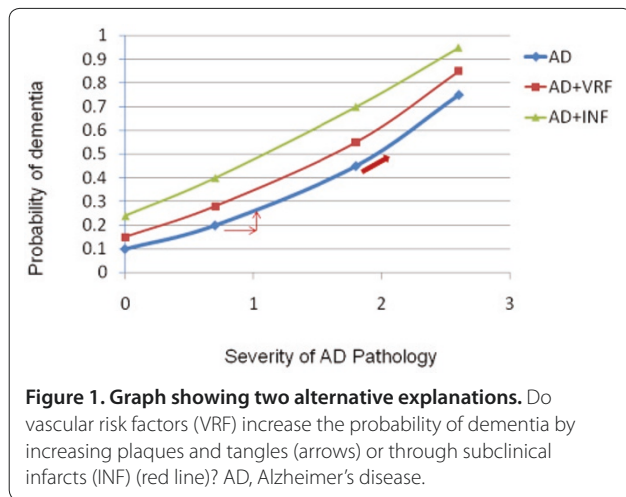
This hypothesis has been driven largely by some [1,2], but not all [3], epidemiologic studies wherein recognized risk factors for atherosclerosis (for example, diabetes mellitus, hypertension, hyperlipidemia, and aggregate risk) are associated with increased risk of incident clinically diagnosed AD. This, in turn, has given rise to the proposition that 'vascular risk factors are also risk factors for AD'.

In this paper, we step back to frame the proposition as a question: are vascular risk factors also risk factors for plaques and tangles or just for concomitant vascular pathology that increases the likelihood of dementia (Figure 1)? In our minds, this question remains open, although data from a growing number of prospective community-based autopsy studies indicate the latter. Our objective is to critically review the literature, highlighting current methodological limitations in diagnosis, sampling, and measurement. We emphasize the need for pathological information, representative sampling, and prospective study design to optimally address the question. We focus on atherosclerosis and three of its major

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Figure 1. Graph showing two alternative explanations. Do vascular risk factors (VRF) increase the probability of dementia by increasing plaques and tangles (arrows) or through subclinical infarcts (INF) (red line)? AD, Alzheimer's disease.

risk factors - diabetes mellitus, hypertension, and hyperlipidemia - as the independent measures. Because of space limitations, we do not cover other common risk factors for atherosclerosis, including smoking, hyperhomocysteinemia, or inflammatory factors. In this review, we also leave aside cerebral amyloid angiopathy, a type of cerebrovascular disease closely associated with the cerebral hallmarks of AD as well as the mutual risk factor apolipoprotein E (APOE) ε4.

Quality of evidence

Quality of evidence is determined by study design, sampling method, and accuracy of diagnosis (Table 1). Since AD is currently defined as a clinical-pathological entity, the ideal methodology for the question posed in this review is a population-based cohort, established in midlife and followed prospectively to autopsy. In this review, we group the literature related to vascular risk factors and AD into three methodological categories: 1) representative and non-representative prospective longitudinal cohort studies including autopsy (level A); 2) representative and non-representative prospective longitudinal studies without autopsy (level B); and 3) cross-sectional neuropathological studies (level C). Cross-sectional clinical studies without autopsy are not included in this review (level D).

The quality of ascertaining vascular risk factors, the criteria for diagnosis of dementia, and the method of rating distribution and severity of neuropathology vary considerably. Information about vascular risk factors ranges from self-report, proxy informants, medical records, to direct clinical and laboratory measures that are ascertained cross-sectionally or longitudinally. Differential misclassification of risk factors by self-report (for example, over-reported in AD group and under-reported in control group) will bias the associations between
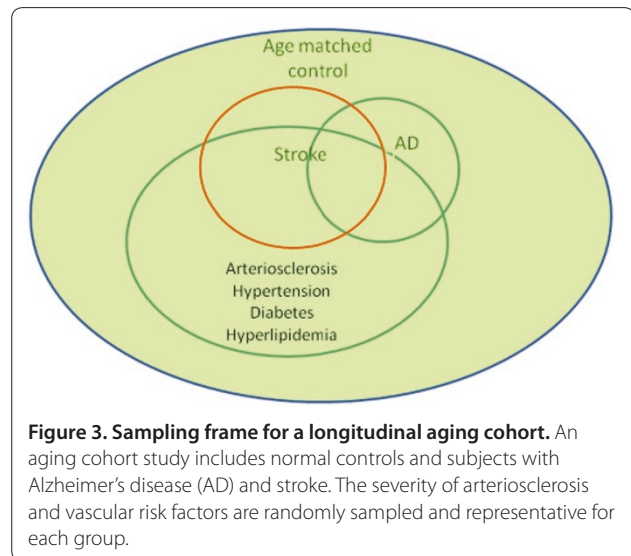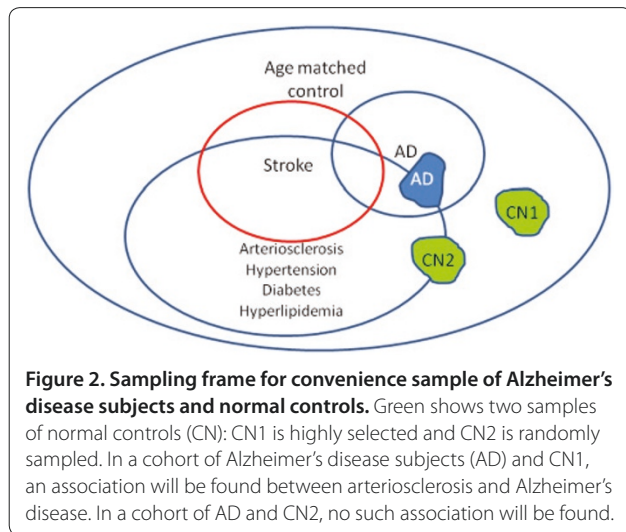
vascular risk factors and AD positively. In addition, temporality of risk factor assessment (for example, mid-life versus late life) may affect the associations observed since neurodegenerative brain changes begin by middle age and exposure to risk factors changes over time. Besides the simple presence versus absence of a risk factor, the duration and magnitude of exposure to a risk factor should also be ideally considered. Epidemiological studies have diagnostic limitations since cases are usually defined based on a predetermined cutoff. Consequently, there is a possibility that 'mild dementia' cases are included in the normal group, which may attenuate the association between dementia and its risk factors.

