# Imaging Vascular Disease and Amyloid in the Aging Brain: Implications for Treatment

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## Abstract

Vascular risk factors (e.g. hypertension, dyslipidemia and diabetes) are well known risk factors for Alzheimer' disease. These vascular risk factors lead to vascular brain injuries, which also increase the likelihood of dementia. The advent of amyloid PET imaging has helped establish that vascular risk factors also lead to Alzheimer's disease via pathways that are independent from vascular brain injuries, at least, when vascular brain injuries are measured as white matter lesions and infarcts. While vascular brain injuries (white matter lesions and infarcts) do not seem to influence amyloid pathology, some evidence from amyloid imaging suggests that increased vascular risk is related to increased amyloid burden. Furthermore, while vascular brain injuries and amyloid have an additive and independent impact on brain integrity, vascular risk factors might potentiate the impact of amyloid on cortical thickness on brain regions vulnerable to Alzheimer's disease. New research should further explore and confirm, or refute, possible interactions between amyloid and vascular risk factors on brain integrity and cognition. Neuroimaging tools used to assess vascular brain integrity should also be expanded. Measuring cortical blood flow or damage to the capillary system might, for instance, give insight about how vascular risk factors can be associated to amyloid burden and impact. These findings also stress the need for monitoring vascular risk factors in midlife as a strategy for Alzheimer's disease prevention. .

*Key words: Alzheimer' disease, amyloid, vascular brain injuries, vascular risk factors, treatment.*

## Introduction

How do vascular factors, such as vascular diseases or vascular brain injuries (VBI, also often called cerebrovascular disease), increase the risk of Alzheimer disease (AD)? Are Alzheimer and vascular pathologies independent diseases, or does the presence of one pathology influence the presence and the impact of the other? Can vascular risk factors be good preventive targets for AD, and if so, why and when should they be targeted? Although the answers to these questions remain unclear, they represent some of the oldest issues in understanding relationships between Alzheimer and vascular diseases. Neuroimaging has long helped us to detect and quantify brain vascular diseases. The more recent advent of amyloid imaging now permits the detection and quantitation of amyloid-beta (Aβ), permitting new types of studies to explore complex relationships between Alzheimer and vascular pathologies. The current review first presents a brief overview of knowledge about the association between AD pathology and vascular factors (both VBI and vascular risk factors) from epidemiology and autopsy studies. We subsequently address what has been learned since the advent of in-vivo Aβ imaging. Possible avenues for prevention and treatments are also explored along with future research directions. This review does not intend to be an exhaustive review of the literature, but more an overview of where we are and where we should go next.

## The cause(s) of Alzheimer's disease

The major obstacle to AD prevention and treatment is that the cause(s) of the disease is still unknown. In 1991, it was proposed that cerebral amyloid deposition represents the key pathogenic mechanism of AD development (1). The amyloid hypothesis suggested that amyloid initiates a cascade of pathological events, including the overexpression of neurofibrillary tangles, that lead to neurodegeneration and cognitive decline (2). The amyloid hypothesis finds its strongest support in the several varieties of familial AD that invariably result from genetic mutations which influence amyloid accumulation. In late onset AD, however, the causes likely include a combination of genetic, environmental, and lifestyle factors that act in concert to influence individual risk for development of disease and its associated symptoms. Specifically, while amyloid deposition seems still to be a key feature of late disease, other factors moderate its impact on brain integrity and cognition. Also, because late onset AD patients do not have a genetic mutation that causes early Aβ production, other genetic and environmental factors must influence Aβ accumulation. Identifying these factors and understanding the mechanism by which they influence the risk of AD is important from a prevention point of view, but also to guide new drug development.

