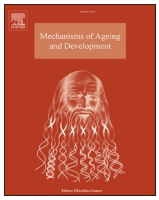
Mechanisms of Ageing and Development 195 (2021) 111444

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev



Connecting vascular aging and frailty in Alzheimer's disease

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ARTICLE INFO

Keywords:
Alzheimer's disease
Vascular aging
Endothelial dysfunction
Cardiovascular diseases
Frailty

ABSTRACT

Aging plays an important role in the etiology of the most common age-related diseases (ARDs), including Alzheimer's disease (AD). The increasing number of AD patients and the lack of disease-modifying drugs warranted intensive research to tackle the pathophysiological mechanisms underpinning AD development. Vascular aging/dysfunction is a common feature of almost all ARDs, including cardiovascular (CV) diseases, diabetes and AD. To this regard, interventions aimed at modifying CV outcomes are under extensive investigation for their pleiotropic role in ameliorating and slowing down cognitive impairment in middle-life and elderly individuals. Evidence from observational and clinical studies confirm the notion that the earlier the interventions are conducted, the most favorable are the effects on cognitive function. Therefore, epidemiological research should focus on the early detection of deviations from a healthy cognitive aging trajectory, through the stratification of adult individuals according to the rate of aging.

Here, we review the interplay between vascular and cognitive dysfunctions associated with aging, to disentangle the complex mechanisms underpinning the development and progression of neurodegenerative disorders, with a specific focus on AD.

1. Introduction

A number of countries in the world are experiencing a growth in the number and proportion of older persons in their population. The two faces of the coin are on one side the improvement and diffusion of a healthier lifestyle and medical care in the population and, on the other side, the increased burden of frailty and disability in the last years of life (O'Donovan et al., 2019). Therefore, the estimation of the burden of disease is becoming an important factor in health policy, and increasing efforts are devoted to delaying the onset of age-related diseases (ARDs) during aging.

Not surprisingly, one strategy to prevent the development of almost all ARDs and their complications includes vascular risk control, suggesting that the age of our vasculature is a critical checkpoint for a healthy aging trajectory (Liberale et al., 2020; Maruhashi et al., 2020). Therefore, systemic inflammation associated with cardiovascular (CV) risk factors plays an important role in the etiology of the most common ARDs, including neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Badji et al., 2020). The increasing number of patients with dementia, including AD, is creating major medical and social challenges, and the lack of disease-modifying drugs warrants further investigation to better clarify the basic

Abbreviations: AChEIs, acetylcholinesterase inhibitors; Aβ, amyloid beta; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; AMPK, 5' AMP-activated protein kinase; APP, amyloid precursor protein; aPTT, activated partial thromboplastin time; ARD, age-related disease; BACE1, Beta-secretase 1; BBB, blood-brain barrier; CBF, cerebral blood flow; CNS, central nervous system; CRP, C-reactive protein; CT, contrast tomography; CV, cardiovascular; CVD, cardiovascular diseases; EC, endothelial cell; FMD, flow-mediated dilation; GLP-1, glucagon-like peptide 1; IL, interleukin; IMT, intima media thickness; IP-10, interferon gamma-induced protein 10; MCI, mild cognitive impairment; MCP-1, monocyte chemoattractant protein 1; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NADP, nicotinamide adenine dinucleotide phosphate; NF-L, neurofilament light; NMD, nitroglycerin-mediated dilation; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PARP-1, poly [ADP-ribose] polymerase 1; PD, Parkinson's disease; PET, positron emission tomography; RANTES, regulated on activation, normal T cell expressed and secreted; RCTs, randomized clinical trials; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; T2DM, type 2 diabetes mellitus; TNFα, tumor necrosis factor-α.

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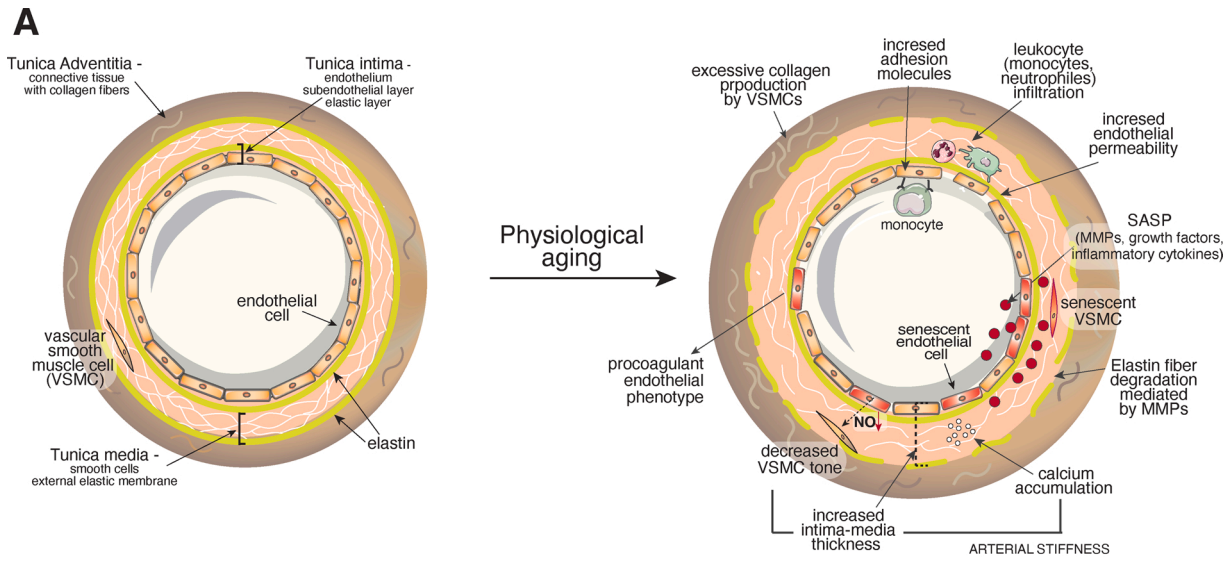
https://doi.org/10.1016/j.mad.2021.111444
Received 30 September 2020; Received in revised form 5 January 2021; Accepted 26 January 2021
Available online 1 February 2021