A pathological diagnosis of AD, based on severity and distribution of NFTs and NPs [4], remains the gold standard for diagnosis. Using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria as the reference standard, a clinical diagnosis of AD, based on typical clinical presentation and the exclusion of other causes of dementia [5], showed 93% sensitivity but only 55% specificity [6]. An evidenced-based review of the literature in 2002 [7] showed small positive likelihood ratios for the diagnosis of dementia subtype (that is, 2 to 5) compared to the generic diagnosis of dementia (that is, >10). It is even more difficult to diagnose dementia due to mixed pathologies, yet in community-based studies, over half of older subjects with dementia harbor mixed pathologies at autopsy [8-10], often showing infarcts up to half of which were not detected during life [11]. In the absence of a true association between vascular risk factors and AD, misclassification of mixed AD/vascular dementia (VaD) cases as clinical AD would positively bias the associations between vascular risk factors and AD. Cerebrospinal fluid markers of amyloid-beta (Aβ) and phospho-tau and amyloid PET imaging have recently been incorporated into clinical research criteria [12] and promise to improve specificity of the clinical diagnosis in the future.

While autopsy studies minimize errors in diagnosis, neuropathological data may be limited in many important ways. Neuropathological data are themselves cross-sectional (that is, can only be collected once); it is difficult, therefore, to determine sequence and causality based on neuropathological findings. At autopsy, severity of atherosclerosis, NFTs, NPs, and number of infarcts are often limited to semi-ordinal measures of severity, which may limit the power to detect small associations. Autopsy samples of convenience are likely to include significant selection bias (level of evidence = C). When a participant is selected from hospitals, memory clinics, or tertiary referral centers, the underlying population is usually not definable. Vascular pathology is relatively under-represented in autopsy studies drawn from memory clinics versus the community [13]. Figure 2 illustrates highly

Table 1. Grading system for quality of evidence

Grade of evidence	Sampling	Design	Information
A1	Representative	Longitudinal prospective	Clinical and autopsy
A2	Non-representative	Longitudinal prospective	Clinical and autopsy
B1	Representative	Longitudinal prospective	Clinical only
B2	Non-representative	Longitudinal prospective	Clinical only
C1	Representative	Cross-sectional	Clinical and autopsy
C2	Non-representative	Cross-sectional	Clinical and autopsy
D1	Representative	Cross-sectional	Clinical only
D2	Non representative	Cross-sectional	Clinical only

Figure 2. Sampling frame for convenience sample of Alzheimer's disease subjects and normal controls. Green shows two samples of normal controls (CN): CN1 is highly selected and CN2 is randomly sampled. In a cohort of Alzheimer's disease subjects (AD) and CN1, an association will be found between arteriosclerosis and Alzheimer's disease. In a cohort of AD and CN2, no such association will be found.

Figure 3. Sampling frame for a longitudinal aging cohort. An aging cohort study includes normal controls and subjects with Alzheimer's disease (AD) and stroke. The severity of arteriosclerosis and vascular risk factors are randomly sampled and representative for each group.

overlapping atherosclerosis, stroke, and AD pathologies in an older population. Figure 2 also shows how retrospective selection of cases may lead to a comparison between AD cases and super healthy controls (CN1) that have neither AD nor vascular disease, leading to a spurious association between vascular risk factors and AD.
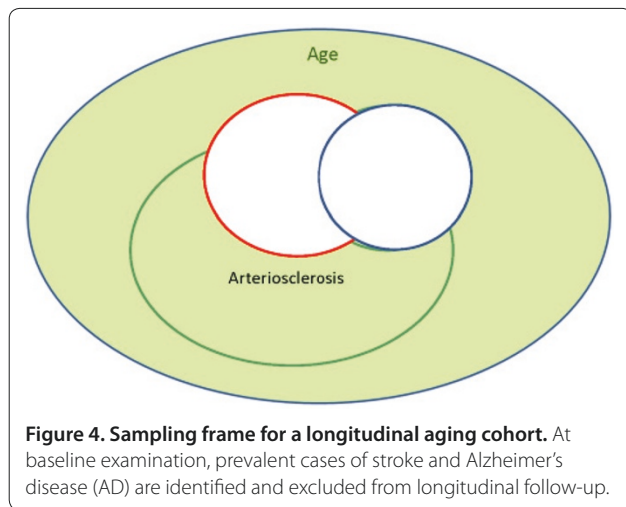
A much stronger study design would be a population-based sample, followed prospectively from midlife to autopsy (level of evidence = A1). In such a cohort, the distribution of vascular risk factors of the cohort should be representative of the population (Figure 3). Establishment of the cohort in midlife, well before the expression of disease, eliminates important aspects of selection bias. If the cohort is established later in life, when subjects at highest risk have already died, associations may be weakened and even reverse direction. If the cohort is assembled later in life and followed prospectively, comparable diagnostic thresholds can be used to first identify and remove prevalent cases and then prospectively identify incident cases (Figures 4 and 5). This prospective design strengthens the etiological significance of

associations between risk factors and incident disease (level of evidence = B). Ideally, prospective longitudinal studies will include autopsy to confirm associations between risk factors and neuropathologically defined disease (level of evidence = A).

Level A evidence
A summary of level A evidence is provided in Table 2. In a 2006 review [14], six studies were identified as true population-based autopsy studies of dementia (grade A1). Three of these studies have published data relevant to our question: 1) the Hisayama study (Japan); 2) the Honolulu Asia Aging Study (HAAS; Hawaii, USA); and 3) the Vantaa 85+ study (Finland). There are also several longitudinal, neuropathological studies drawn from special but non-representative cohorts (grade A2): 1) the Baltimore Longitudinal Study on Aging; 2) the Religious Orders Study (ROS); and 3) the Adult Changes in Thought study.
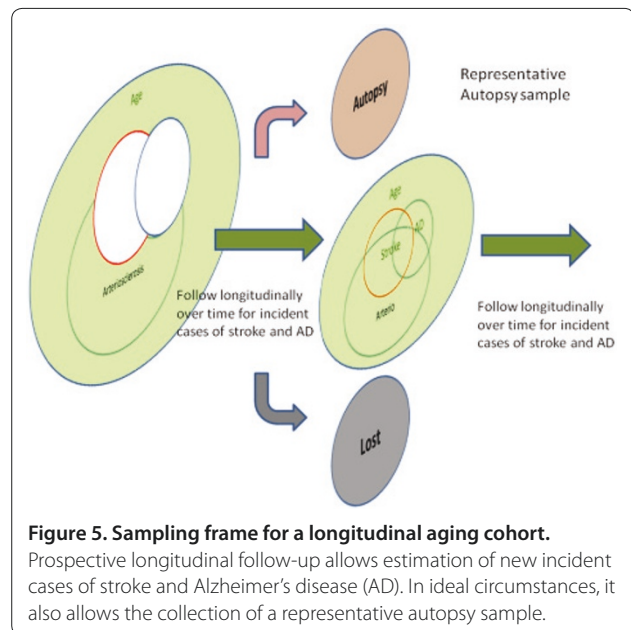
Among 216 autopsied cases of Japanese-American men enrolled in HAAS [15], diabetes was associated with

Figure 4. Sampling frame for a longitudinal aging cohort. At baseline examination, prevalent cases of stroke and Alzheimer's disease (AD) are identified and excluded from longitudinal follow-up.

