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REVIEW

Late-onset alzheimer's disease, atherosclerosis, and cerebrovascular disease. A complex relationship too often neglected: a narrative review

Giovanni Zuliani[1] · **Carlo Cervellati**[1]

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Abstract
Since the 1990s, a long series of preclinical, epidemiological, clinical, and anatomo-pathological studies have questioned the purely "degenerative" origin of Alzheimer's disease (AD), providing growing evidence of a possible "vascular" involvement in the pathogenesis of this type of dementia.Currently, evidence accumulated from preclinical, epidemiological, anatomo-pathological, clinical, neuroimaging, and proteomic studies supports a significant role of cerebral atherosclerosis in the pathogenesis of late-onset sporadic AD (LOAD). It is now well established that cerebral atherosclerosis, through various mechanisms, can promote the deposition of β-amyloid, as well as cause alterations in energy metabolism and neuronal damage.Conversely, β-amyloid can induce not only inflammation and oxidative stress, but also changes in cerebral hemodynamics, pathological angiogenesis, and endothelial dysfunction, thereby contributing to the development of cerebral atherosclerosis.Consistent data suggest that vascular phenomena may precede neurodegenerative ones. In any case, a dangerous vicious cycle is created, in which a clear separation between degenerative and vascular processes is sometimes extremely difficult to establish.

Keywords Alzheimer's disease · Atherosclerosis · β-amyloid · Vascula dementia

Introduction

Alzheimer's disease (AD) is a disorder of the central nervous system (CNS) characterized by an insidious progression that leads to memory loss, cognitive decline, and loss of autonomy. AD is classified as a "neurodegenerative" disease [1, 2]; however, despite extensive research into its pathophysiology, the etiopathogenic mechanisms underlying this form of dementia remain partially unknown.

In 1907, Alois Alzheimer first described the clinical and pathological features of a female patient affected by presenile dementia. In 1910, Emil Kraepelin named this condition "Alzheimer's disease" in his psychiatric textbook. For many years, AD was considered a rare presenile dementia. It was only later that Katzman proposed that presenile and senile dementia should be regarded as a single nosological entity.

Currently, early-onset AD (EOAD, <65 years) and late-onset AD (LOAD, >65 years) account for approximately 10% and 90% of all AD cases, respectively.

Simplifying a highly complex pathogenetic process that unfolds over decades, the accumulation of β-amyloid outside neurons (neuritic plaques) and the accumulation of abnormal tau protein inside neurons (neurofibrillary tangles) are the two hallmark brain changes observed in AD [3]. The neuropathological diagnosis of AD requires the presence of significant amounts of both neuritic plaques and neurofibrillary tangles in the CNS. The accumulation of β-amyloid and tau in the CNS is associated with other pathological processes, including glial activation, neuroinflammation, oxidative stress, mitochondrial dysfunction, and cholinergic insufficiency. The currently accepted theoretical sequence of events is as follows: β-amyloid accumulation, tau-mediated neuronal injury, synaptic dysfunction, neurodegeneration, and cognitive decline [4]. This model

✉ Carlo Cervellati
crvcrl@unife.it

[1] Department of Translational Medicine and for Romagna, University of Ferrara, via L- Borsari 26, 44121 Ferrara, Italy

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implicitly assumes a cause-effect relationship that produces similar pathological outcomes across individuals.

β-amyloid can accumulate in the CNS due to two main mechanisms: (1) Increased production via the action of β- and γ-secretases on amyloid precursor protein (APP), a membrane protein concentrated in synapses. (2) Reduced non-enzymatic and/or enzymatic clearance from the CNS.

To date, it remains unclear what triggers one or both of these harmful mechanisms, or what their relative contribution may be in individual AD patients.

Alzheimer's disease and vascular dementia

In 1955, Roth suggested classifying dementia into two main forms, distinguished based on their clinical presentation: AD and vascular dementia (VD) [5]. The first is associated with a process of neurodegeneration, while vascular lesions in the CNS lead to VD. Numerous studies have subsequently supported this distinction: AD and VD affect the CNS in different ways, resulting in distinct neuropsychological profiles and clinical manifestations. Although these observations are substantially accurate, since the 1990s a series of studies have highlighted many pathophysiological similarities between AD and VD.

In the early 1990s, J.C. de la Torre and colleagues proposed, following a long series of studies [5–13], , that sporadic AD should be considered a vascular-based disease. According to this view, AD would be triggered by vascular factors—including cerebral hypoperfusion and vessel damage—that precede and potentially initiate neurodegeneration. The question posed by de la Torre, namely whether AD is caused by neurodegenerative phenomena (the current paradigm) or whether vascular dysfunction can determine or trigger neurodegeneration, is of great importance. On the other hand, concepts surrounding the pathogenesis of VD have also evolved over time. We have moved away from the "classic" NINDS-AIREN classification [14] to the recent classification by the JACC Scientific Expert Panel [15]. Interestingly, in the "modern" classification of VD, alongside multi-infarct dementia (large vessel disease, LVD) and subcortical dementia (small vessel disease, SVD), additional categories such as post-stroke dementia and mixed dementia have been introduced. In mixed dementia, vascular cognitive impairment coexists with AD or other neurodegenerative conditions. This evolving classification reflects a shift toward a less restrictive framework, acknowledging that in many cases, the pathogenesis of dementia is not exclusively vascular but also involves neurodegenerative processes. This concept is confirmed by many autopsy studies, including that of Boyle and Colleagues [16]. By examining the brains of 1,079 older participants, Boyle and colleagues identified 236 different combinations of neuropathological lesions, considering seven key types: AD, Lewy body disease (LBD), hippocampal sclerosis, macroscopic infarcts, amyloid angiopathy, atherosclerosis, and arteriolosclerosis. Notably, while AD pathology alone accounted for approximately 50% of cognitive decline, cases of "pure" AD, where no other coexisting pathologies were present, were rare, observed in only 9% of individuals.

Thus, two aspects must be considered when dealing with LOAD: (1) In older subjects, who present the highest incidence of dementia, pure forms of dementia are rare, while mixed forms are almost the rule; (2) Regardless of the first consideration, the pathophysiological mechanisms leading to LOAD are not entirely clear and, in any case, much less clear compared with those leading to EAD. It is not clear why only some individuals accumulate significative amounts of β-amyloid in CNS during ageing, nor why only some of them will develop dementia, while others remain cognitively intact.

The amyloid hypothesis of alzheimer's disease

In recent years, the pathogenetic model of AD, based on the *amyloid cascade hypothesis*, has been repeatedly questioned [9, 17–19]. Listed below are many, though not all, of the objections to the amyloid cascade theory:

- β-amyloid and tau initially deposit in different brain regions;
- The topographical spreading patterns of β-amyloid and tau over time overlap only minimally.
- Amyloid plaques are first found in frontal regions, basal ganglia or elsewhere, not adjacent to neurons early lost in AD (hippocampus, entorhinal cortex).
- β-amyloid amount in AD brain is not correlated to the extent of cognitive decline in both humans and AD transgenic mice. The absence of amyloid-related "dose effect" for the amount of neuronal death or severity of cognitive impairment raises serious doubts.
- β-amyloid deposition also occurs in normal elderly people; many of them have relatively large amounts of β-amyloid in their brain post-mortem. By PET imaging, almost 30% of normal elderly people have large amounts of β-amyloid in CNS; this suggests that β-amyloid may be not sufficient to cause AD.
- In normal individuals >70 years with PET evidence of CNS β-amyloid/tau deposition, the incidence of LOAD is less < 20% after 5 years, and < 50% after 14 years of follow-up.

- Very old subjects (90–100 years) can develop a dementia similar to LOAD, with slow evolution and few neuritic plaques; the loss of neurons/synapses can be independent of β-amyloid deposition.
- Neuropathological criteria emphasize that fewer neuritic plaques are required to make diagnosis of EAD, contrary to the expected greater vulnerability of older subjects' brains; this discrepancy suggests that plaque formation might be a marker of the degenerative process.
- In large autopsy studies, tau pathology in CNS is present at young ages (< 40 years), when neuritic plaques are still absent, while subjects exhibiting only neuritic plaques and no neurofibrillary tangle are a minority; this argues against the actual AD model.
- Dementia onset in Down's syndrome is variable, despite the presence of amyloid plaques in 100% of these individuals over 50 years of age.
- APP cleavage and functions is much more complex than solely the production of β-amyloid (see later).
- The real triggers of neuroinflammation, synapse loss and neuronal loss in AD are still unclear.
- The APO E4 genotype (associated with AD) has meany other effects (e.g. hypercholesterolemia, inflammation, reduced myelination).
- In both humans and transgenic mice, cognitive deficit appears before β-amyloid deposition in CNS.
- The most "troubling" observation is the substantial clinical failure of randomized clinical with monoclonal antibodies that interfere with/reduce β-amyloid burden in AD patients' trials (negligible clinical effects after 1.5 years) [20].

These observations (and others not listed) suggest that β-amyloid may be necessary but not sufficient to cause late-onset Alzheimer's disease (LOAD), and they call into question the traditional "causal" model of AD. In this regard, Frisoni and colleagues have proposed a probabilistic mode [19]l. In this framework, β-amyloid remains a crucial factor, but three conceptual variants of AD are identified: autosomal dominant AD, and sporadic AD either related or unrelated to the APOE ε4 genotype.

According to this model, a number of stochastic factors contribute to the wide variability observed in AD. When the combined burden of β-amyloid and tau reaches a certain threshold, cognitive impairment may become clinically manifest. This typically occurs around the age of 50 in autosomal dominant AD, and between 75 and 85 years in sporadic APOE ε4-related or -unrelated AD, respectively. It is important to note that in the latter two cases, we are primarily referring to LOAD, not EOAD).

Furthermore, less than 30% of individuals who do not carry the APOE ε4 allele, most of the population, will reach the pathological threshold for dementia onset during their lifetime.