B

Molecular biomarkers and functional tests of vascular (dys)function	
Procoagulant/ anticoagulant phenotype	Routine coagulation assays von Willebrand factor Tissue factor Thrombomodulin NO (and NO metabolites)
Inflammatory markers/ intercellular communication	Inflammatory citokynes Oxidized LDL Adhesion molecules Endothelial glycocalix alterations
Vascular repair capacity	Endothelial progenitor cells Circulating angiogenic cells
Vascular tone/reactivity	NO bioavailability Intima-media thickness Pulse-wave velocity FMD/NMD Cerebral blood flow Cerebral vascular reactivity to CO2

Fig. 1. Age-related modifications of the arterial wall. (A) On the left panel, the normal vascular anatomy is displayed on a cross section of a young artery. During aging (right panel), senescent endothelial and vascular smooth muscle cells accumulate in the vascular wall and acquire the senescence-associated secretory phenotype (SASP), characterized by the release of pro-inflammatory cytokines, growth factors, and metalloproteinases. Endothelial cells display a prothrombotic phenotype and an increased expression of adhesion molecules, which results in leukocyte recruitment and infiltration of the vascular wall. Maintenance of the vascular tone is impaired due to decreased nitric oxide release by endothelial cells which, together with calcium accumulation and the remodeling of the vascular wall, leads to increased arterial stiffness. **(B)** Summary of the circulating molecular biomarkers and non-invasive functional tests of vascular dysfunction grouped according to the specific physiological vascular function. Parts of the figure were provided by Servier Medical Art (https://smart.servier.com).

mechanisms underpinning AD development and progression, highlighting a key role for neuroinflammation (Hampel et al., 2020). The key contribution of inflammation in the AD pathophysiology has been hypothesized more than 20 years ago (Rogers et al., 1996). Increasing evidence confirmed that neuroinflammation starts decades before the appearance of severe cognitive impairment (Iulita et al., 2019). For this reason, markers of neuroinflammation, including neurofilament light (NF-L), amyloid-beta (Aβ)42, and tau proteins are currently being investigated across diverse body fluids to allow for the early detection of conditions associated with dementia (Lewczuk et al., 2018; Marchegiani et al., 2019).

In the present review, after a brief introduction of basic key concepts related to inflammaging and vascular aging, we will discuss the contribution of the cellular and molecular 'hallmarks' of aging in the pathogenesis of the vascular dysfunction observed in AD, with a specific focus on the methods and biomarkers that can be used to assess vascular aging/vascular dysfunction at its earliest stages. Finally, we will discuss the reciprocal interplay of frailty, cardiovascular diseases (CVDs), and cognitive decline with the aim to disentangle the complex interaction between vascular aging, inflammaging, and frailty in neurodegenerative disorders, specifically focusing on AD.

2. Aging, inflammaging, and vascular aging: key concepts

Understanding the mechanisms underpinning the trajectories of unhealthy aging is becoming one of the most relevant challenges within the field of personalized medicine (Franceschi et al., 2018). Aging is a complex phenomenon that involves virtually all the organs and physiological systems of the human organism (Fulop et al., 2017). Despite many efforts, a standardized definition of aging has still to be achieved, and some groups even argue that the concept of aging does not reflect any biological entity (Cohen et al., 2020). Recently, the term 'old age' replaced 'senility' under the 'General symptoms' category of the 11th Revision of the International Classification of Diseases (ICD-11), and the

new extension code 'ageing-related' was added to identify all those pathological processes that occur and progress at advanced ages due to a loss of organism's adaptation (World Health Organization, 2018). Albeit these modifications are not sufficient to define aging as a separate nosological entity, there is a clear awareness on the pathophysiological role of increasing age in modulating human organ and system functions and on its role as the major risk factor for every ARD. In this review, we will refer mostly to the age-related changes occurring in the vascular system, by keeping in mind that those changes begin far earlier than what it is generally accepted as advanced age, i.e. > 65 yrs (Oren et al., 2003), and are a major determinant of the adverse outcomes that are observed in aged individuals, including cognitive decline and frailty. Starting from the observation that aging is the major risk factor for ARDs and assuming that aging and ARDs share a common set of biological mechanisms, frailty was conceptualized as accelerated aging, and the need to identify biomarkers capable of distinguishing the rate of aging (biological vs. chronological age) was highlighted. Currently, nine pillars are identified as basic mechanisms of aging (Lopez-Otin et al., 2013). Each of them has a recognized role in the pathogenesis of ARDs, with distinctive organ- and tissue-specific variations, as discussed in the next sections. All these pillars are compounded by the degree of a condition defined as "inflammaging" (Franceschi et al., 2000; Kennedy et al., 2014). This term was coined to describe the increased burden of systemic, chronic, low-grade inflammatory condition that increases during aging, characterized by persistent and non-resolved production of pro-inflammatory mediators (Franceschi et al., 2000). Notably, the degree of inflammaging, currently recognized as the most relevant risk factor for the most common ARDs, depends upon a complex interaction between genetic, epigenetic, and stochastic factors being extremely variable between subjects (Capri et al., 2014; Fulop et al., 2018; Marcos-Perez et al., 2020). There are a plethora of sources that can fuel inflammaging, including external factors, such as overt infections during life, and age-related intrinsic factors, such as the increased burden of senescent cells during aging, characterized by a senescence-associated secretory phenotype (SASP) that contribute to the systemic release of cytokines, chemokines, growth factors, proteases, and angiogenic factors (Coppe et al., 2010; Franceschi et al., 2018). Overall, inflammaging basically shares the same molecular mechanisms of an inflammatory response, characterized primarily by the activation of innate immune system cells and endothelial cells (ECs), but with the chronic contribution of senescent cells with SASP.