Figure 5. Sampling frame for a longitudinal aging cohort. Prospective longitudinal follow-up allows estimation of new incident cases of stroke and Alzheimer's disease (AD). In ideal circumstances, it also allows the collection of a representative autopsy sample.

increased risk of large cerebral infarcts (relative risk (RR) = 1.8, 95% confidence interval (CI) 1.1 to 3.0), but not with NPs or NFTs. Strengths in the HAAS study design included a representative autopsy sample (high 42% autopsy rate for an epidemiological study), ascertainment of diabetes in midlife by history, fasting, and 2 hour postprandial glucose, and adjustment for potential confounders (that is, age, education, APOE4 ε4 status, and other vascular risk factors).

The Vantaa 85+ study focused on diabetes among 553 residents of Vantaa, Finland aged ≥85 years [16]. Autopsies were performed in nearly half (48%; n = 291) of the total population. Diabetes at baseline doubled the incidence of clinically defined dementia, AD, and VaD. However, at autopsy, subjects with diabetes were less likely to have Aβ (odds ratio (OR) = 0.48, 95% CI 0.23 to 0.98) and tangles (OR = 0.72, 95% CI 0.39 to 1.33), but more likely to have cerebral infarcts (OR = 1.88, 95% CI 1.06 to 3.34), after adjustment for age, education, APOE ε4 status, and other vascular risk factors. The investigators concluded that older patients with diabetes develop more extensive vascular, but not AD, pathology, proposing that vascular pathology, alone or together with AD, could explain the elevated risk of all-cause dementia associated with diabetes.

In the ROS, diabetes was associated with elevated risk for incident AD (hazard ratio = 1.65, 95% CI 1.10 to 2.47) [17]. In an autopsy study (n = 233) from the same cohort, diabetes was associated with cerebral infarcts (OR = 2.47, 95% CI 1.16 to 5.24), but not with global AD pathology or specific measures of NPs, diffuse plaques, amyloid burden, tangles or tangle densities [18]. These ROS findings strongly suggest that the relationship between diabetes and incident AD may be mediated by the additive effects on dementia of subclinical cerebral infarction.

In the Adult Changes in Thought study, blood pressure measured later in life was associated with cortical microinfarcts, but not with plaques or tangles [19]. Since microinfarcts are too small to be detected by clinical exam or neuroimaging, these dementia cases may be clinically diagnosed as AD.

Among 200 autopsy cases in the prospective Baltimore Longitudinal Study on Aging, quantitative measures of atherosclerosis in the aorta, heart, and intracranial vessels were not associated with the degree of AD-type brain pathology [20]. However, intracranial atherosclerosis significantly increased the odds of dementia within 18 months of death, independent of cerebral infarction, through still unclear pathways.

In summary, no level A evidence supports the hypothesis that diabetes, hypertension or atherosclerosis increases plaques and tangles, although these factors all increase the risk of vascular lesions and dementia. Increased risk of dementia appears to be mediated, at least in part, through subclinical ischemic brain injury, including microinfarcts that escape clinical detection.

Level B evidence
The concept that risk factors for atherosclerosis and stroke (for example, diabetes mellitus, hypertension, hyperlipidemia) are also risk factors for AD stems largely from epidemiologic studies conducted over the past 20 years. The fundamental limitation to interpreting these studies is that disease state is clinically defined. While it is highly likely that AD pathology is present in clinically diagnosed dementia, it is also likely that vascular pathology is also present. In the absence of

Table 2. Longitudinal aging cohort with autopsy

Grade	Study	Original sample	Autopsy sample	AD pathology	Cerebral infarcts
A1	Peila *et al.* 2002 [15]; Honolulu Asia Aging Study 1991	Community-based Japanese-American males (n = 3,734)	216/521 deaths (42.5%)	Negative: type 2 diabetes was not associated with cortical neuritic plaques (RR 0.8, 95% CI 0.5 to 1.4) or tangles (RR 1.0, 95% CI 0.6 to 2.4)	Positive: type 2 diabetes was associated with higher risk of large infarcts (RR 1.8, 95% CI 1.1 to 3.0)
A2	Arvanitakis *et al.* 2006 [18]; Religious Orders Study	Older Catholic nuns, priests, or brothers (n = 1,060)	233 autopsies (94%)	Negative: diabetes was not related to global AD pathology score, or to specific measures of neuritic plaques, diffuse plaques or tangles, or to amyloid burden or tangle density	Positive: diabetes (present in 15% subjects) was associated with an increased odds of infarction (OR 2.47, 95% CI 1.16 to 5.24)
A2	Wang *et al.* 2009 [19]; Adult Changes in Thought	Health Maintenance Organization (n = 2,581)	250/1,167 deaths (21.4%)	Negative: hypertension in midlife was not associated with plaques and tangles	Positive: among persons aged <80 years, each 10 mmHg increase in systolic blood pressure was associated with 1.15 (95% CI 1.0 to 1.33) increased risk of ≥2 microinfarcts
A1	Ahtilouoto *et al.* 2010 [16]; Vantaa 85%+ Study	Community-based, elderly longitudinal study (n = 553)	n = 291 (48% of total cohort; age = 92+ years)	Negative: history of diabetes mellitus was less likely to have Aβ (OR 0.48, 95% CI 0.23 to 0.98) and tangles (OR 0.72, 95% CI 0.39 to 1.33)	Positive: history of diabetes mellitus was more likely to have cerebral infarcts (OR 1.88, 95% CI 1.06 to 3.34)
A2	Dolan *et al.* 2010 [20]; Baltimore Longitudinal Study on Aging	Longitudinal cohort study with autopsy; number of incident dementia cohort = 1,236 (Kawas *et al.* 2000 [48])	n = 200 (16% of incident cohort; 87.6 ± 7.1 years)	Negative: no relationship between the degree of atherosclerosis in intracranial, aorta, or heart and the degree of AD-type brain pathology	Positive: intracranial atherosclerosis significantly increased the odds of infarcts (OR = 1.8, 95% CI 1.2 to 2.7) and for dementia, independent of cerebral infarction

Aβ, amyloid-beta; AD, Alzheimer's disease; CI, confidence interval; OR, odds ratio; RR, relative risk.

symptomatic stroke, however, the default etiologic diagnosis is often AD. With respect to the clinical diagnosis of VaD, the sensitivity, specificity and degree to which 'pure' vascular cases are identified varies widely depending upon choice of criteria and the availability of neuroimaging studies [21]. Thus, one cannot assume that 'clinical AD' means that vascular brain injury is absent, or that 'clinical VaD' means that AD is absent, or that an association between vascular risk factors and incident dementia is necessarily reflected in an association between risk factors and AD pathology.