At this point, we must remember that the Lancet Commission on Dementia [21] estimated that 45% of all dementia cases are attributable to 14 modifiable risk factors. Among these, high LDL cholesterol, hypertension, obesity, smoking, physical inactivity, diabetes, and excessive alcohol intake are classified as vascular risk factors.

Finally, another noteworthy observation cannot be ignored. Thomas and colleagues demonstrated that objectively defined subtle cognitive difficulties, associated with faster amyloid accumulation, can be identified prior to or during the preclinical stage of β-amyloid deposition [22]; in other words, cognitive changes may be occurring before significant levels of β-amyloid have accumulated into the CNS.

Seminal research on vascular pathology in AD

The first large longitudinal studies

In the 1980s, several longitudinal population studies were initiated, enrolling large samples of individuals with late-onset LOAD. Until the early 1990s, most epidemiological studies on AD were cross-sectional. Moreover, the criteria used to select AD patients intentionally excluded those with vascular risk factors, thereby introducing a significant bias. In 1996, Skoog and colleagues evaluated the relationship between blood pressure and incident dementia in a cohort of 382 seventy-year-old individuals followed over a 15-year period [23]. The study demonstrated for the first time that:1. Subjects who developed dementia (LOAD or VD) between 79 and 85 years had higher blood pressure at age 70 compared to controls.

2. Subjects who, at age 85, had white matter lesions (WML) on CT scan had higher blood pressure at age 70 compared to controls. 3. Blood pressure progressively decreased in the years preceding dementia onset; after diagnosis, it was equal to or even lower in AD patients compared to controls.

In 1997, Hoffman and colleagues published another interesting study, evaluating the relationship between atherosclerosis (ATS) and AD [24]. The study included 284 patients with dementia and 1,698 non-demented controls. Several indicators of atherosclerosis (ATS) were considered, including intimal thickness, carotid ATS plaques, ankle-brachial index, and APOE genotype. The study showed that ATS indicators were associated with dementia (both LOAD and VD). Moreover, the prevalence of dementia increased with

the severity of ATS, with a maximum odds ratio of 3.9 for LOAD and 19.8 for VD.

Two "provocative" studies from the 2000s: is AD a vascular disease?

In a "famous" paper published in 2002 *"Alzheimer Disease as a Vascular Disorder: Nosological Evidence"*, J.C. de la Torre summarized the main evidence in favor of the hypothesis that AD may have a vascular basis [6]: (1) There is a clear link between vascular factors and cerebrovascular disease capable of triggering the metabolic, neuropathological, and cognitive changes associated with AD. (2) AD and VD share numerous common risk factors, such as hypertension, diabetes, and others, all of which are associated with atherosclerosis (ATS) and a reduction in cerebral blood flow (CBF).

It must be emphasized that the association between vascular risk factors (VRF) and AD has been confirmed by numerous studies conducted over the past 20 years [25–30]. 3. Different therapies, all capable of improving the symptoms of AD, improve cerebral perfusion; 4. Prodromal AD can be identified by direct/indirect measurement of cerebral perfusion; 5. Clinical symptoms of AD arise from CNS microvascular disease; 6. Significant overlap exists between cerebrovascular and neurodegenerative disease, (both in AD and VD); 7. Cerebral hypoperfusion can trigger a reduction in metabolism with neurodegenerative changes and cognitive impairment. de la Torre concluded that the probability that all this evidence was due to an indirect effect of AD (reverse causality) or to coincidences was very low. According to the author, the scientific community should have considered the concrete possibility that AD is a disease of vascular origin.

In the same year, L.J. Launer published an article with a provocative title *"Demonstrating the case that AD is a vascular disease: epidemiological evidence"* reviewing the evidence in favor of a vascular AD origin [31]. Launer recalled that Alzheimer himself had noted the coexistence of neuritic plaques, neurofibrillary tangles, and cerebrovascular disease. She pointed out that early autopsy studies had reported vascular pathologies in about 20% of AD cases, while the Neuropathology Group of the MRC-CFAS [32] found SVD in 46% of patients with dementia, with notable overlap between AD and ATS. Launer underlined that the sticking point of the question is whether vascular pathology is part of AD or independent of it. Although cerebral/hippocampal atrophy are considered the two pathognomonic findings of AD, many microvascular, blood-brain barrier (BBB), and CBF abnormalities also emerged in autopsy/imaging studies [33, 34]. Cerebral amyloid angiopathy (CAA) is also not a rare finding in AD [35], while ischemic WML, as well as lacunar or hemispheric infarcts, are frequent in AD patients [36–38]. On the other hand, significant cerebral atrophy was reported in many cases of VD as well as in AD [38]. The combination of degenerative and vascular lesions has a greater negative effect on cognitive functions than when considered individually, although it remains unclear whether their effects are additive or whether common pathogenic pathways exist.

Launer summarized several alternative hypotheses that could explain the association between Alzheimer's disease (AD) and cerebral vascular disease (CVD) emerging from epidemiological studies:

1. Methodological hypothesis: It is highly likely that the association is not random; however, many studies are observational and subject to interpretative errors.
2. Diagnostic error: At that time, diagnosis was primarily clinical, as no biomarkers for AD were available. Data from clinical and autopsy studies often differed in the detection of mixed dementia.
3. Classification error: Many studies measured peripheral biological parameters that may not accurately reflect processes occurring in the central nervous system (CNS).
4. Follow-up: The ideal duration of follow-up in dementia studies is unknown, yet it is crucial for understanding the temporal interaction between neurodegeneration, CVD, vascular risk factors (VRF), and cognitive impairment.
5. Biases: Pharmacological treatments, sex, and life expectancy of study cohorts can influence results.
6. Atherosclerosis (ATS): The interaction between ATS, VRF, and AD is complex; these conditions are interrelated and may mediate one another.
7. Common pathways: Shared mechanisms may explain associations such as hypertension and AD (e.g., renin-angiotensin system) or diabetes and AD (e.g., insulin resistance).
8. Reverse causality: AD and β-amyloid may influence blood pressure, increasing it in the early stages and decreasing it in later stages.
9. Launer concluded that although experimental evidence suggests several VRFs are involved in AD pathogenesis, their precise role remains unclear, and new clinical and epidemiological studies—as well as randomized trials for AD treatment—are needed.

The Nun study: cerebral infarcts and LOAD

In 1997, Snowdon and Colleagues published an important article reporting the results of a longitudinal study conducted on a cohort of catholic nuns [39]. The nuns were thoroughly evaluated during their lifetime, and the results

were compared with brain autopsy findings. Among the sisters diagnosed with LOAD, those with lacunar infarcts had a much higher prevalence of dementia; in their presence, even a small number of neuritic plaques and neurofibrillary tangles were sufficient to cause dementia. By contrast, in subjects who did not meet the pathological criteria for AD, cerebral infarcts were poorly associated with dementia. Atherosclerosis in the circle of Willis (Willis-ATS) was strongly associated with lacunar and cortical infarcts. The researchers concluded that cerebrovascular disease plays a very important role in determining both the presence and severity of LOAD.Some years later, Snowdon commented on the main findings of the Nun Study by illustrating the paradigmatic example of two sisters, one demented and one cognitively healthy [33]. According to their results, clinically manifest LOAD depends on two main factors: the degree of AD pathology in the CNS and the individual's resistance to the clinical expression of that pathology. Lacunar infarcts appear to play a decisive role, along with head trauma, depression, and metabolic alterations. Interestingly, some individuals show little brain atrophy despite a significant burden of AD pathology; this phenomenon may be mediated by other factors, such as B-vitamin deficiency.

Regarding resistance to the clinical expression of LOAD, Snowdon noted that many sisters in mild (stage 1–2) or moderate (stage 3–4) Braak & Braak stages did not exhibit any symptoms. Remarkably, even 8% of sisters in stage 5–6 was asymptomatic. This resistance could be related to: (1) brain volume or the number of synapses acquired during development and maintained through an appropriate lifestyle [40]. ; (2) Brain damage (cerebral infarctions, traumas, nutritional deficiencies) undermining CNS resilience. Indeed, PET studies showed that AD patients activate different brain networks compared to healthy subjects in response to verbal memory tasks.

Many other autopsy studies were published in the following years; for brevity, we will mention only one of them in this paragraph. In 2008, Troncoso and Colleagues reported the results of BLSA autopsy program [41]. The older individuals enrolled were thoroughly evaluated over the years before autopsy. The main findings can be summarized as follows: (1) Cerebral infarcts are frequent (44% of cases) and increase the risk of dementia (both symptomatic or not, macroscopic or microscopic); (2) VRF are not independently associated with the risk of dementia; (3) The number of hemispheric infarcts correlate with the risk of dementia; (4) In patients with moderate AD pathology, even a single hemispheric infarct is sufficient to cause dementia; 6. The AD burden is responsible for 50% of dementias, while hemispheric infarcts (alone or with AD) are responsible for 35% of cases. The study did not highlight any data in favor of the hypothesis that AD pathology can cause cerebral infarcts or vice versa.

In a very interesting study published in 2021, Ottoy and Colleagues evaluated the relationship between CVD, β-amyloid, neurodegeneration, and cognitive dysfunction in 120 individuals with mixed CNS disease (SVD + AD pathology) [42]. They investigated the association between vascular burden (measured as white matter lesion, WML, volume) and cognition, testing the indirect effects of β-amyloid deposition (via PET imaging) and neurodegeneration (assessed through cortical thickness or PET) in AD signature regions. The study found that increased total WML volume was associated with poorer cognitive performance, and this relationship was mainly mediated by cortical thinning, particularly in the temporal lobe. The authors concluded that vascular burden primarily affects cognitive function through localized neurodegeneration, which occurs via an amyloid-independent pathway. Overall, available studies suggest that CNS ischemic lesions play an important role in the clinical manifestation of LOAD (Fig. 1), but do not clearly demonstrate their direct involvement in the pathogenetic mechanisms of the disease.