# Vascular and cerebrovascular diseases as risk factors for Alzheimer' disease: knowledge from epidemiology and autopsy research studies

Vascular risk factors such as hypertension, dyslipidemia and diabetes are well known risk factors for AD (3). When looking at the prevalence of vascular factors compared to other risk factors (Table 1), it is evident that vascular factors should be a particular target for AD prevention. Furthermore, individuals with multiple vascular risks have more than twice the risk of developing dementia associated with AD compared to elderly without vascular risk factors (4). These vascular risk factors lead to VBI (e.g. white matter lesions and infarcts), which also increase the likelihood of dementia (3, 5). In fact, autopsy studies suggest that the most prevalent cause of dementia is mixed dementia, often defined by the presence of Alzheimer plus vascular pathologies (6). Autopsy studies further suggest that, while about a quarter of people can be free from dementia when presenting with Alzheimer pathology with no other comorbidity, very few persons (less than 7%) can stay free from dementia when both Alzheimer and vascular pathologies are present (6). Interestingly, autopsy studies also showed that less severe Alzheimer's pathology is needed to develop Alzheimer's dementia in the presence of infarcts or white matter lesions (7). Given the strong co-occurrence between both diseases, Alzheimer's and vascular dementia are often presented as a continuum: with pure Alzheimer's or vascular dementia representing the two extremes, and 'mixed' dementia in between and representing most older people with dementia.

Because both pathologies frequently occur together, it is a major challenge to assign the degree of importance to either of them with regard to their effects on brain and cognitive integrity. Before $A\beta$-imaging, assessing the respective impact of both pathologies was only possible in autopsy-defined groups. However, even with the availability of autopsy data, or now with the availability of quantitative measures of $A\beta$ deposition, assigning a role to each pathology when they are mixed is problematic. This is because such effects likely depend on the amount of each pathology, the length of time the pathology has been present, the location of pathology (particularly true for cerebrovascular disease which can be more focal than $A\beta$), and many aspects of the individual subject's genetic, medical, and environmental background that could increase or limit susceptibility to each pathological process. Another challenging question, based on the strong associations between Alzheimer's and vascular pathologies, is whether the impact of both pathologies are independent and additive, or if the presence of one pathology influences the presence and the impact of the other.

It is possible that 1) both pathologies share common drivers (i.e. age, Apolipoprotein E (ApoE)) but act via independent pathways, 2) that one pathology drives the other pathology and/or 3) that both pathologies interact and that the join effect of both pathologies on brain and cognition is greater than their sum. Autopsy studies reported insufficient data supporting a direct link (options 2 and 3 above) between Alzheimer and vascular pathologies (8). It has therefore been assumed that both diseases occur and act independently, and additively increase the risk of dementia. Figure 1 schematises these independent pathways.

**Table 1.** Risk factors for Alzheimer' disease

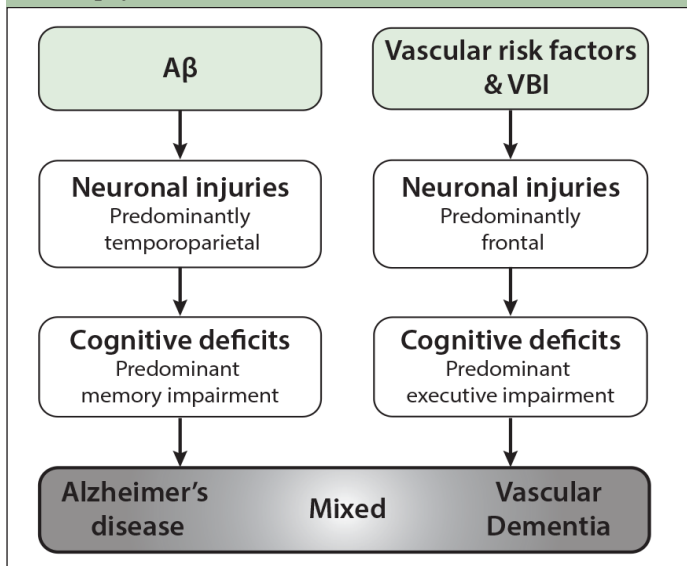| Alzheimer's disease risk factors |
|---|
| *Vascular risk factors and diseases* |
| Hypertension [1] |
| Hypotension |
| Hypercholesterolemia [1] |
| Diabetes mellitus |
| Smoking |
| Thrombotic episodes |
| Congestive heart failure |
| Cardiac arrhythmia |
| Atrial fibrillation |
| |
| *Cerebrovascular risk factors* |
| Ischemic and silent stroke |
| Transient ischemic attack |
| |
| *Other risk factors* |
| Age[1] |
| ApoE4 allele[1] |
| Head injury[1] |
| Low education |
| Low lifetime cognitive activity[1] |
| Psychiatric factors (depression[1], anxiety, apathy) |
| Sleep disorders[1] |

Presented are common risk factors for AD; 1. Factors that have additionally been associated with increased brain $A\beta$. For hypercholesterolemia, both low HDL and high LDL cholesterol, but not total cholesterol, have been associated with increase $A\beta$ (34). Aggregate vascular risk has also been associated with increased $A\beta$ (33).