Diabetes mellitus

A systematic overview of 25 prospective studies with clinical outcomes [22] concluded that people with diabetes have: 1) a greater rate of decline in cognitive function; 2) a 1.5-fold greater risk of cognitive decline; and 3) a 1.6-fold greater risk of future dementia, especially vascular cognitive impairment and dementia, relative to persons without diabetes. Below we discuss several particularly important population- or community-based studies (Table 3).

In the Rotterdam Study, diabetes increased the risk of dementia, mostly for VaD, followed by AD + VaD, then AD [23]. The investigators proposed either that diabetes contributes to AD pathology or that silent cerebral infarcts may uncover imminent AD. In two cohorts recruited successively in the multi-ethnic Washington Heights-Inwood Columbia Aging Project (WHICAP) study, history of diabetes mellitus significantly increased the risk of AD [24], but the association weakened when cases with mixed AD/cerebrovascular disease were removed [25]. In the HAAS [15], diabetes was defined by laboratory testing, and showed progressively diminishing risk with VaD (RR = 2.3, 95% CI 1.1 to 5.0), AD with VaD (RR = 1.8, 95% CI 1.1 to 2.9), and AD without VaD (RR = 1.6, 95% CI 0.9 to 3.0), controlling for age, education, APOE e4 status, and other vascular risk factors. In the ROS, diabetes was associated with a 65% increase in the risk of developing AD (hazard ratio = 1.65, 95% CI 1.10 to 2.47) [17]. In findings that deviate somewhat from the pattern above, subjects with diabetes in the Canadian Study on Health and Aging had a higher risk of incident vascular cognitive impairment (RR = 1.62, 95% CI 1.12 to 2.33) and its subtypes, VaD (RR = 2.03, 95% CI 1.15 to 3.57), and vascular cognitive impairment-no dementia (vascular CIND; RR = 1.68, 95% CI 1.01 to 2.78), but not AD or mixed AD/VaD [26]. In the Hisayama Study (done without neuroimaging), diabetes doubled the risk for VaD, but not AD [11].

In sum, there is robust evidence that diabetes increases cerebral infarcts and cognitive decline; the evidence that diabetes specifically increases AD pathology is mixed at best. Associations between diabetes and clinical AD

Table 3. Diabetes and relative risk of incident dementia

Grade	Study	Age (years)	Follow-up (years)	Definition	DM	No DM	All dementia	VaD	AD + VaD	AD
B1	Yoshitake *et al.* 1995 [11]; Hisayama 1985 to 1992 (n = 828)	>65	7	Hx	70	756		**2.8 (2.6, 3.0)[a]**		2.2 (0.97, 4.9)[a]
B1	Ott *et al.* 1999 [23]; Rotterdam 1990 to 1994 (n = 6,370)	>55	2.1	Hx: Glu >11 mmol/L	692	5,678	1.9 (1.3, 2.8)[b]	2.0 (0.7, 5.6)[b]	**3.0 (1.0, 9.3)[b]**	**1.8 (1.1, 3.0)[b]**
B1	Luchsinger *et al.* 2001 [49]; WHICAP 1992 to 1997 (n = 1,262)	≥65, mean 75.6 (SD 5.9)	4.3	Hx	255	1,007		**3.4 (1.7, 6.9)[c]**		1.3 (0.8, 1.9)[d]
B1	MacKnight *et al.* 2002 [26]; CSHA (n = 5,574)	≥65	4-6	Hx: Glu >11.1 mmol/L	503	5,071	1.26 (0.9, 1.7)[e]	**2.03 (1.15, 3.5)[e]**		1.3 (0.83, 2.1)[e]
B1	Peila *et al.* 2002 [15]; HAAS 1991 to 1996 (n = 2,574)	72-93	2.9	Hx DM: FBS >120 mg/dl	900	1,674	1.5 (1.0, 2.2)[f]	**2.3 (1.1, 5.0)[f]**	**1.8 (1.1, 2.9)[f]**	1.6 (0.9, 3.0)[f]
B1	Cheng *et al.* 2011 [25]; WHICAP 1999 to 2001 (n = 1,488)	>65		Hx			1.7 (1.4, 2.90)[g]	**1.6 (1.0, 2.6)[g]**	1.3 (0.8, 2.2)[g]	
B2	Arvanitakis *et al.* 2004 [17]; Religious Orders Study (n = 990)	75	5.5	Hx	127	697				**1.6 (1.1, 2.5)[h]**
B2	Ahtilouoto *et al.* 2010 [16]; Vantaa 85+ (n = 588)	>85		Hx	87	268	**2.09 (1.34, 3.25)** No APOE4: 1.68 (0.99, 2.83) With APOE4: **3.80 (1.69, 8.53)**			

[a]Adjusted for age. [b]Adjusted for age and sex. [c]Adjusted for gender, history of hypertension, history of heart disease, low density lipoprotein cholesterol level, ethnic group, education, and smoking. [d]Adjusted for gender, ethnic group, education, and presence of the *APOE ε4* allele. [e]Adjusted for demographics and vascular disease. [f]Adjusted for age, education, *APOE ε4* status, diabetes medications, alcohol, smoking status, midlife systolic blood pressure, cholesterol, body mass index, ankle brachial index, stroke, and coronary heart disease. [g]Adjusted for age, sex, education, ethnic group and *APOE ε4*. [h]Adjusted for age, sex, and education. Entries in bold indicate significant RR ratios. AD, Alzheimer's disease; APOE, apolipoprotein E; CI, confidence interval; CSHA, Canadian Study of Health and Aging; DM, diabetes mellitus; FBS, fasting blood sugar; Hx, history; OR, odds ratio; RR, relative risk; SD, standard deviation; VaD, vascular dementia; WHICAP, Washington Heights-Inwood Columbia Aging Project.

could reflect additive effects of subclinical vascular disease (elevated by diabetes) and AD pathology (that is perhaps independent of diabetes).