Atherosclerosis and LOAD

In 2003, Roher and Colleagues reported the results of an autopsy study comparing subjects with LOAD and controls [43]. The study highlights several interesting aspects. 1, in AD patients, the circle of Willis shows a significant degree of stenosis due to numerous atherosclerotic (ATS) plaques. 2, ATS lesions are much more severe in AD patients than in controls. 3, the percentage of arterial occlusion (occlusion index) positively correlates with the density of senile plaques and neurofibrillary tangles, Braak & Braak stage, CERAD neuritic plaque (NP) score, and white matter rarefaction. This study demonstrated, for the first time, a strong quantitative link between Willis-ATS and AD pathology. Arterial stenosis contributes significantly to LOAD pathogenesis, likely through a reduction in cerebral blood flow (CBF), a typical finding in AD (see later). However, it remains unclear why some LOAD patients exhibit only minimal cerebral ATS. This may be due to the heterogeneity of AD. ATS could accelerate or worsen LOAD once it has already begun through other mechanisms. The authors hypothesized that cerebral hypoperfusion induced by ATS may cause, at least in some cases, a deficit in CNS energy metabolism, leading to the accumulation of neuritic plaques and neurofibrillary tangles. Thus, these lesions may represent a "late" manifestation in LOAD pathophysiology.

In 2015, Gupta & Iadecola reviewed the relationship between ATS and AD [44], based on epidemiological,

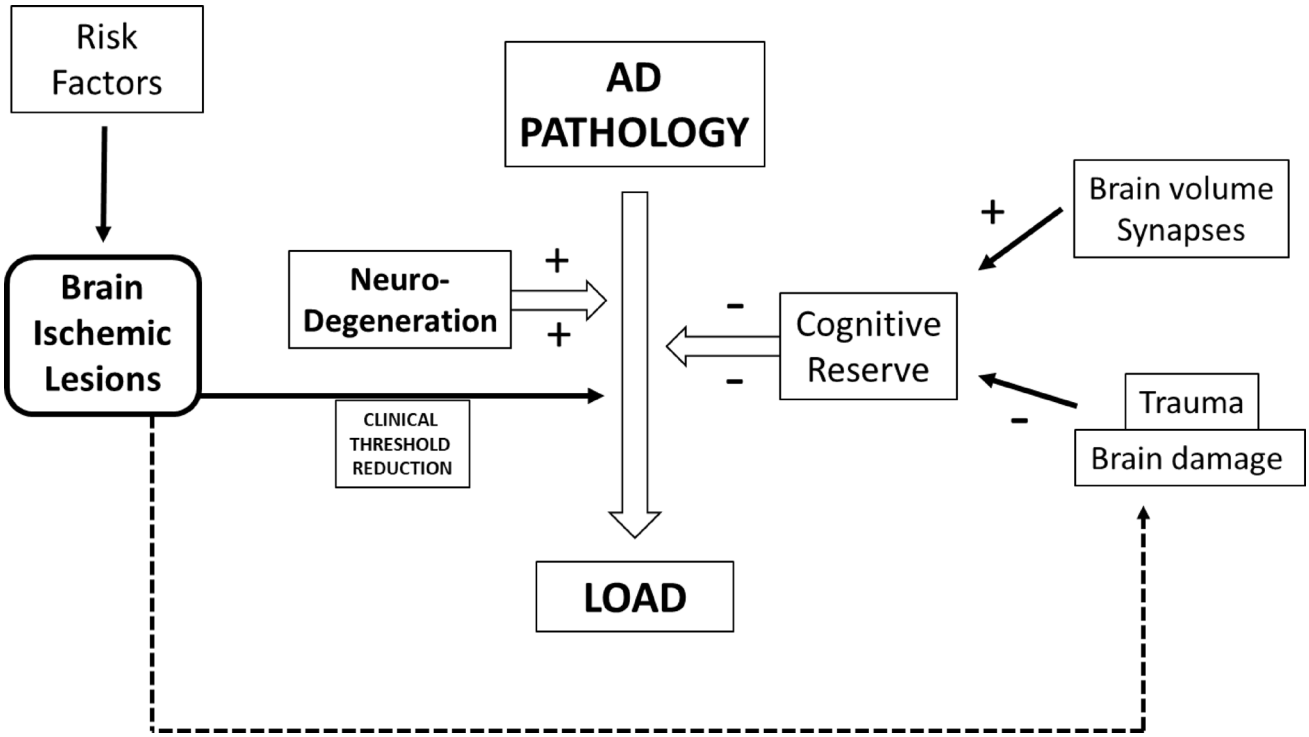

Fig. 1 Contribution of brain crebral infacrts on the progression of AD pathology to the clincial manisfestation of LOAD

clinical, and experimental data. They highlighted three key points: (1) Cerebral ATS, together with increase in the stiffness of small/large arteries, causes cerebral hypoperfusion and chronic hypoxia; this determines an increase in APP degradation via activation of BACE1 (see later) and γ-secretase, with accumulation of β-amyloid [45]; (2) The reduction in CBF, together with vascular stiffness, and alterations of microcirculation compromises β-amyloid clearance, increasing its levels in CNS [46, 47]; (3) In turn, β-amyloid has deleterious effects on cerebral circulation (vasoconstriction and reduced vasodilation) and likely promotes ATS by causing chronic inflammation, endothelial dysfunction, and oxidative stress [48, 49].

In 2005, Honig and Colleagues examined the association between CVD and LOAD pathology in an autopsy series of 1054 subjects (921 AD and 133 controls) [50]. They found no association between neuritic plaques/neurofibrillary tangles and history of stroke, cerebral infarcts or SVD; conversely, LVD and ATS were strongly associated with an increased frequency of neuritic plaques.

In 2007, Beach and Colleagues published a study addressing the validity of the association between ATS and LOAD [51]. They evaluated, in a large autopsy series, 397 older subjects, including controls, AD, VD, and non-AD dementias. Willis-ATS was more severe in subjects with LOAD and VD compared to controls, while it was similar in controls and non-AD dementias. Increasing ATS grade was associated with a higher risk of LOAD and VD, greater neuritic plaque density, and higher Braak & Braak neurofibrillary tangle stage. The authors concluded that the association between intracranial ATS and LOAD is not an artifact of diagnostic misclassification. In 2016, Iturria-Medina and Colleagues published a very interesting article [52] evaluating topographic/temporal alterations of CNS, as well as many peripheral proteins, in relation to AD progression. They analyzed images and proteins/biomarkers from plasma and cerebrospinal fluid (CSF) in 1,171 subjects, including controls, individuals with mild cognitive impairment (MCI), and AD patients.Through a multifactorial, data-driven analysis, the authors derived dynamic indices of abnormalities for each marker, representing an attempt to establish a temporal order in AD progression. They evaluated β-amyloid deposition (Florbetapir PET), glucose metabolism (FDG-PET), cerebral blood flow (arterial spin labeling), and brain activity/structural patterns (MRI imaging and structural analysis).

The authors found a significant predominance of vascular dysregulation over all other markers. Across all CNS regions and time points, vascular factors were altered approximately 80% more than other markers. This was followed by β-amyloid deposition, metabolic dysfunction, deterioration of function, and gray matter atrophy. Additionally, notable abnormalities were observed in proteins associated with vascular system integrity. Although the model does not allow for causal conclusions, the study demonstrates that CNS vascular abnormalities represent, from a

temporal perspective, the earliest pathological finding in AD. These results starkly contradict the currently accepted theoretical sequence of events in AD development, which posits β-amyloid accumulation as the initial step in the pathological cascade [4].

In the same year, another interesting study was published [53], Based on the observation that LOAD and small vessel disease (SVD) are the most frequent causes of cognitive deterioration in the elderly—and are often associated with each other—Kim and colleagues evaluated the presence and role of tau (via PET imaging) in patients with cognitive decline of subcortical vascular origin. The study revealed some interesting and unexpected findings: (1) SVD is associated with increased tau deposition, independently of β-amyloid; (2) tau load mediates the association of both β-amyloid and SVD with cognitive impairment. Overall, the study suggests that β-amyloid and SVD independently promote tau accumulation, which in turn appears to be the final pathway leading to cognitive impairment.

In 2020, Eglit and colleagues examined the role of Willis-ATS in the association between hypertension and AD pathology by analyzing neuropathological data from 2,198 older subjects [54]. Hypertension is indirectly associated with increased AD pathology through its association with Willis-ATS. Similar indirect effects are observed for systolic and diastolic blood pressure measures. The authors concluded that hypertension may promote AD pathology indirectly, through intracranial ATS, by limiting CBF and/or dampening perivascular clearance. Willis-ATS may be an important point of convergence between VRF, CVD, and AD pathology.

In 2020, Wingo and colleagues published an article with the challenging title *"Cerebral atherosclerosis contributes to Alzheimer's dementia independently of its hallmark amyloid and tau pathologies"* [55]. They studied thousands of brain proteins in more than 400 older subjects who were thoroughly evaluated using nine pathological parameters: cerebral atherosclerosis (ATS), β-amyloid, neurofibrillary tangles, macroscopic infarcts, microscopic infarcts, amyloid angiopathy, TDP-43, Lewy bodies, and hippocampal sclerosis. The authors identified the "proteomic signature" of cerebral ATS. The main findings of the study are as follows: (1) Cerebral ATS is associated with AD, independently of the other parameters evaluated. (2) Cerebral ATS is associated with significant alterations in the metabolism and functioning of oligodendrocytes. These alterations are not attributable to vascular risk factors (VRF) or to the consequences of brain infarctions. (3) There is no statistical interaction between cerebral ATS and β-amyloid/neurofibrillary tangles, suggesting that ATS contributes to AD independently (additive effect).

4. Tau is also independently associated with AD, with a proteomic profile partially overlapping that of cerebral ATS. 5. β-amyloid is not directly related to AD-associated proteomic changes.

In the editorial dedicated to the article, Iadecola questioned how cerebral ATS could lead to cognitive deterioration independently of neurodegenerative disease and cerebral infarctions. He suggested that ATS may result from long-term neurovascular dysfunction, leading to axonal damage and cognitive decline through reduced microperfusion. Other factors, including BBB integrity, neurovascular function, neurotrophic support from the endothelium, and neuroimmune responses, may also be involved.