## $A\beta$ imaging

In 2004, the first in-vivo radiotracer to specifically track brain $A\beta$ was reported (9). The Pittsburgh Compound B (PIB)-PET tracer is a 11C radiotracer that binds to fibrillar deposits of $A\beta$ protein in plaques and cerebrovascular amyloid (CAA). Since then several 18F-labeled (half-life of 110 min) compounds have been created. Using

these radiotracers it is now possible to track brain and cognitive changes associated with "pure" Alzheimer or vascular dementia, as well as subtle cognitive changes that are independent from both pathologies, which might include what is often termed normal aging. It is also possible to assess the relationship between Aβ, VBI and vascular risk factors in-vivo and test if Aβ and vascular factors act via independent or common pathways.

**Figure 1.** Independent Alzheimer and vascular pathways: an autopsy based model



Autopsy studies suggest that Alzheimer and vascular pathologies increase the risk of AD via independent and additive pathways. Because both pathologies frequently co-occur and because vascular risk factors such as hypertension and diabetes are well known risk factors for AD, mixed dementia is often considered the most frequent type of dementia. VBI : vascular brain injuries. Aβ: amyloid-beta

## Aβ and vascular brain injuries: independent or dependant pathways?

Supporting autopsy findings, many in-vivo studies assessing a relationship between Aβ and VBI (white matter lesions or infarcts) found no or slight correlation between the two factors in cognitively normal older adults, or older adults in preclinical or clinical phases of AD (10-18), even though increased white matter lesions have sometimes been reported in AD patients (14, 15). Increased PIB-PET signal has in turn been associated with increased white matter lesions in persons presenting cerebral amyloid angiopathy (CAA) (19). Therefore CAA might have a stronger relationship with VBI than parenchymal Aβ. Whether transient Aβ increase follows an acute vascular event in humans, as has been suggested in rodents (20), still needs to be tested.

Concerning the impact of Aβ and VBI on brain and cognitive integrity, it seems that both factors mainly act via independent pathways, which is also in line with autopsy studies. Lower cerebrospinal fluid Aβ (which is inversely associated with brain Aβ) has been associated with decreased temporoparietal metabolism

while greater white matter lesions have been associated with decreased frontal metabolism in individuals with mild cognitive impairment that subsequently progressed to dementia (21). Hippocampal volume and precuneus thickness have further been found to mediate (account for) the relationship between Aβ and memory (22-24), while frontal thickness has been reported to mediate the relationship between VBI and executive function (22) in cognitively impaired patients. These results do not imply that VBI cannot target brain regions typically affected by AD pathology (18, 25), but they suggest that VBI has a predominant impact on frontal functions. Similarly, while VBI is primarily associated with executive dysfunctions, it is not restricted to them, or to the impact of frontal-executive dysfunctions on other cognitive domains (10, 11, 26).

**Figure 2.** Alzheimer and vascular independent and shared pathways : an in-vivo based model
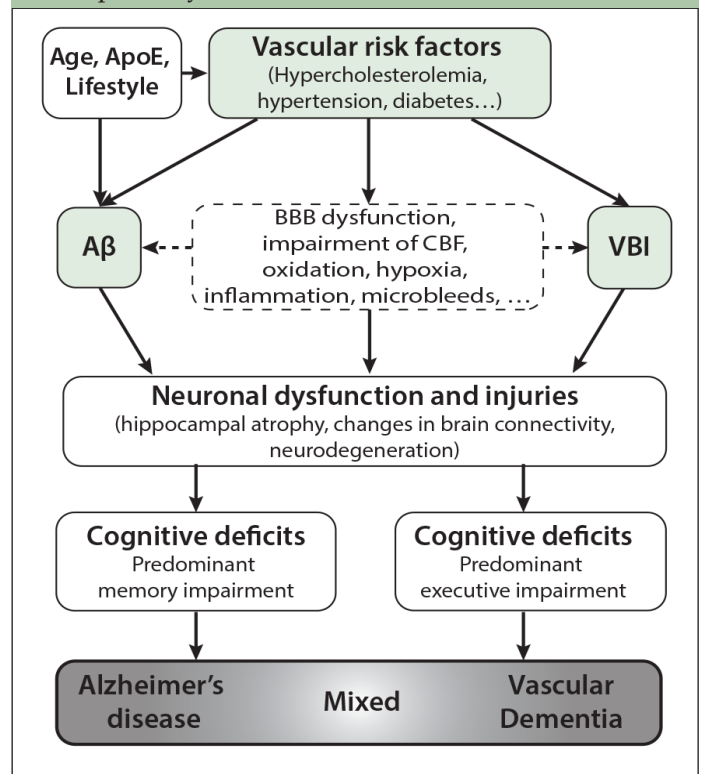