Hypertension
Measurement of blood pressure is complex: parameters relevant to dementia outcomes include the stage of life during which blood pressure is measured, modeling of diastolic versus systolic measures, and whether or not blood pressure is treated. Systolic blood pressure increases, while diastolic blood pressure decreases with age. Measures such as blood pressure variability and reactivity have also been considered. Here we summarize studies of systolic or diastolic blood pressure in longitudinal population or community studies with incident clinical dementia outcomes (Table 4).

In an initial report from HAAS, untreated, elevated systolic or diastolic midlife blood pressure predicted higher rates of all cause dementia and, specifically, AD dementia in late life [27]. This finding has not been clearly replicated. In the Uppsala study, midlife systolic blood pressure in men was positively associated with vascular and mixed dementias, but not AD [3]. The ROS found no effects of late-life blood pressure on dementia incidence [28]. A recent report from the Kungholmen project showed positive associations between late-life systolic blood pressure and AD as well as all-cause dementia [2]. In the Hisayama study [11], every 1 standard deviation (23 mmHg) increase in systolic blood pressure was associated with a 53% increase in the risk of VaD (RR = 1.53, 95% CI 1.16 to 2.01), but was not associated with AD risk. Studies have shown additive effects on cognitive decline related to hypertension alone and combined with other risk factors, including diabetes [29] and APOE ε4 [30].

The literature on blood pressure effects is often interpreted as showing that midlife, but not late life, elevations are associated with dementia and AD. However, the evidence does not entirely support that conclusion; the epidemiological literature is inconsistent with respect to both late-life and midlife blood pressure

Table 4. Hypertension and relative risk of incident dementia

Grade	Study	Age (mean ± SD)	Mean follow-up (years)	Definition	Number of subjects		RR (95% CI)			
					HTN	NL	All dementia	VaD	AD + VaD	AD
B1	Yoshitake *et al.* 1995 [11]; Hisayama (n = 828)	73.6 ± 5.9[a]	7	Per 1 SD increase (23 mmHg)				**1.6 (1.2, 2.2)[b]**		1.0 (0.7, 1.4)[b]
B1	Launer *et al.* 2000 [27]; HAAS (n = 3,734)	52.7 ± 4.7 (men)	27	Untreated SBP ≥160	227	2,295	**4.85 (1.99, 11.83)[c]**	**10.68 (3.49, 32.64)[c]**	1.75 (0.58, 5.29)[c]	-
				Untreated DBP ≥90	132	1,128	**4.32 (1.72, 10.85)[c]**	**4.61 (1.61, 13.19)[c]**	2.78 (0.54, 14.25)[c]	**6.6 (2.0, 21.4)[c]**
B1	Kivipelto *et al.* 2002 [35] (n = 2,293)	50.2 ± 6.0	21	SBP 140-159	-	-	1.9 (0.8, 4.8)[d]			1.6 (0.7, 4.2)[d]
				SBP ≥160	-	-	**2.8 (1.1, 7.2)[d]**			**2.6 (1.1, 7.2)[d]**
				DBP 90-94	-	-	1.4 (0.5, 3.6)[d]			1.2 (0.4, 3.3)[d]
				DBP ≥90	-	-	**2.3 (1.1, 5.1)[d]**			2.0 (0.9, 4.6)[d]
B1	Qiu *et al.* 2010 [2]; Kungsholmen (n = 1,270)	81.5 ± 5.0	5.1	SBP 140-159	127	278	1.22 (0.89, 1.68)[e]			**1.47 (1.02, 2.12)[e]**
				SBP ≥160	127	351	1.49 (0.94, 2.37)[e]			**1.84 (1.06, 3.18)[e]**
B1	Rönnemaa *et al.* 2011 [3]; Uppsala (n = 2,268)	49.6 ± 0.6	29	Per 1 SD increase (18 mmHg)			**1.2 (1.0, 1.3)[f]**	**1.3 (1.1, 1.6)[f]**	**1.1 (1.0, 1.2)[f]**	1.0 (0.8, 1.2)[f]
		71.0 ± 0.6	13	Per 1 SD increase (19 mmHg)			**1.2 (1.0, 1.3)[f]**	**1.6 (1.2, 2.1)[f]**	**1.1 (1.0, 1.3)[f]**	1.0 (0.8, 1.2)[f]
B2	Shah *et al.* 2006 [28]; ROS (n = 824)	75 ± 7	6.0	Per 1 mmHg increase in SBP						0.995 (0.986, 1.004)[g]
				Per 1 mmHg increase in SBP						1.000 (0.985, 1.015)[g]

[a]Sample mean age and pooled standard deviation (SD) calculated based on mean age ± SD of the male and female groups provided in the paper. [b]Adjusted for age. [c]Adjusted for age, education, *APOE ε4* status, smoking and alcohol consumption. [d]Adjusted for age, *APOE ε4* status, education, gender, smoking and alcohol consumption. [e]Adjusted for age, gender, education, *APOE ε4* status, follow-up survival status, baseline Mini-Mental State Examination, body mass index, coronary heart disease, and use of blood pressure lowering drugs. [f]Adjusted for age and education. [g]Adjusted for age, gender, and education. Entries in bold indicate significant relative risk (RR) ratios. AD, Alzheimer's disease; DBP, diastolic blood pressure; HAAS, Honolulu Asia Aging Study; HTN, hypertension; NL, normal; ROS, Religious Orders Study; SBP, systolic blood pressure; SD, standard deviation; VaD, vascular dementia.

effects. The limited data from longitudinal autopsy studies do not clarify the picture.

Hyperlipidemia

APOE is associated with cholesterol transport. The ε4 allele is the strongest known genetic risk factor for AD [31], and is also associated with dyslipidemia and coronary heart disease [32]. Cholesterol levels decrease with increasing age [33,34]. Therefore, in seeking associations between cholesterol and risk of AD, it is important to control for apoE genotype and to consider age at the time cholesterol was measured as well as the use of lipid-lowering medications.