In summary, based on available literature data, it can be stated not only that ATS is associated with AD, but also that ATS actively participates in the pathogenesis of AD, unlike CNS ischemic lesions, through a variety of known and unknown biological mechanisms (see Fig. 2).

How to explain the association between LOAD and atherosclerosis?

Vascular risk factors

Many studies have highlighted, in the last 20 years, a significant association between VRF and dementia, including AD [21, 23, 24, 27, 29, 55–59] (Fig. 2).

In 2018, a very interesting article was published by Rabin and Colleagues [54]. In a sample of normal older subjects they evaluated: (1) Whether vascular risk (FHS-CVD risk score [including: age, blood pressure, total/HDL cholesterol, diabetes, smoking]) and β-amyloid act in additive or synergistic way in promoting cognitive decline; (2) The independent effect of VRF on progression of cognitive decline. They found that the speed of cognitive decline is associated with both FHS-CVD risk score and brain β-amyloid load. The significant interaction suggests a synergistic effect, in agreement with autopsy studies demonstrating that vascular pathology reduces the preclinical phase of AD. The FHS-CVD risk score is associated with cognitive decline progression independent of amyloid load, hippocampal volume, cerebral glucose metabolism and WML, confirming that cardiovascular risk and CNS ischemic lesions have a different meaning.

In 2021 Cortes-Canteli and Colleagues evaluated the association between brain metabolism, sub-clinical ATS, and VRF in 547 middle-aged asymptomatic individuals with subclinical ATS [60]. They found that global F18-FDG uptake on PET was negatively correlated with the 30-year Framingham Heart Study cardiovascular disease (FHS-CVD) score, with the association being primarily driven by

hypertension. Carotid ATS plaque burden was also inversely associated with global brain F18-FDG uptake. The brain areas most affected by hypometabolism were the parieto-temporal regions and the cingulate gyrus. The authors concluded that, in middle-aged individuals, cardiovascular risk, hypertension, and subclinical carotid ATS burden are associated with brain hypometabolism in regions known to be affected in AD.

In 2022 Wagen and Colleagues examined the potential drivers and correlates of "brain age" (neuroimaging-based biomarker). They assessed 456 individuals with twenty-four prospective waves of data collection (including MRI and amyloid-PET imaging) [61]. The brain-predicted age difference (brain-PAD) was calculated by subtracting the brain-predicted age from the chronological age. Female sex is associated with a 5.4-year younger brain-PAD compared to males. An increase in brain-PAD is associated with: high FHS-CVD score, CVD, lower cognitive performance, and increased serum neurofilament light. The authors concluded that brain-PAD is associated with both cardiovascular risk and markers of neurodegeneration.

In 2022 Jiang and Colleagues evaluated, in 1521 normal individuals >50 years, the association between VRF and AD biomarkers, and whether they were synergistically associated with cognition [62]. Compared to low cardiovascular risk (< 10%), high risk (≥ 20%) is associated with increased blood t-tau and neurofilament light. Hypertension synergistically interacts with both t-tau and neurofilament light. They concluded that VRF play critical roles on cognition, both through independent and neurodegenerative pathways.

In the same year, Chariris anc Colleagues investigated associations of obesity with the expression of.

AD-related genes, in 5619 individuals from the Framingham study [63]. They found that obesity metrics are associated with the expression of 21 AD-related genes; after adjustment for VRF, 13 associations remain significant for BMI and 8 for WHR.

In 2023 Dhana and Colleagues evaluated the association of cardiovascular health (CVH - based on diet, physical activity, body mass index, smoking, dyslipidemia, hypertension, and diabetes) with cognitive outcomes in 1702 subjects [64]. In multivariable-adjusted model, CVH is associated with a lower risk of AD; CVH is also associated with a slower rate of cognitive decline and less volume in WML.

Valenti and Colleagues reviewed the available studies on the treatment of VRF in patients with AD [65]. Observational studies suggest that treatment of hypertension and statin therapy may be associated with improved outcomes, although these studies are subject to potential bias. Unfortunately, the few randomized controlled trials available, mostly small and of short duration, do not provide definitive evidence. More recently, Shang and colleagues investigated whether anti-diabetic, lipid-lowering, anti-hypertensive, and non-steroidal anti-inflammatory drugs might alter the course of cognitive decline in 7,653 subjects with mild AD [66]. The combination of all four class of drugs results in a significant 46% MMSE and 32% CDR-SB delay in 5 years cognitive decline, and with 47% MMSE and 33% CDR-SB delay in 10 years cognitive decline.

To date, the association between VRF and AD has not been definitively explained in a univocal way, since there may be different possible explanations for different risk factors: (1) The relationship between risk factors and AD could be mediated by ATS, as strongly suggested by some studies ([43, 54]; (2) The relationship could be explained by common pathogenic pathways between risk factors and AD (e.g. insulin resistance, paraoxonase, homocysteine); (3) Risk factors may directly affect CNS metabolism, causing its early reduction in areas known to be affected in AD [60].

Secretases activity: the possible role of β-secretase 1 (BACE1)

The premise to this paragraph is that, as reviewed by Iadecola in his editorial [67] to the article of Roher [43], chronic oligoemia of CNS leads to increase processing of APP by β- and γ-secretases, with increased formation/accumulation of β-amyloid. Observational studies suggest that treatment of hypertension and statin therapy may be associated with improved outcomes, although these studies are subject to potential bias. Unfortunately, the few randomized controlled trials available—mostly small and of short duration—do not provide definitive evidence.More recently, Shang and colleagues investigated whether anti-diabetic, lipid-lowering, anti-hypertensive, and non-steroidal anti-inflammatory drugs might alter the course of cognitive decline in 7,653 subjects with mild AD [68], and it is elevated both in brain and blood of AD patients [69]. Serum BACE1 activity was determined in 115 LOAD patients and 151 controls. We showed that serum BACE1 activity is significantly higher in AD, independent of age, sex, hypertension, diabetes, and vascular disease. Successively, we evaluated serum BACE1 activity in VD, mixed dementia (AD + VD), and non-AD dementias (LBD, fronto-temporal dementia, etc.) [70]. We demonstrated, for the first time, that serum BACE1 activity is increased in LOAD (+ 30%), VD (+ 35%), and mixed dementia (+ 22%), but not in other types of dementia. Therefore, BACE1 could represent a mechanistic link between AD and VD; indeed, BACE1 is a stress response protein, sensitive to factors reducing CNS energy metabolism (including ischemia). In turn, BACE1 hyperactivity can undermine vascular CNS integrity, given the vasoactive properties of β-amyloid. We proposed a theoretical

pathogenetic cascade leading, depending on the single case, to LOAD, VD, or mixed dementia: (1) Dysregulation of BACE1 (because of brain ATS and oligoemia); (2) Secondary increase in β-amyloid production in the CNS; (3) Evolution towards VD, mixed dementia or LOAD depending on whether the clearance of β-amyloid would be preserved, partially, or severily impaired (in addition to other pathogenetic factors).

In the same year, Durrant and Colleagues investigated, in APP transgenic mouse, the mechanisms through which β-amyloid promotes excessive/altered angiogenesis (a known phenomenon in AD) [71]. They demonstrated that: (1) Pathological angiogenesis is a very early event, occurring before β-amyloid deposition; (2) It is dependent on APP processing by BACE1 and mediated by a reduction in NOTCH3 signalling (see later); (3) Partial inhibition of BACE1 activity normalizes angiogenesis.

We successively estimated the diagnostic accuracy of serum BACE1 as possible biomarker in AD and MCI converting to AD (MCI-AD), all positive for the AD core CSF biomarkers. We confirmed that BACE1 activity is increased (>60%) in AD and MCI-AD compared to controls; we were able to discriminate patients from controls with very high sensitivity (98%) and specificity (100%) [72].

Finally, in 2022, we attempted to identify the potential determinants of BACE1 serum activity [73] in 504 healthy individuals and 175 LOAD patients. Age was the strongest independent predictor of BACE1 variance, followed by female sex, HDL-C, and hypertension. It cannot be missed as all these variables are associated with an increased risk of LOAD. The probability of having elevated BACE1 was particularly high in women after 70 years of age [73].

NOCTH pathway impairment

Notch signaling is an evolutionarily conserved pathway that is fundamental for neuronal development. It also plays roles in the mature brain, being involved in both vascular (e.g., endothelial stabilization, smooth muscle cell response) and non-vascular (e.g., neuronal degeneration/apoptosis) processes (Fig. 2). NOTCH signaling is dysregulated in AD and in CNS ischemic injuries. As underlined by Drachman [18], γ-secretase cleaves NOTCH producing NICD (Notch Intra-Cellular Domain) which drives the angiogenic process. Interestingly, NOTCH and APP compete for γ-secretase, based on the amount of substrate present; each increase in β-amyloid secretion corresponds to a reduction in NOTCH signalling, and vice versa. Moreover, in APP transgenic mouse the pathological early angiogenesis (before β-amyloid deposition) is dependent on APP processing by BACE1 and is mediated by a reduction in NOTCH3 signalling [71]. It was also demonstrated that NOTCH signaling plays an important role in neuronal plasticity and learning and memory processes (involving hippocampus) [74]; this means that alterations in NOTCH signaling may contribute to cognitive deficits. It is therefore conceivable that a reduction/impairment in NOTCH signalling may contribute to brain dysfunction in AD through alterations of CNS microcirculation, increase in γ-secretase activity, and negative effect on cognition.

Cerebral blood flow and arterial stiffness

In 2005, Ruitember and Colleagues evaluated the relationship between cerebral perfusion (transcranial doppler ultrasonography) and dementia in 1720 adult/older individuals [75]. They found that higher CBF is associated with a lower likelihood of developing dementia, less cognitive decline, and larger hippocampal and amygdala volume. On the contrary, low CBF is associated with both dementia and markers of early dementia. They concluded that cerebral hypoperfusion precedes and possibly contributes to the onset of dementia, including AD.