3. A brief overview of vascular aging

The link between aging and vascular function has been well expressed in the axiom that "a man is only as old as his arteries" (William Osler, 1892). In this framework, longevity is substantially a vascular issue (Schiele and Meneveau, 2009; Thijssen et al., 2016). A number of age-related CV and cerebrovascular diseases are due to alterations in arterial function or are exacerbated by arterial dysfunction suggesting the clinical relevance of better elucidating the mechanisms underlying arterial/endothelial aging (Ungvari et al., 2018). The two main components of the vasculature, i.e. the vascular endothelium and the media arterial wall, undergo several structural and functional changes during aging (Fig. 1A) (Izzo et al., 2018). The reduction in the vasodilatory capacity of the vascular endothelium is due to the loss of endothelium-derived vasodilators, e.g. nitric oxide (NO), and increased production of vasoconstrictors, e.g. endothelin-1. In addition, important pathobiological changes occur with aging in the vascular system, including elastin fragmentation, collagen accumulation, and medial vascular smooth muscle cell (VSMC) loss, causing reduced vascular compliance and increased arterial stiffness (Stein, 2004). In the aged vasculature, a shift towards the irreversible non-enzymatic glycation-based cross-linking between collagen and elastin occurs to stabilize the increased fragmentation of the collagen fibers secondary to enhanced matrix metalloproteinase (MMP) activity. These phenomena not only further contribute to arterial stiffness, but they also activate an inflammatory stress response to advanced glycation end products (AGEs) which establishes a vicious cycle (Maruyama, 2012). Vascular aging can be also characterized by the deposition of calcium phosphate crystals in both the arterial intima (typically related to atherosclerosis) and media (called Mönckeberg sclerosis), so that arterial aging can be viewed as a function of the coronary artery calcium content (McClelland et al., 2009). Altogether, these alterations leading to increased aortic stiffness develop at a variable rate during aging, allowing the identification of two extreme phenotypes, namely early and supernormal vascular aging, characterized by positive and negative offsets from chronological age, respectively (Bruno et al., 2020).

Moving deeper into aging vasculature, it is possible to notice that endothelial dysfunction represents the first step of vascular alterations and its onset depends both on the quality of vascular tissue which the individual has inherited (genetic predisposition) and the amount of wear and tear to which he was subjected (environmental factors) (reviewed in (Kovacic et al., 2011a) and (Kovacic et al., 2011b)). The increasing effort to understand the biological mechanisms driving the age-related changes in endothelial cells suggested that also the increased burden of senescent vascular cells could play a crucial role in promoting endothelial dysfunction (Katsuumi et al., 2018). The presence of cells displaying markers of senescence was demonstrated in advanced atherosclerotic plaques (Gorenne et al., 2006; Minamino et al., 2002), but whether senescent cells accumulate as a result of the plaque formation or themselves promote atherosclerosis is still unclear (Wang and Bennett, 2012). These two scenarios likely coexist and do not exclude each other. Indeed, senescent cells are endowed with a proatherogenic phenotype (Childs et al., 2016), and the proinflammatory atherosclerotic milieu can induce the acquisition of senescence markers in VSMCs (Kunieda et al., 2006) and endothelial cells (Riahi et al., 2015). Similarly, senescent vascular cells have been invoked in the pathogenesis of heart failure (Gogiraju et al., 2015) and systemic metabolic dysfunction associated with obesity (Yokoyama et al., 2014). Senescent endothelial cells are characterized by the acquisition of the SASP, reduced replicative ability, telomere attrition (Wilson et al., 2008), and metabolic alterations (Sabbatinelli et al., 2019). Interestingly, increasing observations in animal models and in humans indicate that genomic instability characterized by DNA damage accumulation – a characteristic associated with cellular senescence – can contribute to vascular aging by interfering with the regulation of the vascular tone (Bautista-Nino et al., 2016). Fig. 1A summarizes the key age-related modifications occurring in the vascular wall and Fig. 1B lists the currently available circulating biomarkers and functional tests reflecting these alterations.

A multitude of invasive techniques for assessing endothelial function have been described. Brachial artery flow-mediated dilation (FMD) was the first non-invasive technique to assess endothelial function in the peripheral conduit arteries and remains today the most widely applied method (Lekakis et al., 2011; Vlachopoulos et al., 2015), allowing for the diagnosis of incipient endothelial dysfunction also in otherwise healthy subjects (Sabbatinelli et al., 2020). Non-invasive circulating biomarkers that truly reflect the state of vascular aging are needed to improve early detection of individuals at high risk of developing not only CVD but also all the other ARDs, including neurodegenerative diseases (Hamczyk et al., 2020; Klohs, 2019).

4. Age-related vascular dysfunction in neurodegenerative disorders

The classical neuropathologic hallmarks of AD are the extracellular accumulation of Aβ plaques and intraneuronal aggregates of hyperphosphorylated tau (neurofibrillary tangles) (Masters et al., 2015). However, recent community-based autopsy studies have shown that vascular alterations are present in >50 % of cases of clinically diagnosed AD (Iadecola and Gottesman, 2018), highlighting a still

Table 1
Summary of the evidence on the role of the vascular aging features in the onset and progression of Alzheimer's disease (AD). References are grouped based on the relevant key hallmarks of aging, as described by López-Otín and colleagues (Lopez-Otin et al., 2013).