The literature regarding cholesterol and risk of AD is inconsistent and difficult to interpret (Table 5). Regarding midlife cholesterol, studies from two community cohorts reported positive associations between elevated total cholesterol and development of dementia and AD [33,35]; a third study showed a similar trend [36]. In contrast, measured cholesterol later in life tends to show either no association [37] or an inverse association [38-40]. Interestingly, analysis of longitudinal cholesterol data from Finland [33] showed that, compared to men who remained dementia free, men who developed AD had higher cholesterol levels in midlife but greater declines in total cholesterol levels over 30 years, and thus lower cholesterol levels in late life. This trajectory would explain the reversal of associations depending on the age at which cholesterol levels were determined. However, in the Framingham study neither midlife cholesterol averaged over 30 years nor late-life cholesterol were associated with AD risk [34]. Inverse associations are found in more recent studies that adjusted for cerebrovascular disease and *APOE* genotype [38,39]. Thus, the relationship between cholesterol and risk of AD remains far from clear.

Table 5. Cholesterol and relative risk of subsequent dementia

Grade	Study	Age@Chol (years)	Follow-up (years)	Definition (mmol/L)	Number of subjects		RR (95% CI)			
					High	NL	All dementia	VaD	AD + VaD	AD
Mid-life cholesterol and relative risk of subsequent dementia										
B1	Notkola *et al.* 1998 [33]; Finnish cohorts (n = 444)	40-59 (men)	30	Chol ≥6.5 mmol/L averaged over 4 visits	184	260				**3.1 (1.2, 8.5)**[a]
B1	Kalmijn *et al.* 2000 [36]; HAAS (n = 3,734)	52.7 ± 4.7 (men)	27	Per 1 SD = 0.92			1.10 (0.95, 1.26)			
B1	Kivipelto *et al.* 2002 [35]; FIN-MONICA (n = 2,293)	50.2 ± 6.0	21	Chol ≥6.5 mmol/L	NA	NA			**2.6 (1.2, 6.0)**[b]	**2.8 (1.2, 6.7)**[b]
Late-life cholesterol and relative risk of subsequent dementia										
B1	Tan *et al.* 2003 [34]; 1988 Framingham (n = 1,026)	76.1	12	Per 0.3 mmol/L average chol over previous 15 visits (1950-1980)						0.95 (0.87, 1.04)[c]
				Per 0.3 mmol/L cholesterol at visit 20 (1988)						0.97 (0.90, 1.05)[c]
B1	Reitz *et al.* 2004 [38]; 1992 WHICAP - prospective (n = 1,168)	78.4 ± 6.2	4.8 ± 2.9	Chol ≥5.9 mmol/L	291	877		1.61 (0.7, 3.74)[d] 1.05 (0.42, 2.60)[e]		**0.55 (0.32, 0.95)**[d] **0.48 (0.26, 0.86)**[e]
				LDLc ≥3.67 mmol/L			**2.45 (1.05, 5.7)**[d] 2.07 (0.85, 5.06)[e]			0.88 (0.51, 1.51)[d] 0.80 (0.46, 1.40)[e]
B2	Li *et al.* 2005 [37]; Group Health Cooperative (n = 2,141)	≥65	5.6 ± 1.8	Triglyceride >254 mg/dL			1.16 (0.81,1.67)[f]			1.0 (0.71, 2.15)[f]
				HDLc <1.2 mmol/L			1.04 (0.69, 1.55)[f]			1.23 (0.71, 2.15)[f]
B1	Mielke *et al.* 2005 [40]; Göteborg (n = 973)	70	18	Chol >8.0 mmol/L	56	326	0.31 (0.11, 0.85)[g]			
B1	Reitz *et al.* 2010 [39]; 1999 WHICAP (n = 1,130)	75.7 ± 6.3	3.96	HDLc >1.42 mmol/L	284	846				**0.4 (0.2, 0.9)**[h]
				3.1 < LDLc < 3.7 mmol/L	283	847				**0.5 (0.2, 0.9)**[h]

Note that 1 mmol/L cholesterol = 38.6 mg/dl cholesterol. [a]Adjusted for age and APOE4. [b]Adjusted for age and APOE4, education, sex, smoking, alcohol. [c]Adjusted for age, sex, APOE4, coronary artery disease, body mass index, and lipid-lowering medication. [d]Adjusted for sex, age, education and race. [e]Adjusted for body mass index, APOE4, diabetes, heart disease, hyperten sion. [f]Adusted for age, sex, education, Cognitice Abilities Screening Instrument, body mass index, hypertension, coronary artery disease, cerebrovascular disease, diabetes mellitus. [g]Adjusted for body mass index, diastolic blood pressure, sex, education, smoking. [h]Adjusted for age, sex, education, ethnic group *APOE ε4* genotype, diabetes, hypertension, heart disease, body mass index, lipid-lowering treatment. Entries in bold indicate significant relative risk (RR) ratios. Age@Chol, age of subject when cholesterol was measured; AD, Alzheimer's disease; Chol, cholesterol; FIN-MONICA, Finnish part of Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; HAAS, Honolulu Asia Aging Study; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; NA, not available; NL, normal; SD, standard deviation; VaD, vascular dementia; WHICAP, Washington Heights-Inwood Columbia Aging Project.

Aggregate risk factors

Because vascular risk factors frequently, but variably, cluster and because they may modify dementia risk through a common pathogenic pathway, examination of single risk factors may fail to identify true associations. A small number of epidemiological studies have examined the effects of aggregate vascular risk (Table 6). In WHICAP, the risk of incident AD increased in a dose-related fashion in relation to the number of vascular risk factors [24]. Qiu and colleagues [2] defined two distinct