In 2014, Hughes and Colleagues examinated the association between arterial stiffness and β-amyloid CNS deposition over time (2 years) in 81 non-demented older individuals [76]. Pulse wave velocity (PWV) was measured in the central (carotid- and heart-femoral), peripheral (femoral-ankle), and mixed (brachial-ankle) vascular beds. Brachial-ankle PWV is higher among β-amyloid positive participants both at baseline and follow-up, while femoral-ankle PWV is higher among β-amyloid positive subjects at follow-up. Central stiffness is associated with a change in β-amyloid deposition over time. The authors concluded that arterial stiffness is strongly associated with the progressive deposition of β-amyloid in CNS.

We recently performed a systematic review/meta-analysis to investigate changes in CBF in AD patients [77]; the analysis included 685 individuals (395 LOAD and 290 age-matched controls). We confirmed that, in middle cerebral artery, AD patients have significantly lower CBF velocity compared to controls. The mean CBF is directly correlated with MMSE score, but inversely correlated with age. In AD patients, the pulsatility index is significantly higher, while the breath-holding index test is significantly lower compared with controls.

In 2022, Cooper and Colleagues assessed the associations of aortic stiffness and pressure pulsatility with β-amyloid plaques and tau burden in the CNS of 270 middle-aged/older healthy adults [78]. Carotid-femoral PWV, central pulse pressure (CPP), and forward wave amplitude (FWA) were evaluated. In multivariable models, higher CPP and FWA are associated with greater entorhinal/rhinal tau burden; the associations are more prominent in older participants.

Aortic stiffness and pressure pulsatility measures are not associated with amygdala, inferior temporal, precuneus tau burden, nor to global amyloid-β plaques. The authors concluded that abnormal central vascular hemodynamics are associated with higher tau burden in specific brain regions, suggesting that aortic stiffness may be a target for prevention of tau-related pathologies.

Overall, a picture emerges in which ageing, inflammation and genetics may, by promoting cerebral/ sistemic ATS, reduce CBF and modify arterial stiffness thus favoring LOAD onset (but also mixed dementia and VD); on the other hand, the same factors, together with ischemia/ hypoxia, could favor the deposition of β-amyloid at arterial level, modifying anyway arterial stiffness (Fig. 2).

Clearance of β-Amyloid

Besides an increase in its production, β-amyloid can accumulate in the CNS by an impairment in its clearance [46, 47]. Some studies even suggest that decreased β-amyloid clearance might be more responsible for LOAD development rather than increased β-amyloid synthesis [79].

Vascular cells, glia, and neurons make up the neurovascular unit (NVU); the BBB lies within the NVU and restricts entry of molecules into the CNS. The functional integrity of NVU is essential for normal neuronal and synaptic functioning. As reviewed by Sagare [80], The efficiency of β-amyloid clearance from brain interstitial fluid across the BBB is influenced by: 1. β-amyloid binding to transport proteins (APO E, APO J) and BBB receptors (LRP1, LRP2, RAGE), which control CNS β-amyloid efflux and influx, respectively.

2. Activity of β-amyloid-degrading enzymes.

It is known that hypoxia downregulates MEOX2 gene expression in brain endothelial cells, leading to hypoplasia, brain hypoperfusion, and loss of LRP1, with reduced β-amyloid clearance. On the other hand, hypoxia increases MYOCD gene expression in vascular smooth muscle cells, again leading to brain hypoperfusion and loss of LRP1, with β-amyloid deposition in the arterial wall. Interestingly, hypoxia seems to be upstream of both these pathological processes and may be strongly related to ATS and reduction of CBF [80].

Some proteolytic enzymes also contribute to β-amyloid degradation in the CNS (neprilysis, metalloproteinases, etc.) [81]. They cleave β-amyloid producing less neurotoxic and more easily cleared fragments. With ageing, and under pathological conditions, the activity of these enzymes decline leading to a deficit of β-amyloid clearance, although these enzymes may be unexpectedly over-expressed in AD, likely as a compensatory mechanism to β-amyloid toxicity [81]. It has been demonstrated that hypoxia leads to reduced neprelysin levels and activity both in cellular models and in vivo [82]. It is evident that all the mechanisms exposed in this paraghaph are not mutually exclusive but can be present simultaneously in then same patient and influence each other (Fig. 2).

What about vascular dementia?

It is legitimate to ask whether VD really exists or, given the strong association between systemic/cerebral ATS and LOAD, we are inevitably faced with a "mixed" pathology. First, we must remember that the NINDS-AIREN criteria for VD diagnosis have low sensitivity (< 60%) but high specificity (>90%); second, in all autopsy studies a small percentage of patients with dementia have pure vascular damage. In this regard, Oveisgharan and Collegues investigated, in sample of 1799 older individuals evaluated for about 8 years before death, how common pure VCI was at autopsy [83]. Participants were categorized into 3 groups: pure VCI (21%), pure neurodegenerative group (23%), or mixed group (56%). Cognitive impairment is present in 42% of VCI, 67% of degenerative pathologies, and in 78% of mixed groups. Among VCI, only macro-infarcts and arteriolosclerosis in basal ganglia are associated with cognitive impairment, supporting the existence of pure VCI. Result worth highlighting, CVD explains only 10% of the variability of cognitive decline, leaving room for other unidentified mechanisms. It is worth remembering at this point the study of Kim [53], demonstrating that SVD is associated to increased tau deposition, and that tau load mediates the association of SVD with cognitive impairment. Furthermore, we cannot ignore that, in the Swedem register, a clear AD-like biomarker profile in cerebrospinal fluid (CSF) emerged in 65% of LOAD, 60% of mixed dementia, and 20% of VD [84]. In particular, CSF β-amyloid 1–42 was positive in 80% of LOAD, 60% of mixed dementia, but also in more than 40% of VD patients.

In summary, VD and LOAD share many physiopathological characteristics. It is time to remember the increase of serum BACE1 activity in AD and VD [70], suggesting that this mechanism might be a "cornerstone" of both dementias. However, since most LOAD patients also display significant cerebral ATS, the possibility that increased BACE1 might be actually the consequence of CVD, and not of neurodegeneration, cannot be ruled out a priori.

We also reported other pathophysiological factors shared by LOAD and VD, including endothelial dysfunction [85, 86], oxidative unbalance [85, 86], and decreased serum arylesterase activity of PON-1 [87]. On the other hand, there are some interesting differences exist between these two types of dementia. For example, blood levels of homocysteine and uric acid [86], lipoprotein-associated phospholipase

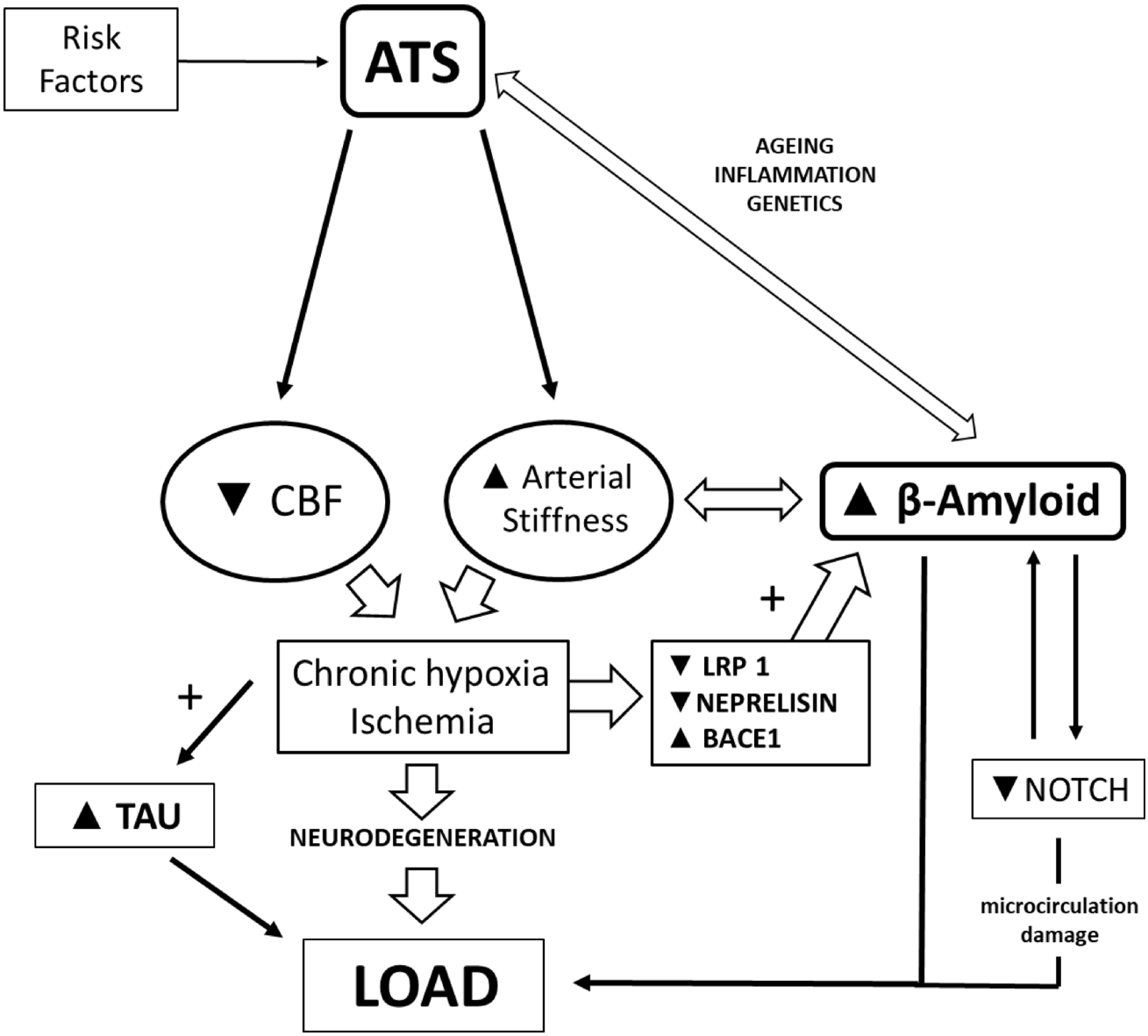

Fig. 2 Contribution of Atheroslcerosis to Arterial stifness, BACE1 hyperactivation and NOTCH dysregulation finally leading to LOAD onste

A2 [88], klotho [89], and TRAIL [90] are higher in VD compared with LOAD. By contrast, neutrophil/lymphocyte ratio is higher, while serum ATG5 and Parkin are lower in LOAD compared to VD [91, 92]. These results suggest that, although there is a strong overlap between LOAD and VD, there are, however, some pathophysiological differences that allosw us to consider them two different conditions from a nosological point of view.