Hallmarks of aging	Findings relevant to cerebrovascular aging and AD	References
Cellular senescence	- Age-related increase in the proportion of p16-positive astrocytes - Aβ triggers senescence and SASP in astrocytes in a p38MAPK-dependent manner	(Bhat et al., 2012)
	Microglial cell senescence associated with telomere shortening is exacerbated by the presence of Aβ	(Flanary et al., 2007)
	Exposure of ECs to Aβ1-42 oligomers alters VEGFR-1 expression and induces senescence	(Singh Angom et al., 2019)
Telomere shortening	*In vitro* and *in vitro* proof-of-principle of telomere shortening in astrocytes	(Flanary and Streit, 2004)
	Microglia in telomerase deficient mice show an enhanced pro-inflammatory response after intraperitoneal infusion of lipopolysaccharide	(Raj et al., 2015)
Altered intercellular communication	Cerebrovascular reactivity in response to hypercapnia is impaired in cortical arterioles of TgF344-AD rats due to the accumulation of Aβ	(Joo et al., 2017)
	Aβ42 binds to RAGE on the surfaces of cerebral ECs inducing ROS generation from NADPH oxidase	(Askarova et al., 2011)
	Aβ in the basolateral surface of AD brain ECs promotes transmigration of monocytes across the BBB	(Giri et al., 2002)
	- Levels of vascular endothelial (VE) cadherin are decreased in brain vessels of AD patients and mouse model of AD - Aβ induces VE cadherin cleavage at the endothelial cell surface *in vitro*	(Lee et al., 2018)
Mitochondrial dysfunction	Aβ exposure induces mitochondrial DNA hypermethylation in BBB hCMEC/D3 cells	(Liu et al., 2020)
	Acute Aβ exposure of ECs induce loss of mitochondrial membrane potential and rise of cytochrome *c* release	(Solito et al., 2013)
	Aβ triggers cerebral EC apoptosis by activating mitochondrial caspase-3	(Xu et al., 2001)
Genomic instability	Exposure to air pollutants induces histone post-translational modifications and the DNA double-strand-break marker γ-H2AX and accumulation of hyperphosphorylated tau and Aβ plaques	(Calderon-Garciduenas et al., 2020)
	Mice knock-out for the DNA repair enzyme uracil-DNA glycosylase, deficient of folic acid, and with elevated levels of homocysteine develop cognitive impairment due to chronic cerebral hypoperfusion	(Jadavji et al., 2015)
		(Fluteau et al., 2015)
Stem cell exhaustion	Aβ impairs glutamine synthetase neuroprotective activity against DNA damage in astrocytes Local tangle AD pathology induces DNA damage in astrocytes	(Waller et al., 2018)
	Endothelial progenitor cell (EPC) transplantation repairs the BBB, stimulates angiogenesis, and reduces Aβ deposition in AD	(Zhang et al., 2018)
	Bone marrow-derived EPCs reduce the accumulation of Aβ, restore neurotransmitter levels, and suppress pro-inflammatory cytokines	(Safar et al., 2016)
	Patients with AD have reduced circulating EPCs	(Lee et al., 2009)
Deregulated nutrient-sensing	mTOR attenuation preserves BBB integrity through upregulation of tight junction proteins and downregulates matrix metalloproteinase-9 activity in a mouse model of AD	(Van Skike et al., 2018)
	The GLP-1 agonist geniposide inhibits mTOR and enhances autophagy and lysosomal degradation of Aβ fibrils	(Zhang et al., 2019)
Loss of proteostasis	Aβ40 induces the failure of the ER stress-adaptive unfolded protein response, deregulates the ubiquitin-proteasome system, and impairs the autophagic protein degradation pathway	(Fonseca et al., 2014)
	Aβ40 inhibits the proliferative activity of human brain vascular ECs through the induction of autophagy	(Hayashi et al., 2009)
	MiR-146a downregulates IRAK-1in IL-1β and Aβ42-stressed human astroglial cells	(Cui et al., 2010)
Epigenetic alterations	Aβ reduces global DNA methylation whilst increasing the Aβ-degrading enzyme neprilysin gene methylation in cerebral ECs	(Chen et al., 2009)

mTOR, mammalian target of rapamycin; RAGE, receptor for advanced glycation endproducts; VEGFR-1, vascular endothelial growth factor-1.

underappreciated contribution of age-related vascular factors in the mechanisms of AD.

Cerebrovascular disease is a common comorbidity in patients with AD and contributes additively to cognitive impairment and to a lower threshold for the development of dementia (Klohs, 2019). However, accumulating evidence suggests that dysfunction of the cerebral vasculature and AD neuropathology interact in multiple ways. Age-related vascular changes accompany or even precede the development of AD, raising the possibility that they may have a pathogenic role (Cortes-Canteli and Iadecola, 2020).

Vascular lesions are common findings in patients with AD. The hypothesis that AD pathogenesis is linked to an impairment in cerebral microcirculation was postulated many decades ago (de la Torre and Mussivand, 1993), and supported by many studies highlighting a higher prevalence of dementia in subjects with lacunar or larger brain infarcts (Loeb et al., 1992; Snowdon et al., 1997). A neuropathological study revealed that large infarcts, lacunae, multiple microinfarcts, hemorrhage, atherosclerosis, and arteriolosclerosis are prevalent in 80 % of cases diagnosed with AD (Toledo et al., 2013). Collectively, these evidences suggest that vascular pathology is likely a pathogenic contributor to age-related dementia, including AD, inextricably linked to disease onset and progression.

4.1. The hallmarks of aging in the pathogenesis of neurovascular dysfunction

The key hallmarks of aging described by López-Otín and colleagues (Lopez-Otin et al., 2013) can link vascular dysfunction with cognitive decline characterizing the neurodegenerative diseases, including AD. Table 1 summarizes evidence supporting the role of vascular aging features in the pathogenesis of AD.

The vascular endothelium in the brain is an essential part of the blood-brain-barrier (BBB), the highly selective interface that separates brain interstitial space from blood. The progressive accumulation of dysfunctional and/or senescent endothelial cells during aging can contribute to the impaired transport of metabolites across the BBB, thus affecting brain health and cognitive functioning and promoting the development of neurodegenerative diseases. Extensive DNA damage and the accumulation of senescent endothelial cells have been reported in the aging brain. The persistence of the DNA-damage response is associated with reduced cerebral blood flow (CBF), impairment of the BBB, and reduced Aβ clearance (Garwood et al., 2014). In addition, senescent endothelial cells accumulating in the cerebral microvascular endothelium have been shown to express reduced levels of soluble amyloid precursor protein (APP) α (sAPPα) and, on the other hand, increased levels of beta-secretase 1 (BACE1) and Aβ40. This shift towards the amyloidogenic pathway of APP contributes to cerebral endothelial dysfunction and may also be involved in AD pathogenesis (Sun et al., 2018). On the other hand, exposure of astrocytes to synthetic or cell-derived Aβ results in the induction of the senescence program (Bhat et al., 2012). Interestingly, one of the mechanisms linking hypertension to AD pathogenesis is the enhanced Aβ deposition in cerebral blood vessels. In a mouse model, treatment with angiotensin II enhances β-secretase APP processing, thus increasing Aβ production and the Aβ42/40 ratio. Notably, Aβ and angiotensin II acted synergistically in worsening the cerebrovascular dysfunction, and the administration of angiotensin II increased endothelial ROS production (Faraco et al., 2016).

Mitochondrial dysfunction is a major trigger of oxidative stress in senescent endothelial cells (Giuliani et al., 2018). Increased superoxide synthesis by NADPH oxidases results in reduced NO bioavailability, and thus in the impairment of the ability to promptly adjust CBF to ensure neural activity, the so-called neurovascular coupling (Tarantini et al., 2017). Notably, restoration of proper neurovascular response resulted in the amelioration of cognitive function in AD mice (Tong et al., 2012). Increasing oxidative stress also involves the activation of the NAD^+-consuming enzyme poly(ADP-ribose) polymerase 1 (PARP-1) (Hurtado-Bages et al., 2020), which was linked to systemic vascular dysfunction in aged mice (Wang et al., 2018). These findings have been recapitulated also in the cerebral vasculature, where NAD^+ depletion impairs neurovascular responses, thus accelerating cognitive decline. In a mouse model, restoration of endothelial NAD^+ levels promoted the activity of sirtuins, resulting in delayed EC senescence and improvement of endothelium-dependent vasodilation in the central nervous system (CNS) (Tarantini et al., 2019). The role of the nutrient sensor AMPK in AD still remains controversial. While several studies showed that AMPK activators could exert positive effects on amyloidogenesis by increasing Aβ degradation and reducing tau phosphorylation (Assefa et al., 2020), the abnormal AMPK activation in AD mouse models leads to dysregulated vascular homeostasis and reduced vessel density (Lopez-Lopez et al., 2007).