Table 6. Aggregate vascular risk for incident dementia

Grade	Study	Age (years)	Mean follow-up (years)	Definition	Number of risk factors	Aggregate risk (95% CI)			
						All dementia	VaD	AD + VaD	AD
B1	Kalmijn *et al.* 2000 [36]; HAAS	52.7 ± 4.7	27	Random postload glucose, SBP, DBP, BMI, subscapular skinfold thickness, total cholesterol, and triglycerides	Per 1-unit increase in z-score	1.06 (1.02, 1.10)[a]	1.11 (1.05, 1.18)[a]	1.06 (0.97, 1.15)[a]	1.0 (0.94, 1.06)[a]
						1.04 (1.00, 1.08)[b]	1.09 (1.01, 1.15)[b]	1.04 (0.96, 1.14)[b]	1.00 (0.94, 1.05)[b]
						1.05 (1.01, 1.09)[c]	1.10 (1.04, 1.17)[c]	1.03 (0.94, 1.13)[c]	1.00 (0.95, 1.06)[c]
						1.03 (0.99, 1.07)[d]	1.08 (1.01, 1.15)[d]	1.03 (0.94, 1.13)[d]	0.99 (0.94, 1.06)[d]
B1	Luchsinger *et al.* 2005 [24]; WHICAP	76.2 ± 5.9	5.5	Self-report history of diabetes, or hypertension, or heart disease, or current smoking	1				1.7 (1.1, 2.6)[e]
					2				2.5 (1.6, 3.9)[e]
					≥3				3.4 (2.1, 5.7)[e]
B1	Qiu *et al.* 2010 [2]; Kungsholmen	81.5 ± 5.0	5.1	Vascular risk profile: SBP ≥160, DBP <70, pulse pressure <70, diabetes, stroke, heart failure	1	1.11 (0.79, 1.58)[f]			1.09 (0.75, 1.60)[f]
					2	1.65 (1.12, 2.42)[f]			1.77 (1.16, 2.71)[f]
					≥3	2.48 (1.46, 4.20)[f]			2.66 (1.39, 5.08)[f]
				Atherosclerosis risk profile: SBP ≥160, diabetes, stroke	1	1.28 (1.00, 1.64)[f]			1.33 (1.00, 1.78)[f]
					≥2	2.13 (1.46, 3.11)[f]			2.09 (1.31, 3.34)[f]
				Hypoperfusion risk profile: DBP <70, pulse pressure <70, heart failure	1	1.15 (0.90, 1.47)[f]			1.27 (0.96, 1.69)[f]
					≥2	1.88 (1.30, 2.70)[f]			2.06 (1.31, 3.34)[f]
B2	Ronnemaa *et al.* 2011 [3]; Uppsala	49.6 ± 0.6	29	SBP >140 mmHg, BMI >28, fasting glucose >7 mmol/L, cholesterol >7mmol/L, current smoking	1	1.4 (1.0, 1.9)[g]	2.1 (0.9, 4.6)[g]	1.3 (0.9, 1.9)[g]	0.9 (0.6, 1.5)[g]
					2	1.7 (1.2, 2.3)[g]	2.8 (1.3, 6.2)[g]	1.5 (1.0, 2.2)[g]	1.2 (0.8, 2.0)[g]
					≥3	2.1 (1.5, 3.2)[g]	5.1 (2.2, 11.9)[g]	1.4 (0.9, 1.4)[g]	0.5 (0.2, 1.2)[g]
		71.0 ± 0.6	13	SBP >140 mmHg, BMI >28, fasting glucose >7mmol/L, cholesterol >7mmol/L, current smoking	1	1.8 (1.2, 2.6)[g]	4.1 (1.0, 17.7)[g]	1.6 (1.1, 2.5)[g]	1.3 (0.8, 2.3)[g]
					2	1.7 (1.1, 2.6)[g]	6.8 (1.6, 29.2)[g]	1.4 (0.9, 2.2)[g]	1.0 (0.6, 1.9)[g]
					≥3	1.7 (1.0, 2.9)[g]	7.7 (1.6, 37.1)[g]	1.1 (0.5, 2.1)[g]	0.4 (0.1, 1.3)[g]

[a]Adjusted for age and education. [b]Adjusted for age, education, and history of stroke. [c]Adjusted for age, education, and coronary heart disease. [d]Adjusted for age, education, and adult brachial index. [e]Adjusted for age, gender, education, *APOE ε4* status, and ethnicity. [f]Adjusted for age, gender, education, *APOE ε4* status, follow-up survival status, baseline Mini-Mental State Examination, body mass index, coronary heart disease, and use of blood pressure lowering drugs and, if applicable, for atherosclerosis profile and hypoperfusion profile. [g]Adjusted for age and education. AD, Alzheimer's disease; BMI, body mass index; DBP, diastolic blood pressure; HAAS, Honolulu Asia Aging Study; SBP, systolic blood pressure; VaD, vascular dementia; WHICAP, Washington Heights-Inwood Columbia Aging Project.

risk profiles, one for atherosclerotic risk, the other for hypoperfusion risk; both risk profiles were associated with elevated risk of incident dementia and AD. However, findings from the Uppsala Longitudinal Study of Adult Men found a graded association between number of vascular risk factors and all-cause dementia, mixed AD/VaD, and VaD, but no association with AD alone [3].

Thus, although the data are not entirely consistent, the preponderance of evidence suggests that higher aggregate levels of vascular risk raise the risk of clinically diagnosed incident AD.

In summary, diabetes, hypertension, and hyperlipidemia in midlife, as well as aggregate risk factors for atherosclerosis, are associated with increased risk for

Table 7. Cross-sectional autopsy studies examining stroke risk factors and Alzheimer's disease pathology

Grade	Study	N (mean age at death ± SD)		Association	Conclusions
		Clinical AD	Control		
C2	Heitner *et al.* 1997 [47]; USA		49 DM, 52 non-DM	Negative	No differences between diabetic and age-matched non-diabetic cases in severity of AD pathology
C2	Itoh *et al.* 1999 [45]; Japan	48 (84.7 ± 7.3)	99 (85.9 ± 7.9)	Negative	No association between cerebral atherosclerosis and density of NPs (r = −0.1, P = 0.23)
C2	Roher *et al.* 2004 [42]; USA	10 (87.9 ± 5.9)	10 (86.7 ± 4.1)	Positive	Atherosclerosis score was correlated with NPs (r = 0.71, *P*-value not provided) and NFTs (r = 0.63, *P*-value not provided).
C2	Honig *et al.* 2005 [44]; USA	921 dementia (78.8 ± 8.8)	133 non-dementia (82.9 ± 10.0)	Positive	Severe atherosclerosis was associated with NPs (OR = 5.7, 95% CI 1.3 to 25.5) after adjustment for age, sex, and cerebral infarct, not Braak stage
C2	Beeri *et al.* 2006 [43]; USA	57 definite (88.9 ± 7.2); 12 probable (87.6 ± 9.3); 12 possible (85.4 ± 10.6)	18 (85.7 ± 10.6)	Positive	Coronary artery disease was significantly associated with all NPs and NFTs in the hippocampus (r ranging from 0.22 to 0.29), especially for *APOE ε4* allele carriers (r = 0.34 to 0.47). Aortic atherosclerosis was not associated with either NPs or NFTs
C2	Beach *et al.* 2007 [41]; USA	215 (82.6 ± 8.2)	92 (84.3 ± 6.8)	Positive	Severe atherosclerosis was associated with higher risk of AD (OR 1.31, 95% CI 1.04 to 1.69) after adjustment for age, gender, and *APOE ε4*
C2	Aho *et al.* 2006 [50]; Finland	-	541 (484 with CVL, 68 ± 1; 57 without CVL, 71 ± 2)	Negative	No association between atherosclerosis and frequency of Aβ positivity after adjustment for age and Braak stage (no details provided)
C2	Luoto *et al.* 2009 [46]; Finland	-	466 (70.8 ± 11.5)	Negative	Neither NPs (r = 0.19, P = 0.70) nor NFTs (r = 0.18, P = 0.36) were associated with cerebral atherosclerosis after adjustment for age