Conclusions

A vast literature highlights an increasing difficulty in separating, from a pathophysiological point of view, LOAD and ATS/CVD; this is even more challenging at the molecular level, given the numerous common pathogenetic pathways (Fig. 3). The relationship between CVD and LOAD is extremely complex. In the elderly, the contribution of ATS to the pathogenesis and clinical manifestation of LOAD is incontrovertible. Probably, the rigid clinical separation between LOAD and VD has lost part of its meaning in many older patients who come to our memory clinics. Indeed, both lacunar and hemispheric, microscopic or macroscopic, symptomatic or asymptomatic brain infarcts have

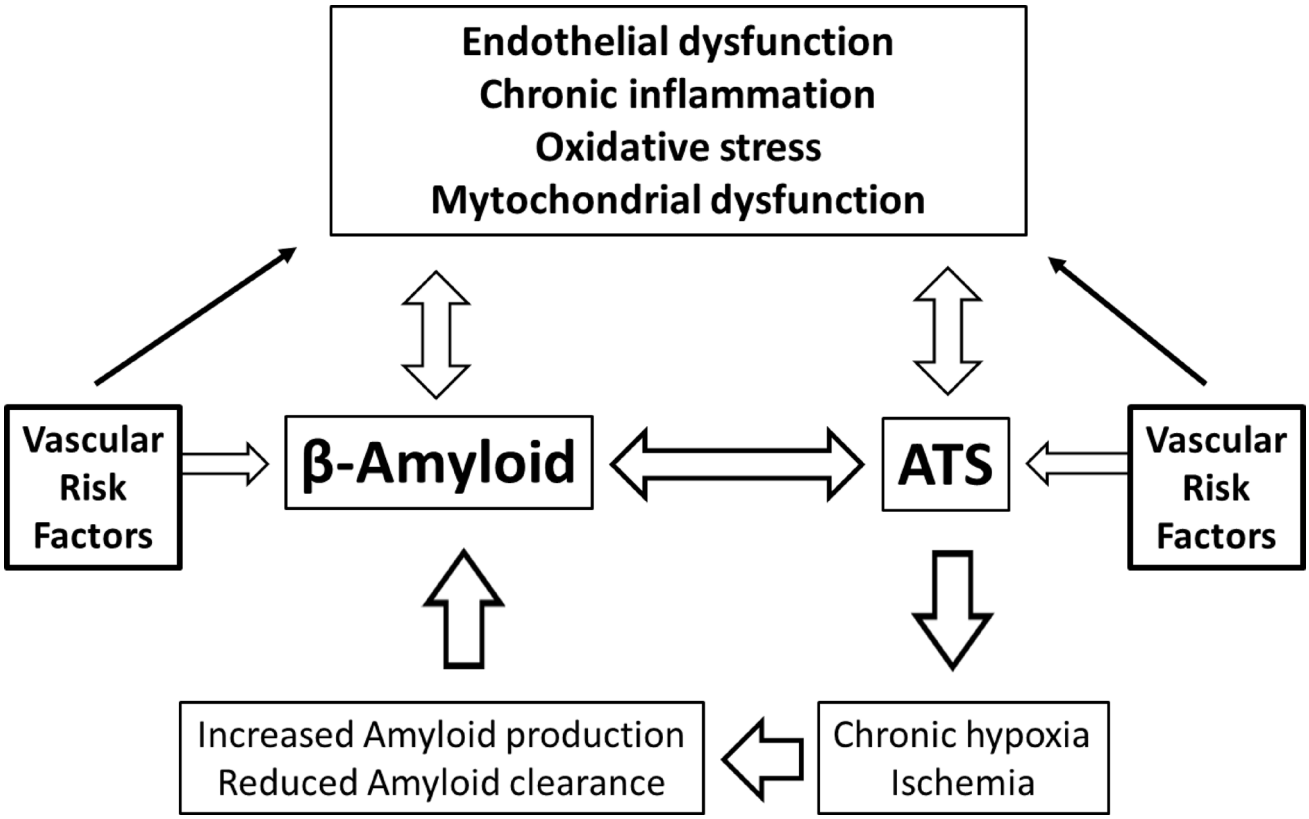

Fig. 3 This diagram illustrates the overlapping processes of beta-amyloid formation and cerebral atherosclerosis in the development of LOAD

been associated with LOAD. Moreover, SVD has been correlated with increased tau CNS load, and tau seems to mediate the effect of SVD on cognitive functions. Cerebral ATS has been associated with LOAD (independent of cerebral infarctions and VRF), with an increase in β-amyloid production, a reduction in its clearance, and with Braak & Braak stage and CERAD NP score. A different argument may apply to EAD, in which the contribution of cerebral ATS/CVD may be relative, if not even absent.

An inverse but similar reasoning can be made for VD. Only in relatively young patients, with severe subcortical or hemispheric vascular lesions, is an exclusively vascular pathogenesis conceivable, and therefore a diagnosis of "pure" VCI would be made (< 8% in our Ferrara memory clinic, 10–15% in autopsy studies). Most older patients with dementia are probably faced with "mixed" forms (CVD + neurodegeneration), regardless of the evidence of ischemic lesions on CT scan/MRI. Indeed, ATS may promote β-amyloid formation, while β-amyloid, in turn, can promote vascular dysfunction/ATS in the CNS—remembering that, in subjects without AD pathology, cerebral infarcts are poorly associated with dementia onset [93]. Lastly, we cannot ignore evidence suggesting that treatment of VRF in LOAD patients (not independently involved in LOAD pathogenesis) [65, 66] was associated with a lower cognitive decline over time. These treatments may contribute to the stabilization or improvement of cerebral ATS, which in turn may have a positive effect on AD progression.

It seems appropriate to remember that Alois Alzheimer, before describing the first neurofibrillary tangles and neuritic plaques, had previously reported a condition he called "the arteriosclerotic atrophy of the brain." Those two words, "atrophy" and "arteriosclerotic," seem to identify the first foundations of current scientific knowledge, demonstrating an ever-increasing overlap between vascular and neurodegenerative phenomena in the brain.

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References

1. Diagnostic (2013) and Statistical Manual of Mental Disorders, 5th Edition. American Psychiatric Publishing, Inc; https://doi.org/10.1176/appi.books.9780890425596.893619
2. Blessed G, Tomlinson BE, Roth M (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 114:797–811. https://doi.org/10.1192/bjp.114.512.797
3. Swerdlow RH (2007) Pathogenesis of alzheimer's disease. Clin Interv Aging 2:347–359
4. Roth M (1955) The natural history of mental disorder in old age. J Mental Sci 101:281–301. https://doi.org/10.1192/bjp.101.423.281
5. de la Torre JC, Mussivan T (1993) Can disturbed brain microcirculation cause alzheimer's disease? Neurol Res 15:146–153. https://doi.org/10.1080/01616412.1993.11740127
6. de la Torre JC (2002) Alzheimer disease as a vascular disorder. Stroke 33:1152–1162. https://doi.org/10.1161/01.STR.0000014421.15948.67
7. de la Torre JC (1994) Impaired brain microcirculation May trigger alzheimer's disease. Neurosci Biobehav Rev 18:397–401. https://doi.org/10.1016/0149-7634(94)90052-3
8. de la Torre JC (2000) Critically attained threshold of cerebral hypoperfusion: the CATCH hypothesis of alzheimer's pathogenesis. Neurobiol Aging 21:331–342. https://doi.org/10.1016/S0197-4580(00)00111-1
9. de la Torre JC (2004) Is alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol 3:184–190. https://doi.org/10.1016/S1474-4422(04)00683-0
10. De La Torre JC (2008) Pathophysiology of neuronal energy crisis in alzheimer's disease. Neurodegener Dis 5:126–132. https://doi.org/10.1159/000113681
11. de la TORRE JC. Hemodynamic consequences of deformed microvessels in the brain in alzheimer's disease. Ann N Y Acad Sci (1997) ;826:75–91. https://doi.org/10.1111/j.1749-6632.1997.tb48462.x
12. de la Torre JC (1999) Critical threshold cerebral hypoperfusion causes alzheimer's disease? Acta Neuropathol 98:1–8. https://doi.org/10.1007/s004010051044
13. de la Torre JC, Stefano GB (2000) Evidence that alzheimer's disease is a microvascular disorder: the role of constitutive nitric oxide. Brain Res Rev 34:119–136. https://doi.org/10.1016/S0165-0173(00)00043-6
14. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH et al (1993) Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. ;43:250–60. https://doi.org/10.1212/wnl.43.2.250
15. Iadecola C, Duering M, Hachinski V, Joutel A, Pendlebury ST, Schneider JA et al (2019) Vascular cognitive impairment and dementia. J Am Coll Cardiol 73:3326–3344. https://doi.org/10.1016/j.jacc.2019.04.034
16. Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA (2018) Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol 83:74–83. https://doi.org/10.1002/ana.25123
17. Morris GP, Clark IA, Vissel B (2014) Inconsistencies and controversies surrounding the amyloid hypothesis of alzheimer's disease. Acta Neuropathol Commun 2:135. https://doi.org/10.1186/s40478-014-0135-5
18. Drachman DA (2014) The amyloid hypothesis, time to move on: amyloid is the downstream result, not cause, of alzheimer's disease. Alzheimer's Dement 10:372–380. https://doi.org/10.1016/j.jalz.2013.11.003
19. Frisoni GB, Altomare D, Thal DR, Ribaldi F, van der Kant R, Ossenkoppele R et al (2022) The probabilistic model of alzheimer disease: the amyloid hypothesis revised. Nat Rev Neurosci 23:53–66. https://doi.org/10.1038/s41583-021-00533-w
20. Lacorte E, Ancidoni A, Zaccaria V, Remoli G, Tariciotti L, Bellomo G et al (2022) Safety and efficacy of monoclonal antibodies for alzheimer's disease: A systematic review and Meta-Analysis of published and unpublished clinical trials. J Alzheimer's Disease 87:101–129. https://doi.org/10.3233/JAD-220046
21. Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S et al (2024) Dementia prevention, intervention, and care: 2024 report of the lancet standing commission. Lancet 404:572–628. https://doi.org/10.1016/S0140-6736(24)01296-0
22. Thomas KR, Bangen KJ, Weigand AJ, Edmonds EC, Wong CG, Cooper S et al Objective subtle cognitive difficulties predict future amyloid accumulation and neurodegeneration. Neurology 2020;94. https://doi.org/10.1212/WNL.0000000000008838
23. Skoog I, Nilsson L, Persson G, Lernfelt B, Landahl S, Palmertz B et al (1996) 15-year longitudinal study of blood pressure and dementia. Lancet 347:1141–1145. https://doi.org/10.1016/S0140-6736(96)90608-X
24. Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F et al (1997) Atherosclerosis, Apolipoprotein E, and prevalence of dementia and alzheimer's disease in the Rotterdam study. Lancet 349:151–154. https://doi.org/10.1016/S0140-6736(96)09328-2
25. Rajan KB, Barnes LL, Wilson RS, Weuve J, McAninch EA, Evans DA (2018) Blood pressure and risk of incident alzheimer's disease dementia by antihypertensive medications and APOE ε4 allele. Ann Neurol 83:935–944. https://doi.org/10.1002/ana.25228
26. Cheng G, Huang C, Deng H, Wang H (2012) Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J 42:484–491. https://doi.org/10.1111/j.1445-5994.2012.02758.x
27. Gudala K, Bansal D, Schifano F, Bhansali A (2013) Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. J Diabetes Investig 4:640–650. https://doi.org/10.1111/jdi.12087
28. Singh-Manoux A, Dugravot A, Shipley M, Brunner EJ, Elbaz A, Sabia S et al (2018) Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II study. Alzheimer's Dement 14:178–186. https://doi.org/10.1016/j.jalz.2017.06.2637