Proposed conception of the relationship between AD and vascular factors. While Aβ burden and vascular brain injuries (VBI, white matter lesions and infarcts) still have distinct pathways, vascular risk factors are associated with both Aβ burden and VBI. Vascular risk factors are also associated with brain integrity via a pathway that is independent from Aβ and VBI. Accordingly, vascular risk factors should be a particular target for prevention. Aβ: amyloid-beta. BBB: blood brain carrier. CBF: cerebral blood flow

The association between white matter structural integrity, measured with diffusion tensor imaging (DTI), and Aβ needs to be further explored given the inconsistent results reported in the literature (13, 27). Furthermore, even an association between these DTI changes and white matter lesions (13, 27) does not exclude the possibility that they are not all from vascular origin. The question of whether VBI potentiates the

association between Aβ and functional connectivity, or if VBI and Aβ affect different brain networks, also needs further exploration. Indeed, while evidence suggests a link between Aβ and brain network functions measured with functional MRI (26), the independent or shared impact of white matter lesions on brain connectivity is unknown.

**Figure 3.** Impact of Aβ, VBI and vascular risk factors on cortical thickness in older adults with a spectrum of vascular diseases
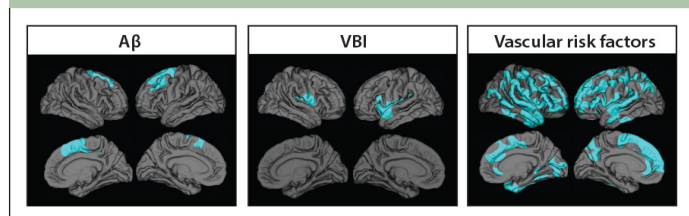


Legend: Statistical cortical maps showing the association among Aβ, VBI (white matter hyperintensity), vascular risk (FCRP score) and cortical thickness in a sample of 66 older (64 for VBI) adults enriched for vascular diseases. Results suggest that increased vascular risk, increased Aβ burden and increased VBI are associated with thinner cortex. Statistical surface maps were created using a vertex-wise statistical thresholds of p < 0.05. The analyses are corrected for age, cognitive status, and multiple comparisons. This figure is based on a previously publication (38)

With the constant improvement of neuroimaging tools, it is now possible to go beyond the assessment of WML/infarcts (or DTI) and explore other cerebrovascular mechanisms that might be related to Aβ. Indeed the multiple pathways by which amyloid and vascular factors could be linked do not necessary involve white matter lesions or infarcts (3, 28, 29), a fact that should be keep in mind and further explored. A recent study suggested for instance an association between Aβ and lower cerebral blood flow assessed using MRI-based arterial spin labelling (30). One explanation might be that lower blood flow diminishes Aβ clearance, which in turn reduces cerebral blood flow via a harmful vicious cycle (28). Assessing the integrity of the blood brain barrier using an MR contrast (28), brain vasoreactivity using carbon dioxide inhalation (31), or cerebral blood volume (as a proxy of capillary density) using a contrast agent and functional MRI (32), in relationship to Aβ would also be of interest. Even if still difficult to examine using existing neuroimaging tools, assessing the link between Aβ and microinfarcts might lead to new insight about the relationship between vascular factors and Aβ.