Aβ, amyloid-beta; AD, Alzheimer's disease; CI, confidence interval; CVL, cerebrovascular lesion; DM, diabetes mellitus; NFT, neurofibrillary tangle; NP, neuritic plaque; OR, odds ratio; SD, standard deviation.

incident dementia; first for VaD, but also for AD + VaD, and to a lesser extent for AD alone. When relative risk was reported by subgroup, the strength of association diminished in the following order: VaD > AD + VaD > AD (five of five studies for diabetes mellitus; four of four studies for HTN; one study for high cholesterol and one study of aggregate risk). The trends across dementia subgroups is consistent with the hypothesis that vascular risk factors increase atherosclerosis, which promotes subclinical vascular brain injury that exerts an additive effect with AD pathology to symptomatically unmask dementia. These data cannot prove or disprove the alternative hypothesis that vascular risk factors or atherosclerosis increase AD pathology. The advent of biochemical markers for AD (for example, amyloid imaging and cerebrospinal fluid Aβ and phospho-tau) may allow this question to be revisited in the future with improved specificity for the diagnosis of AD in clinical settings.

Level C evidence

Several sources of selection bias may occur in convenience autopsy samples, including why the patient presented to medical attention, reasons for providing autopsy consent, and criteria for including the autopsy cases for study. In general, limited information regarding vascular risk factors is available on autopsy samples, and the focus of these studies is on cross-sectional pathology measures of atherosclerosis and AD (Table 7). The methods of assessing atherosclerosis severity vary widely among studies, including gross visual inspection of the Circle of Willis [41], cross-sectional measurements of arterial lumen narrowing [42], and microscopic evaluation of major branches of the Circle of Willis [20].

Three groups of investigators have reported associations between atherosclerosis and AD pathology (either NPs or NFTs) among cases drawn from AD brain banks. In a study from Sun Health Research Institute, which focuses on cognitive impairment in late life, Roher and colleagues [42] first called attention to correlations between atherosclerosis in the Circle of Willis and tangle and plaque scores in a sample composed of ten AD and ten normal controls. In this small sample, the correlations between atherosclerosis and AD pathology appear to be driven by the absence of either type of pathology in the normal controls. In a larger and more heterogeneous sample from the same center (n = 397) [41],

atherosclerosis was significantly greater in VaD (n = 30) and AD (n = 215), compared to non-AD (n = 60) and normal controls (n = 92). In a logistic regression analysis, adjusted for age, gender and *APOE ε4* genotype, the odds ratios for increasing severity of AD pathology per unit increase in atherosclerosis were significantly elevated: NP score >1 (OR = 1.30, 95% CI 1.07 to 1.57); Braak Stage >4 (OR = 1.27, 95% CI 1.06 to 1.52). In a study of 99 cases drawn from the Mount Sinai Dementia Brain Bank [43] (81 AD and 18 controls), atherosclerosis in coronary arteries and the aorta were correlated with NP and NFT scores, particularly among *APOE ε4* carriers. In a large convenience autopsy sample from the National Alzheimer's Coordinating Center, severity of atherosclerosis was associated with frequency of NP, but not Braak and Braak Stage, among 921 AD and 133 neuropathologically normal controls [44].

On the other hand, other autopsy studies drawn from non-dementia settings have not shown positive associations between atherosclerosis and AD pathology. From cases autopsied at a Geriatric Hospital in Japan, Itoh and colleagues [45] noted lower atherosclerosis scores in AD (n = 48) than non-AD patients (n = 99) (*P* < 0.05). No significant associations were noted between severities of atherosclerosis in the aorta, coronary, or cerebral arteries and hippocampal plaques or tangles. In a study of medico-legal (coroner) cases over age 50 years (n = 466) unselected for either atherosclerosis or AD [46], amyloid plaque percentage area in the frontal lobe was associated with age (*P* < 0.0001) and *APOE ε4* allele (*P* < 0.0001), but not with atherosclerosis in the Circle of Willis. Similarly, hippocampal tangle counts were associated with age, but not cerebral atherosclerosis score. In a study focused on patients with stroke, Aβ load, Aβ40, and Aβ42 aggregates in the cortex and thalamus increased with age, but not with atherosclerosis in the Circle of Willis. Finally, in a retrospective autopsy study, no differences in severity of AD pathology were found among 49 cases with diabetes compared to 52 age-matched normal controls [47].

Thus, in autopsy studies drawn from convenience samples, the relationship between atherosclerosis and AD pathology differs depending on the settings from which the sample is drawn. Associations between intracranial atherosclerosis and severity of plaques and sometimes tangles are reported from AD brain banks, but not from stroke banks, or from cases unselected for atherosclerosis or AD. These level C findings are inconclusive, due to sample selection, relative crudeness of the pathology measures, and to a variable sample size.

Conclusion

A few representative, prospective studies with autopsy (evidence level A) fail to show a positive association between vascular risk factors and AD pathology. Not surprisingly, vascular risk factors increased the likelihood of cerebral infarcts. No associations have been demonstrated between diabetes and AD pathology or between intracranial atherosclerosis and AD pathology. Some prospective, representative, epidemiologic studies (evidence level B) show associations between diabetes, hypertension, hyperlipidemia, and aggregate vascular risk factors and incident AD; these studies have attracted considerable attention in the literature. However, when relative risk has been reported by subgroup, the strength of association diminished in the following order: VaD > AD + VaD > AD. The declining trends across dementia subgroups is more consistent with the hypothesis that atherosclerosis promotes subclinical vascular brain injury that increases the likelihood of dementia. Convenience autopsy studies from AD brain banks (evidence level C) report positive associations between intracranial atherosclerosis and severity of plaques and sometimes tangles. However, these associations are not confirmed when samples are drawn from other non-dementia brain bank settings. We conclude that, at the present time, there is no level A or B evidence that the vascular risk factors reviewed here increase AD pathology.

Abbreviations

Aβ, amyloid-beta; AD, Alzheimer's disease; APOE, apolipoprotein E; CI, confidence interval; HAAS, Honolulu Asia Aging Study; NFT, neurofibrillary tangle; NP, neuritic plaque; OR, odds ratio; ROS, Religious Orders Study; RR, relative risk; VaD, vascular dementia; WHICAP, Washington Heights-Inwood Columbia Aging Project.

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