Impaired proteostasis is a main hallmark of neurodegenerative disorders (Hipp et al., 2019). On the other hand, EC senescence due to impaired proteostasis could be triggered by AD itself. Indeed, Aβ induces the accumulation of ubiquitinated proteins in mouse brain ECs following the failure of the unfolded protein response and deregulation of the ubiquitin-proteasome system (Fonseca et al., 2014). This eventually leads to EC apoptosis and worsening of the BBB damage observed in AD.

It should be noted that these mouse models don't entirely reflect the biology of AD, since they are limited to the less common genetic form of the disease (King, 2018). However, these observations provided important insights into the mechanisms of cerebrovascular dysfunction in AD, even if animal models that allow the translation of these results into the clinical practice for the treatment of sporadic AD are still lacking.

Evidence supporting the pathogenic role of inflammatory processes in AD and PD comes from the study of microglia, i.e. the population of resident myeloid cells that initiate immune responses in the CNS and provide trophic support to neurons and other glial cells (Sarlus and Heneka, 2017). The chronic age-related activation of microglia results in the impairment of Aβ clearance which, along with the increased burden of pro-inflammatory mediators, leads to neurotoxicity and persistence of microglial activation due to the accumulation of neuronal damage-associated molecular patterns (DAMPs) (Norden and Godbout, 2013). Notably, transcriptomic analyses of human brain samples revealed a high degree of heterogeneity in the phenotype of microglial cells (Olah et al., 2020, 2018). Microglia from human aged brains is endowed with a specific phenotype which is characterized by the over-expression of genes related to the amyloid formation pathway and the downregulation of genes participating in the TGF-β pathway, suggesting the loss of microglial ability to respond to the age-related Aβ accumulation. Notably, this peculiar microglial phenotype is associated with genes linked to AD susceptibility (Olah et al., 2018).

Endothelial cells in microvessels from AD patients show an increased expression of vascular adhesion molecules and release higher amounts of many of the SASP components, including tumor necrosis factor-α (TNFα), interleukin (IL)-1β, IL-6, IL8, and matrix metalloproteinases. These findings are consistent with the detection of increased levels of soluble vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) in AD patients. AD is also accompanied by significant alterations of blood cells, including a decline in lymphocyte and monocyte number and function (Klohs, 2019). In AD, brain ECs are exposed to proinflammatory signals coming both from the systemic circulation, related to aging and other age-related comorbidities, and from the brain itself, where Aβ triggers inflammatory responses in astrocytes and activated microglia (Govindpani et al., 2019). This self-amplifying inflammatory cascade also involves the release of various chemokines, including MCP-1, RANTES, CXCL1, CXCL2, IL-8, and IP-10, which facilitate the recruitment of inflammatory cells and their migration across the impaired BBB (Zuena et al., 2019).

Sustained neuroinflammation is recognized among the main triggers of dopaminergic neuron loss in PD (Wang et al., 2015). Here, abnormal accumulation of α-synuclein initiates a synergistic response in microglia and astrocytes, which leads to alterations in EC morphology and alterations of the BBB (Guan et al., 2013). PD, similarly to AD, is accompanied by most of the manifestations of the aging process, including mitochondrial dysfunction, oxidative stress, and dysfunction of the autophagic processes, which ultimately result in disproportionate, yet ineffective, responses to environmental and endogenous stressors (Calabrese et al., 2018).

5. Identifying and targeting vascular dysfunction in neurodegenerative disorders

Beyond the aforementioned vascular alterations occurring in the brain during AD, systemic vascular aging was shown to exert a critical role in the development and progression of neurodegenerative disorders. Currently, a number of circulating biomarkers and non-invasive functional tests are available to evaluate aortic stiffness and endothelial function at the systemic level (Fig. 1B), while assessment of the organ-specific vascular function still remains a challenge.

Aortic stiffness is currently assessed through the measurement of pulse-wave velocity (PVW) using a variety of non-invasive methods, including ultrasonography, magnetic resonance imaging (MRI), and dedicated piezoelectric mechano-transducers (Milan et al., 2019). PWV

represents the speed of propagation of the pulses generated by the heart along two finite points of the arterial network, conventionally the carotid and the femoral arteries. PWV serves as a 'tissue' biomarker of vascular disfunction, without providing clues on the specific cellular type (e.g. ECs, VSMCs) mostly accountable for the accumulating damage (Lacolley et al., 2017). In healthy subjects, PVW has been shown to approximately double between the ages of 20 and 80, and the rate of PWV increase is even more pronounced in subjects with high arterial blood pressure and/or CV risk factors (Reference Values for Arterial Stiffness, 2010). PVW, alone or in combination with circulating biomarkers of inflammation and vascular damage, has been shown to be a significant predictor of CV events independent of classical CV risk factors (Currie and Delles, 2017; Niiranen et al., 2017; Ohkuma et al., 2017). Moreover, multiple reports showed that aortic stiffness is associated with the risk of incident mild cognitive impairment (MCI) and/or dementia in large cohorts in non-demented elderly subjects (Pase et al., 2016; Rouch et al., 2018), supporting the notion that cognitive impairment should be considered as a manifestation of target-organ damage in the context of the early vascular aging syndrome (Scuteri and Wang, 2014).