29. Anstey KJ, Ashby-Mitchell K, Peters R (2017) Updating the evidence on the association between serum cholesterol and risk of Late-Life dementia: review and Meta-Analysis. J Alzheimers Dis 56:215–228. https://doi.org/10.3233/JAD-160826
30. Zhong G, Wang Y, Zhang Y, Guo JJ, Zhao Y (2015) Smoking is associated with an increased risk of dementia: A Meta-Analysis of prospective cohort studies with investigation of potential effect modifiers. PLoS ONE 10:e0118333. https://doi.org/10.1371/journal.pone.0118333
31. LAUNER L. Demonstrating the case that AD is a vascular disease: epidemiologic evidence. Ageing Res Rev (2002) ;1:61–77. https://doi.org/10.1016/S0047-6374(01)00364-5
32. Pathological correlates of (2001) late-onset dementia in a multicentre, community-based population in England and Wales. Lancet 357:169–175. https://doi.org/10.1016/S0140-6736(00)03589-3
33. Snowdon DA (2003) Healthy aging and dementia: findings from the Nun study. Ann Intern Med 139:450–454. https://doi.org/10.7326/0003-4819-139-5_Part_2-200309021-00014
34. Farkas E, Luiten PGM (2001) Cerebral microvascular pathology in aging and alzheimer's disease. Prog Neurobiol 64:575–611. https://doi.org/10.1016/S0301-0082(00)00068-X
35. Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC, Weiner MW et al (2016) Early role of vascular dysregulation on late-onset alzheimer's disease based on multifactorial data-driven analysis. Nat Commun 7:11934. https://doi.org/10.1038/ncomms11934
36. Scheltens PH, Barkhof F, Valk J, Algra PR, van der Hoop RG, Nauta J et al (1992) White matter lesions on magnetic resonance imaging in clinically diagnosed alzheimer's disease: evidence for heterogeneity. Brain 115:735–748. https://doi.org/10.1093/brain/115.3.735
37. Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD (1999) Cerebrovascular disease and threshold for dementia in the early stages of alzheimer's disease. Lancet 354:919–920. https://doi.org/10.1016/S0140-6736(99)02355-7
38. Fein G, Di Sclafani V, Tanabe J, Cardenas V, Weiner MW, Jagust WJ et al (2000) Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. Neurology 55:1626–1635. https://doi.org/10.1212/WNL.55.11.1626
39. Snowdon 1 DA (1997) LHGJAMKPRPAGWRM. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA ;277(10):813-7 1997;277:813–7
40. Stern Y (2002) What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc 8:448–460
41. Troncoso JC, Zonderman AB, Resnick SM, Crain B, Pletnikova O, O'Brien RJ (2008) Effect of infarcts on dementia in the Baltimore longitudinal study of aging. Ann Neurol 64:168–176. https://doi.org/10.1002/ana.21413
42. Ottoy J, Ozzoude M, Zukotynski K, Adamo S, Scott C, Gaudet V et al (2023) Vascular burden and cognition: mediating roles of neurodegeneration and amyloid PET. Alzheimer's Dement 19:1503–1517. https://doi.org/10.1002/alz.12750
43. Roher AE, Esh C, Kokjohn TA, Kalback W, Luehrs DC, Seward JD et al (2003) Circle of Willis atherosclerosis is a risk factor for sporadic alzheimer's disease. Arterioscler Thromb Vasc Biol 23:2055–2062. https://doi.org/10.1161/01.ATV.0000095973.42032.44
44. Gupta A, Iadecola C (2015) Impaired AÎ^2 clearance: a potential link between atherosclerosis and Alzheimerâ€™s disease. Front Aging Neurosci 7. https://doi.org/10.3389/fnagi.2015.00115
45. Sun X, He G, Qing H, Zhou W, Dobie F, Cai F et al (2006) Hypoxia facilitates alzheimer's disease pathogenesis by up-regulating BACE1 gene expression. Proc Natl Acad Sci 103:18727–18732. https://doi.org/10.1073/pnas.0606298103
46. Hawkes CA, Härtig W, Kacza J, Schliebs R, Weller RO, Nicoll JA et al (2011) Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy. Acta Neuropathol 121:431–443. https://doi.org/10.1007/s00401-011-0801-7
47. Roberts KF, Elbert DL, Kasten TP, Patterson BW, Sigurdson WC, Connors RE et al (2014) Amyloid-β efflux from the central nervous system into the plasma. Ann Neurol 76:837–844. https://doi.org/10.1002/ana.24270
48. Thomas T, Thomas G, McLendon C, Sutton T, Mullan M (1996) β-Amyloid-mediated vasoactivity and vascular endothelial damage. Nature 380:168–171. https://doi.org/10.1038/380168a0
49. Niwa K, Porter VA, Kazama K, Cornfield D, Carlson GA, Iadecola C (2001) Aβ-peptides enhance vasoconstriction in cerebral circulation. Am J Physiol Heart Circ Physiol 281:H2417–H2424. https://doi.org/10.1152/ajpheart.2001.281.6.H2417
50. Honig LS, Kukull W, Mayeux R (2005) Atherosclerosis, AD. Neurology 64:494–500. https://doi.org/10.1212/01.WNL.0000150886.50187.30
51. Beach TG, Wilson JR, Sue LI, Newell A, Poston M, Cisneros R et al (2006) Circle of Willis atherosclerosis: association with alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta Neuropathol 113:13–21. https://doi.org/10.1007/s00401-006-0136-y
52. Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC (2016) Early role of vascular dysregulation on late-onset alzheimer's disease based on multifactorial data-driven analysis. Nat Commun 7:11934. https://doi.org/10.1038/ncomms11934
53. Kim HJ, Park S, Cho H, Jang YK, San Lee J, Jang H et al (2018) Assessment of extent and role of Tau in subcortical vascular cognitive impairment using ^{18}F-AV1451 positron emission tomography imaging. JAMA Neurol 75:999. https://doi.org/10.1001/jamaneurol.2018.0975
54. Eglit GML, Weigand AJ, Nation DA, Bondi MW, Bangen KJ Hypertension and alzheimer's disease: indirect effects through circle of Willis atherosclerosis. Brain Commun 2020;2. https://doi.org/10.1093/braincomms/fcaa114
55. Wingo AP, Fan W, Duong DM, Gerasimov ES, Dammer EB, Liu Y et al (2020) Shared proteomic effects of cerebral atherosclerosis and alzheimer's disease on the human brain. Nat Neurosci 23:696–700. https://doi.org/10.1038/s41593-020-0635-5
56. Guerrero-Bonmatty R, Gil-Fernández G, Rodríguez-Velasco FJ, Espadaler-Mazo J (2021) A combination of Lactoplantibacillus plantarum strains CECT7527, CECT7528, and CECT7529 plus Monacolin K reduces blood cholesterol: results from a Randomized, Double-Blind, Placebo-Controlled study. Nutrients 13:1206. https://doi.org/10.3390/nu13041206
57. Singh-Manoux A, Dugravot A, Shipley M, Brunner EJ, Elbaz A, Sabia S et al (2018) Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II study. Alzheimers Dement 14:178–186. https://doi.org/10.1016/j.jalz.2017.06.2637
58. Zuin M, Roncon L, Passaro A, Cervellati C, Zuliani G (2021) Metabolic syndrome and the risk of late onset alzheimer's disease: an updated review and meta-analysis. Nutr Metabolism Cardiovasc Dis 31:2244–2252. https://doi.org/10.1016/j.numecd.2021.03.020
59. Zuin M, Roncon L, Passaro A, Bosi C, Cervellati C, Zuliani G (2021) Risk of dementia in patients with atrial fibrillation: short versus long follow-up. A systematic review and meta-analysis. Int J Geriatr Psychiatry 36:1488–1500. https://doi.org/10.1002/gps.5582
60. Cortes-Canteli M, Gispert JD, Salvadó G, Toribio-Fernandez R, Tristão-Pereira C, Falcon C et al (2021) Subclinical atherosclerosis and brain metabolism in Middle-Aged individuals. J Am Coll Cardiol 77:888–898. https://doi.org/10.1016/j.jacc.2020.12.027