## Aβ and vascular risk factors: independent or dependant pathways?

Although VBI and vascular risk factors, such as hypertension, cholesterol and diabetes, are linked, vascular risk factors can occur in the absence of VBI and vice versa. Vascular risk factors and VBI should therefore be considered and treated as two separate entities. While no clear association has been found between Aβ and VBI,

there is strong evidence suggesting that vascular risk factors (aggregate or independent risk) are associated with increased brain Aβ (33-36). Importantly, some of these observations were found in late middle age subjects (36), suggesting that intervention targeting vascular risk factors should probably be started in midlife. Supporting that idea, the impact of vascular risk factors on brain integrity can already be detected in young adults (37). While the process by which vascular risk factors might lead to Aβ are mainly unknown, assessing these "other cerebrovascular mechanisms" are of interest since changes in cerebral blood flow, diminution of blood brain barrier permeability and vascular oxidative metabolism are all possible mechanisms by which vascular risk factors might increase Aβ burden (28).

In one of our previous studies we suggested that vascular risk factors interact with Aβ to reduce cortical thickness in brain regions known to be vulnerable to AD (38). This observation was independent of VBI and found when looking at aggregate vascular burden (assessed using the total Framingham cardiovascular risk profile, FCRP, score) or levels of circulating high-density lipoprotein (HDL) cholesterol. These data suggest that the impact of Aβ on cortical thickness might be potentiated by the presence of vascular burden and/or vice versa. In this same study, we also presented results suggesting that vascular risk factors can be associated with cortical thinning independently of Aβ and VBI. Therefore, vascular risk factors could influence AD risk via at least three pathways: 1) by increasing VBI, 2) by facilitating Aβ burden (and having a synergistic effect with it on brain integrity), and 3) by direct effects on the brain independently of Aβ and VBI (Figure 2). This last pathway should not be neglected as vascular risk factors can start early in life and therefore probably have a wide spread impact by the time a person reaches 65 years old, as suggested in Figure 3. Even if vascular risk factors do not lead to dementia by themselves, they probably diminish the "brain reserve", conceptualised as a buffer that allows individuals to stay free from cognitive impairment in the presence of brain pathology. These "frail" brains might also be more vulnerable to other brain pathologies, as the interaction with Aβ suggests (38).

In this same study, it was also suggested that cholesterol-lowering medications might be protective against the negative impact of vascular risk factors and Aβ on cortical thickness. Both higher FCRP and higher Aβ burden were associated with less cortical thinning in subjects that were taking cholesterol-lowering drugs when compared with subjects who were not taking cholesterol drugs. This finding, which needs replication, is in line with other studies suggesting that statins confer some level of neuro-protection against late-life development of AD (39, 40, see also 41). Given that statin treatment has shown no reliable effect on clinical symptoms in subjects with dementia, it is more than

**Table 2.** Preventive and treatment targets for Alzheimer' disease

| Prevention targets in mid and late life | Treatment targets in presymptomatic AD |
|---|---|
| *Treatment of VRF and VD* | *Anti-Aβ treatment* |
| - Anti-hypertensive drugs | - Anti-Aβ antibodies |
| - Anti-hyperlipidemic drugs | - Blocking Aβ production enzymes |
| - Anti-platelet agents | |
| - Anti-diabetes drugs | *Targeting ApoE and ApoE receptors* |
| | - Convert an ApoE4 to an ApoE3-like molecule (By blocking domain interaction in ApoE4) |
| *Treatment of psychiatric symptoms* | |
| - Anti-depressive drugs | - Increase ApoE levels (this might however have adverse effect on Aβ expression and neurotoxicity) |
| - Anxiolytic agents | |
| - Therapy | - Regulate cholesterol homeostasis using Liver X receptors that up-regulate ApoE and ABCA1 |
| *Lifestyle changes* | |
| - Physical exercise | *Other* |
| - Cognitive stimulation | - Reducing inflammation |
| - Weight control | - Improving brain insulin resistance |
| - Mediterranean diet | - Anti-tangle formation treatments |
| - Smoking discontinuation | - Nerve growth factor enhancement |
| | - Control abnormal brain activity |

Presented are prevention and treatment targets for AD. This table is intended to present avenues that should be explored and is not restricted to available treatments or treatments that have been found to be beneficial.

plausible that statins only have an impact when started in midlife. Also, not all classes of statins necessarily confer the same protective benefit (40), an effect that needs to be better understood.