FMD and nitroglycerin-mediated dilation (NMD) are considered as the most reliable non-invasive tools to evaluate endothelium-dependent and -independent vasodilation, respectively. While FMD is directly related to the ability of EC to release NO, NMD assesses the ability of VSMCs to react to an exogenously administered NO donor (Thijssen et al., 2019). Endothelium-dependent vasodilation decreases with age, as a result of progressive endothelial dysfunction (Seals et al., 2011). On the contrary, NMD was not shown to be significantly related to age, supporting the evidence that VSMC reactivity to NO is preserved during aging (Gerhard et al., 1996). Many studies attempted to establish a connection between systemic vascular dysfunction, cardiovascular diseases, and neurodegeneration. However, evidence on the association between peripheral vascular function and cognitive impairment are still conflicting. In a cohort of 83 cognitively normal elderly subjects, a negative association was demonstrated between FMD and the burden of Aβ, evaluated by PET imaging. A FMD cut-off of 4.45 % was identified to discriminate between elevated and normal levels of Aβ (Liu et al., 2019). A randomized study showed that elderly individuals with MCI had lower FMD values at baseline compared to non-MCI, age-matched individuals. Interestingly, MCI subjects randomized to receive a 7-month program including cognitive, social and exercise training showed an increase in FMD and in hematopoietic stem cell mobilization, along with a significant improvement of the ADAS-Cog score, whereas non-training MCI patients showed a decline in FMD and carotid distensibility over the follow-up period (Bruno et al., 2018). Similarly, a 6-month exercise training intervention induced a 3.7 % mean increase of FMD, associated with increased VEGF and NO circulating levels, in a group of 39 AD patients (Pedrinolla et al., 2020). On the contrary, another study from the same group showed no alterations of endothelial function in MCI and AD individuals (mean FMD = 7.8 ± 2.6 %), and no associations between FMD and the Mini-Mental State Examination (MMSE) score (Pedrinolla et al., 2019). Regarding PD, a decreased FMD was found in patients treated with L-dopa compared to patients treated with L-dopa and entacapone, untreated patients, and control subjects. An inverse relationship has been demonstrated between FMD and hyperhomocysteinemia, which could explain the FMD reduction observed in the L-dopa group (Yoon et al., 2014). Overall, limited and conflicting evidences are available so far, mainly due to the advanced age and reduced cooperation of the patients.

Besides the assessment of peripheral vascular dysfunction, non-invasive methods to specifically evaluate cerebrovascular function can represent reliable predictors of cognitive impairment. Indeed, it should be mentioned that there is no agreement on the possibility to infer cerebrovascular function by measuring endothelial function at the brachial artery level (Carr et al., 2020). This observation supports the evaluation of functional tests to assess specific features of the cerebral vascular bed that can be more strongly associated with the risk of dementia. Cerebrovascular hypoperfusion assessed by MRI has been shown to be associated with accelerated cognitive decline, especially in memory and executive domains, and with incipient dementia and AD (Wolters et al., 2017). An additional tool to evaluate cerebrovascular function comes from the imaging assessment of cerebrovascular reactivity to carbon dioxide (CO_2), which provides information on the extent of vasodilation in response to changes in the arterial content of CO_2. A large number of studies showed that this parameter is altered in subjects with MCI and AD, and that alterations in cerebrovascular reactivity to CO_2 often precede the impairment of CBF (Glodzik et al., 2013). Finally, the cerebrovascular resistance index, which represents the ratio of cerebral perfusion pressure (i.e. the difference between mean arterial pressure and intracranial pressure) to CBF has been shown to predict the development of AD better than CBF alone and independent of neuronal hypometabolism (Yew et al., 2017). Thus, it is conceivable that indexes combining measures of peripheral and cerebrovascular function could provide additional insights into the contribution of arterial hypertension to the vascular changes observed in AD.

Vascular dysfunction can also be inferred through the assessment of circulating biomarkers related to the proinflammatory and procoagulant state of the endothelium. Longitudinal cohort studies revealed that high levels of C-reactive protein (CRP) and IL-6 were associated with an increased risk of silent brain infarcts, microbleeds, white matter hyperintensities (Gu et al., 2019), and with a reduction in regional CBF (Warren et al., 2018). Moreover, high IL-6 levels predicted the decline in reasoning and in MMSE over a 10-year follow-up period (Singh-Manoux et al., 2014). Similarly, detectable circulating CRP levels were associated with reduced episodic and recognition memories, as well as smaller left temporal lobe volume (Bettcher et al., 2012). IL-1β was found to be higher in AD subjects compared to matched controls. Notably, AD patients with concomitant depression showed higher levels of IL-6 and TNFα compared to non-depressed AD patients and healthy controls. Interestingly, IL-6 and TNFα levels were negatively related to the MMSE score (Khemka et al., 2014). A meta-analysis evaluating the associations between all-cause dementia or AD and inflammatory markers showed that while CRP, IL-6, α1-antichymotrypsin, and lipoprotein-associated phospholipase A2 are associated with a higher risk of all-cause dementia, none of these molecules can be considered a specific predictor of AD development (Darweesh et al., 2018).

Prothrombotic alterations of the dysfunctional endothelium are accountable for the coagulation abnormalities reported in many ARDs, including AD. Coagulation assays on AD patient plasma revealed a prolonged activated partial thromboplastin time (aPTT), resulting in impaired clot formation rate and cerebral microbleeds. Notably, these abnormalities were more pronounced in younger AD patients and were related to MMSE score and neurodegeneration, assessed by the means of cerebrospinal fluid NF-L levels (Suidan et al., 2018). On the other hand, a number of studies highlighted the enhanced prothrombotic state of AD patients. Higher plasma levels of activated factor VII (Gupta et al., 2005), von Willebrand factor (Wolters et al., 2018), and plasminogen activator inhibitor-1 (PAI-1) (Oh et al., 2014) were found in AD patients. Moreover, increased D-dimer (Stott et al., 2010) and factor V Leiden (Bots et al., 1998) are both associated with an increased risk of developing dementia. AD is accompanied by local fibrinolysis disturbances that are believed to be related to the presence of Aβ in fibrin clots, which interferes with the binding of plasminogen (Cortes-Canteli et al., 2010).

6. The connection between frailty, comorbidity, and vascular aging in Alzheimer's disease

Frailty is a complex clinical syndrome encompassing functional decline in multiple physiologic systems that ultimately results in the impaired ability to cope with environmental stressors (Chen et al., 2014). Multiple attempts have been conducted to develop a set of clear diagnostic criteria for frailty. On one hand, Fried et al. defined frailty as

the presence of three out of five of the following criteria: unintentional weight loss, self-reported exhaustion, weakness, slowness, and low physical activity (Fried et al., 2001). On the other hand, Rockwood and Mitnitski considered frailty as related to the accumulation of age- or disease-associated deficits involving multiple systems or functional domains, which increase the likelihood of an individual of being frail (Rockwood and Mitnitski, 2007). Frailty prevalence is higher in women, increases with age, and is associated with a number of socio-economic factors. The presence of frailty determines specific health care needs and can affect the prognosis of the associated comorbidities (Kojima et al., 2019).