61. Wagen AZ, Coath W, Keshavan A, James S-N, Parker TD, Lane CA et al (2022) Life course, genetic, and neuropathological associations with brain age in the 1946 British birth cohort: a population-based study. Lancet Healthy Longev 3:e607–e616. https://doi.org/10.1016/S2666-7568(22)00167-2
62. Jiang X, O'Bryant SE, Johnson LA, Rissman RA, Yaffe K Association of cardiovascular risk factors and blood biomarkers with cognition: the HABS-HD study. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 2023;15. https://doi.org/10.1002/dad2.12394
63. Charisis S, Lin H, Ray R, Joehanes R, Beiser AS, Levy D et al (2023) Obesity impacts the expression of alzheimer's disease–related genes: the Framingham heart study. Alzheimer's Dement 19:3496–3505. https://doi.org/10.1002/alz.12954
64. Dhana A, DeCarli CS, Dhana K, Desai P, Holland TM, Evans DA et al (2023) Cardiovascular health and cognitive outcomes: findings from a biracial population-based study in the united States. Alzheimer's Dement 19:4446–4453. https://doi.org/10.1002/alz.13421
65. Valenti R, Pantoni L, Markus HS (2014) Treatment of vascular risk factors in patients with a diagnosis of alzheimer's disease: a systematic review. BMC Med 12:160. https://doi.org/10.1186/s12916-014-0160-z
66. Shang Y, Torrandell-Haro G, Vitali F, Brinton RD (2025) Combination therapy targeting alzheimer's disease risk factors is associated with a significant delay in alzheimer's disease–related cognitive decline. Alzheimer's Dementia: Translational Res Clin Interventions 11. https://doi.org/10.1002/trc2.70074
67. Iadecola C (2003) Atherosclerosis and neurodegeneration. Arterioscler Thromb Vasc Biol 23:1951–1953. https://doi.org/10.1161/01.ATV.0000102660.99744.85
68. Cervellati C, Trentini A, Rosta V, Passaro A, Bosi C, Sanz JM et al (2020) Serum beta-secretase 1 (BACE1) activity as candidate biomarker for late-onset alzheimer's disease. Geroscience 42:159–167. https://doi.org/10.1007/s11357-019-00127-6
69. Shen Y, Wang H, Sun Q, Yao H, Keegan AP, Mullan M et al (2018) Increased plasma Beta-Secretase 1 May predict conversion to alzheimer's disease dementia in individuals with mild cognitive impairment. Biol Psychiatry 83:447–455. https://doi.org/10.1016/j.biopsych.2017.02.007
70. Zuliani G, Trentini A, Rosta V, Guerrini R, Pacifico S, Bonazzi S et al (2020) Increased blood BACE1 activity as a potential common pathogenic factor of vascular dementia and late onset alzheimer's disease. Sci Rep 10:14980. https://doi.org/10.1038/s41598-020-72168-3
71. Durrant CS, Ruscher K, Sheppard O, Coleman MP, Özen I (2020) Beta secretase 1-dependent amyloid precursor protein processing promotes excessive vascular sprouting through NOTCH3 signalling. Cell Death Dis 11:98. https://doi.org/10.1038/s41419-020-2288-4
72. Nicsanu R, Cervellati C, Benussi L, Squitti R, Zanardini R, Rosta V et al (2022) Increased serum Beta-Secretase 1 activity is an early marker of alzheimer's disease. J Alzheimers Dis 87:433–441. https://doi.org/10.3233/JAD-215542
73. Cervellati C, Vergallo A, Trentini A, Campo G, Vieceli Dalla Sega F, Rizzo P et al (2022) Age, Sex, hypertension and HDL-C alter serum BACE1 activity in cognitively normal subjects: implications for alzheimer's disease. J Prev Alzheimers Dis 9:708–714. https://doi.org/10.14283/jpad.2022.78
74. Wang Y, Chan SL, Miele L, Yao PJ, Mackes J, Ingram DK et al (2004) Involvement of Notch signaling in hippocampal synaptic plasticity. Proceedings of the National Academy of Sciences. ;101:9458–62. https://doi.org/10.1073/pnas.0308126101
75. Ruitenberg A, den Heijer T, Bakker SLM, van Swieten JC, Koudstaal PJ, Hofman A et al (2005) Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam study. Ann Neurol 57:789–794. https://doi.org/10.1002/ana.20493
76. Hughes TM, Kuller LH, Barinas-Mitchell EJM, McDade EM, Klunk WE, Cohen AD et al (2014) Arterial stiffness and β-Amyloid progression in nondemented elderly adults. JAMA Neurol 71:562. https://doi.org/10.1001/jamaneurol.2014.186
77. Zuin M, De Vito A, Romagnoli T, Polastri M, Capatti E, Azzini C et al (2024) Cerebral blood flow in alzheimer's disease: A Meta-Analysis on transcranial doppler investigations. Geriatrics 9:58. https://doi.org/10.3390/geriatrics9030058
78. Cooper LL, O'Donnell A, Beiser AS, Thibault EG, Sanchez JS, Benjamin EJ et al (2022) Association of aortic stiffness and pressure pulsatility with global Amyloid-β and regional Tau burden among Framingham heart study participants without dementia. JAMA Neurol 79:710. https://doi.org/10.1001/jamaneurol.2022.1261
79. Weller RO, Massey A, Kuo Y, Roher AE (2000) Cerebral amyloid angiopathy: accumulation of Aβ in interstitial fluid drainage pathways in alzheimer's disease. Ann N Y Acad Sci 903:110–117. https://doi.org/10.1111/j.1749-6632.2000.tb06356.x
80. Sagare AP, Bell RD, Zlokovic BV (2012) Neurovascular dysfunction and faulty amyloid -Peptide clearance in alzheimer disease. Cold Spring Harb Perspect Med 2:a011452–a011452. https://doi.org/10.1101/cshperspect.a011452
81. Yoon S-S, AhnJo S-M (2012) Mechanisms of Amyloid-β peptide clearance: potential therapeutic targets for alzheimer's disease. Biomol Ther (Seoul) 20:245–255. https://doi.org/10.4062/biomolther.2012.20.3.245
82. Kerridge C, Kozlova DI, Nalivaeva NN, Turner AJ (2015) Hypoxia affects Neprilysin expression through caspase activation and an APP intracellular Domain-dependent mechanism. Front Neurosci 9. https://doi.org/10.3389/fnins.2015.00426
83. Oveisgharan S, Dawe RJ, Yu L, Kapasi A, Arfanakis K, Hachinski V et al (2022) Frequency and underlying pathology of pure vascular cognitive impairment. JAMA Neurol 79:1277. https://doi.org/10.1001/jamaneurol.2022.3472
84. Skillbäck TB, Jönsson L, Skoog I, Blennow K, Eriksdotter M, Zetterberg H et al (2025) Cerebrospinal fluid biomarkers for alzheimer disease among patients with dementia. JAMA Neurol 82:580. https://doi.org/10.1001/jamaneurol.2025.0693
85. Zuliani G, Cavalieri M, Galvani M, Passaro A, Munari MR, Bosi C et al (2008) Markers of endothelial dysfunction in older subjects with late onset alzheimer's disease or vascular dementia. J Neurol Sci 272:164–170. https://doi.org/10.1016/j.jns.2008.05.020
86. Cervellati C, Romani A, Seripa D, Cremonini E, Bosi C, Magon S et al (2014) Oxidative balance, homocysteine, and uric acid levels in older patients with late onset alzheimer's disease or vascular dementia. J Neurol Sci 337:156–161. https://doi.org/10.1016/j.jns.2013.11.041
87. Cervellati C, Romani A, Bergamini CM, Bosi C, Sanz JM, Passaro A et al (2015) PON-1 and ferroxidase activities in older patients with mild cognitive impairment, late onset alzheimer's disease or vascular dementia. Clin Chem Lab Med 53:1049–1056. https://doi.org/10.1515/cclm-2014-0803
88. Zuliani G, Marsillach J, Trentini A, Rosta V, Cervellati C (2023) Lipoprotein-Associated phospholipase A2 activity as potential biomarker of vascular dementia. Antioxidants 12:597. https://doi.org/10.3390/antiox12030597
89. Brombo G, Bonetti F, Ortolani B, Morieri ML, Bosi C, Passaro A et al (2018) Lower plasma Klotho concentrations are associated with vascular dementia but not Late-Onset alzheimer's disease. Gerontology 64:414–421. https://doi.org/10.1159/000488318
90. Tisato V, Rimondi E, Brombo G, Volpato S, Zurlo A, Zauli G et al (2016) Serum soluble tumor necrosis Factor-Related Apoptosis-Inducing ligand levels in older subjects with dementia and mild

cognitive impairment. Dement Geriatr Cogn Disord 41:273–280. https://doi.org/10.1159/000446275
91. Castellazzi M, Patergnani S, Donadio M, Giorgi C, Bonora M, Bosi C et al (2019) Autophagy and mitophagy biomarkers are reduced in Sera of patients with alzheimer's disease and mild cognitive impairment. Sci Rep 9:20009. https://doi.org/10.1038/s41598-019-56614-5
92. Cervellati C, Pedrini D, Pirro P, Guindani P, Renzini C, Brombo G et al Neutrophil–Lymphocytes ratio as potential early marker for alzheimer's disease. Mediators Inflamm 2024;2024. https://doi.org/10.1155/2024/6640130
93. Roman GC (1997) Brain infarction and the clinical expression of alzheimer disease. JAMA: J Am Med Association 278:113. https://doi.org/10.1001/jama.1997.03550020045023