## Apolipoprotein E, Aβ and vascular factors

ApoE is a well-known genetic risk factor for AD (3, 42), with ~ 60% of AD patients presenting at least one ε4 allele (43). Interestingly, ApoE seems to be a common upstream driver to both Aβ and vascular burden, reinforcing the association between these two factors. ApoE, for example has been suggested to play a key role in Aβ accumulation and clearance, with ApoE4 being associated with increased Aβ burden (44) and ApoE2 being associated with lower Aβ burden (45). Because of its role in lipid metabolism regulation, ApoE4 also influences vascular risk factors and cardiovascular diseases (46), which in turn affects the risk of AD, as presented previously. Other mechanisms by which ApoE4 might influence the clinical expression of AD include neuronal inflammation, less efficient neuronal repair, diminished blood barrier integrity, increased tau phosphorylation, neurofibrillary tangle formation, neuronal mitochondrial dysfunction, and decreased GABAergic interneuron selectivity (47, 48). Given its wide range of functions, ApoE is probably a key factor to target for AD prevention and treatment.

## Alzheimer's disease prevention and treatment

Because the disease starts up to 30 years before the onset of dementia (49), and because vascular risk factors already impair the brain in middle age (37), preventive strategies for AD (table 2) should be implemented as early as possible. Most of these strategies should also be adopted in late life as they may still confer a benefit. For instance, while monitoring vascular risk may be a good prevention target in midlife, treating vascular risk in late life as been found to improve cognition in individuals with mild cognitive impairment (50).

In addition to targeting vascular risk factors, one obvious treatment target for AD is anti-amyloid therapies. Even if these therapies failed in dementia patients, they might have beneficial impact at preclinical or presymptomatic stages of the disease (51). Clinical trials enrolling subjects with autosomal-dominant familial AD and cognitively normal amyloid-positive older adults from the general population are currently ongoing. Given the possible vascular side effect of anti-amyloid therapies (52), vascular brain health will be monitored closely in these trials as they may predict adverse side effects.

Several other avenues should be tested for AD prevention and treatment in addition to Aβ and vascular therapies as the disease is multifactorial. More importantly research should be done to assess the mechanism by which these other factors can

diminish the risk of AD since it might lead to new treatments. For instance, depression is a well-known risk factor for dementia. More recently it was suggested that individuals with a lifetime history of depression present increased brain Aβ (53). While depression might be secondary to Aβ accumulation, it is also important to assess if anti-depresant medication can slow Aβ accumulation, and hopefully AD progression, as was recently suggested (54). Similarly, enhanced lifetime cognitive activity has been shown to buffer the effect of ApoE4 on Aβ burden (55). While this information is valuable by itself for preventative strategies, understanding the mechanism by which cognitive activity might influence Aβ burden could point to new treatment strategies. Such strategies could include approaches such as the antiepileptic levetiracetam (56) (assuming that cognitive activity attenuate Aβ secretion via modulation of neural activity) or cognitive training protocols (57).

As mentioned previously, ApoE is a major risk factors for both Alzheimer and vascular pathologies. Increasing effort should therefore focus on developing and testing drugs that modify ApoE expression and function. Promoting ApoE levels, increasing ApoE receptor 2, blocking domain interaction in ApoE4, or restoring brain vascular integrity are all potential interesting targets (48, 58-60).

## Conclusion

The absence of a relationship between Aβ and VBI (here defined as white matter lesions and infarcts), as well as their independent impact on cognition and brain integrity, suggests that both factors mainly act via independent pathways. Vascular risk factors however, seem to have a more direct impact on AD since increased vascular risk factors have been associated with increased Aβ burden. Furthermore, increased vascular risk factors might potentiate the impact of Aβ burden on cortical thickness. Given these findings, and the fact that vascular risk factors are often treatable, they should represent key factors for prevention.

Finally, while everyone is impatiently awaiting the results of anti-amyloid therapies in asymptomatic individuals, other treatments strategies should also be targeted. Among them, drugs that modify ApoE metabolism and function might be promising. Effort should also be made to understand how protective and risk factors such as lifestyle, psychiatric symptoms and sleep, influence AD risk.

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