Frailty is often accompanied by comorbidity, i.e. the occurrence of two or more manifest diseases in the same individual. However, these two conditions need to be considered as distinct entities, even if there is a complex interaction between them in determining the risk of developing disability. Indeed, the biological mechanisms determining frailty, including inflammaging, can themselves promote the development of chronic diseases, which in turn may worsen frailty and determine the occurrence of disability. Multiple evidence showed that subjects with frailty carry specific alterations in circulating biomarkers, including CRP, pro-inflammatory cytokines, and coagulation parameters, even after adjustment for the presence of CV comorbidities (Walston et al., 2002).

Epidemiological studies have been conducted to establish a bidirectional connection between conditions associated with dementia, including AD, and physical frailty. The results point out that a clear interaction exists between physical frailty and the risk of incipient dementia, but evidence becomes conflicting when trying to extend this connection to the major determinants of frailty, including CV diseases. The Italian Longitudinal Study of Aging reported frailty as a short-term risk factor for all-cause and vascular dementia. However, while the Charlson comorbidity index significantly differed between the subjects who did or did not develop dementia, the prevalence of the main CVDs, except for stroke, was the same across the two groups (Solfrizzi et al., 2013). The Danish Centenarian Study, a population-based survey on 276 centenarians, revealed that almost half of the subjects with dementia had cerebrovascular lesions, even if no difference was reported in comparison to non-demented participants (Andersen-Ranberg et al., 2001). Notably, the 90+ Study revealed that the relative weight of cerebrovascular lesions is lower in the oldest old subjects, i.e. those who underwent successful aging, compared to nonagenarians (Legdeur et al., 2019). A prospective study on a large cohort of elderly subjects demonstrated that the presence of frailty associated with cognitive impairment determines a greater risk of developing AD and MCI compared to cognitive impairment alone, pointing out the crucial need of assessing physical frailty beyond cognitive impairment when evaluating the risk of dementia (Shimada et al., 2018). A recent meta-analysis of studies assessing dementia as a primary or secondary outcome confirmed that older adults with frailty are at higher risk of developing cognitive disorders compared to their non-frail counterparts (Borges et al., 2019). Similar findings were reported also for subjective cognitive decline, which is associated with AD pathologic changes and brain volume shrinkage (Gifford et al., 2019), and for dementia with Lewy bodies, characterized by a higher burden of frailty compared to AD (Borda et al., 2019).

These observations prompted the assessment of multidimensional interventions as tools to reduce the burden of physical and/or cognitive frailty. Worth mentioning is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) assessing the effects of an intervention program focused on four domains, i.e. nutrition, exercise, cognitive training, and CV risk factor management, on cognitive performance in 1'260 at-risk individuals aged 60–77 years (Rosenberg et al., 2018). The 24-month intervention proved beneficial regardless of the participants' clinical and demographical characteristics, paving the way for a worldwide initiative encompassing a number of clinical trials designed along the lines of the original FINGER trials, namely the worldwide FINGER (WW-FINGERS) initiative (Kivipelto et al., 2020).

Cardiovascular diseases are among the most investigated determinants of frailty and of the fragilization rate. Evidence from longitudinal studies support the role of CVDs, including diabetes, coronary heart disease, and atrial fibrillation, as predictors of incipient dementia and causative factors for AD (de Bruijn and Ikram, 2014; Rosa et al., 2020). A frailty index composed of non-traditional risk factors for AD, including heart disease, hypertension, history of stroke, diabetes, and impairment of renal function, discriminated patients with AD or dementia from non-cognitively impaired patients (Song et al., 2011). In middle-aged individuals, hypertension acts as an independent predictor of advanced age dementia (Suri et al., 2019). The association becomes non-significant after the age of 80, when low diastolic blood pressure, mainly due to arteriosclerosis, is associated with cognitive impairment (Qiu et al., 2009).

AD shares a common substrate of vascular dysfunction and metabolic derangements with type 2 diabetes (T2DM) (Boccardi et al., 2019). Insulin resistance has been demonstrated to induce neuroinflammation, lipotoxicity, and oxidative stress in the CNS, along with neuronal cell death and impairment of neuronal plasticity (Tsalamandris et al., 2019). T2DM is associated with an increased risk of cerebrovascular disease, which is related to persistent endothelial dysfunction and prothrombotic state (Schneider et al., 2017). Repeated subclinical ischemic events (Ma et al., 2018), neuroinflammation promoted by the increased concentration of pro-inflammatory cytokines (Maldonado-Ruiz et al., 2017), and the non-enzymatic glycation of Aβ and tau proteins (Batkulwar et al., 2018) are considered as the main pathophysiological events linking T2DM to the development of AD.

The relationship between frailty and CV health is evident also at the subclinical stage. A longitudinal study on an old population showed that endothelial dysfunction, evaluated by the levels of asymmetric dimethylarginine – an inhibitor of the endothelial nitric oxide synthase – is associated with the frailty status (Alonso-Bouzon et al., 2014). The risk of incident dementia is also related to imaging markers of large vessel disease, including intima-media thickness (IMT) (Silvestrini et al., 2009), carotid plaque scores (Wang et al., 2017), and arterial calcification assessed by CT (Goluke et al., 2020). These associations may underlie common pathogenic mechanisms acting also at the small artery level or represent the expression of chronic cerebral hypoperfusion.

The identification of different disease trajectories in subjects with dementia poses specific challenges related to the development of new treatment strategies, or repurposing of the already available ones, in order to postpone or even reverse frailty and AD-associated comorbidities.

An emerging area of clinical research involves the effects of currently available pharmacological treatments for AD on CV outcomes. Acetylcholinesterase inhibitors (AChEIs), which were developed as symptomatic treatments for AD, are being explored for their potential to delay cognitive decline in AD patients (Kim et al., 2017). Notably, due to their cholinergic activity, these drugs can impact on cardiovascular function and therefore be responsible for a number of cardiac side effects, mainly bradycardia and QTc prolongation (Malone and Lindesay, 2007). A large meta-analysis on >250′000 subjects with dementia revealed that the use of AChEIs is associated with bradycardia and hypertension, but with a 37 % lower risk of CV events (Isik et al., 2018). Evidence available so far point out possible pleiotropic roles for these drugs beyond the cardioprotective role related to increased parasympathetic activity. Indeed, AChEIs exert positive effects on anti-inflammatory pathways, NO signaling, mitochondrial biogenesis, and calcium regulation (He et al., 2015).

The SPRINT-MIND study highlighted the importance of intensive blood pressure control to improve cognitive function. Interestingly, blood pressure control reduced the incidence of MCI and slowed down the progression from MCI to overt dementia, without reducing the risk of developing dementia at the later age (Group et al., 2019). Similar

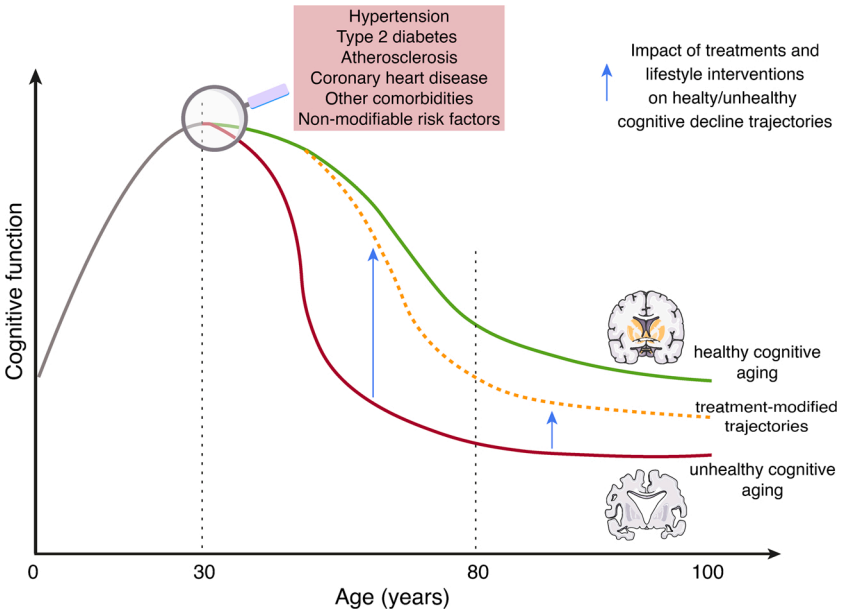


Fig. 2. The effect of vascular aging on the age-related trajectory of cognitive decline. The trajectory of the age-related cognitive decline depends upon genetic, environmental, and stochastics factors, many of which are accountable for the progression of endothelial disfunction and the onset of cardiovascular diseases. The gap between healthy and unhealthy cognitive decline trajectories is wider in the middle-aged and in the elderly individuals aged <80 years. In these subjects, drug and lifestyle interventions have been shown to exert the most beneficial effects on cognitive function. Parts of the figure were provided by Servier Medical Art (https://smart.servier.com).

findings came from the Rotterdam study, showing a 8 % reduction in risk for dementia per year of antihypertensive treatment before the age of 75, with no effects after this age threshold (Haag et al., 2009).

Most data from randomized clinical trials (RCTs) and observational studies revealed that adequate glycemic control exerts favorable effects on cognitive function. Pleiotropic neuroprotective effects have been demonstrated for all the available glucose-lowering agents with mechanisms involving many of the aforementioned features of vascular aging, including cellular senescence, neuroinflammation, and oxidative stress. Clinical data are available so far for insulin (Craft et al., 2012), metformin (Koenig et al., 2017), thiazolidinediones (Sato et al., 2011), and GLP-1 agonists (Gejl et al., 2017), and convincing evidence on sodium-glucose cotransporter 2 inhibitors (Hierro-Bujalance et al., 2020) and dipeptidyl-peptidase IV inhibitors (Kosaraju et al., 2017) are emerging from animal studies. A meta-analysis of 40 studies revealed a negative relationship between HbA1c levels and working memory/executive function (Mansur et al., 2018), and a similar association was reported for cognitive performance (Mimenza-Alvarado et al., 2020). On the other hand, RCTs assessing the impact of different degrees of glycemic control on cognitive function showed variable outcomes. Indeed, the ACCORD-MIND trial showed a greater brain volume in the intensive treatment arm compared to the standard treatment group, but not differences in cognitive performance between groups (Launer et al., 2011). Similarly, a prospective study on patients with T2DM revealed that cognitive decline was not related to HbA1c levels (van den Berg et al., 2010). Overall, the interaction between glucose control and cognitive decline is far from linear and possibly influenced by other factors, including patient's age, lifestyle, and presence of T2DM complications, such as diabetic neuropathy. However, it is conceivable that slowing down the age-related cognitive decline may improve patient's adherence to glucose-lowering therapies and self-awareness of functional impairments associated with T2DM complications (Biessels and Whitmer, 2020).

These results emphasize the relevance of modulating ARD trajectories at their earliest stages, when therapeutic interventions aimed at delaying or ameliorating cognitive impairment were proven to exert the most notable effects (Fig. 2).

7. Conclusions and future perspectives

Disentangling the multifactorial causes of vascular aging can be considered a critical step to delay the development of the most common ARDs, including neurodegenerative diseases. The important interactions between AD and vascular diseases, both common among older people, are highlighted by the findings that vascular risk factors and small-vessel disease are independent risk and predisposing factors for the clinical presentation of AD. The molecular research connecting the mechanisms of aging and vascular function is rapidly evolving, but many questions need to be addressed. New and expanding research on the molecular mechanisms of vascular aging, including inflammaging, may bring new therapeutic options for neurodegenerative diseases.

In addition, epidemiological efforts should be directed towards the stratification of middle-aged individuals according to the presence of CV risk factors, comorbidity, and outcome measures related to frailty and disability to allow for the early identification of unhealthy aging trajectories. In this setting, lifestyle interventions such as nutrition, physical activity, and prevention of obesity could be important for the prevention of vascular aging and cognitive decline.

Funding

This work was supported by the Italian Ministry of Health ["Ricerca Finalizzata" grant, year 2018, project RF-2018-12368164, to L.S. and F. O.].

Declaration of Competing Interest

The authors report no declarations of interest.

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