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SECONDARY HYPERTENSION: NERVOUS SYSTEM MECHANISMS (M WYSS, SECTION EDITOR)

Hypertension and Age-Related Cognitive Impairment: Common Risk Factors and a Role for Precision Aging

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Abstract

Purpose of Review *Precision Aging*® is a novel concept that we have recently employed to describe how the model of precision medicine can be used to understand and define the multivariate risks that drive age-related cognitive impairment (ARCI). Hypertension and cardiovascular disease are key risk factors for both brain function and cognitive aging. In this review, we will discuss the common mechanisms underlying the risk factors for both hypertension and ARCI and how the convergence of these mechanisms may be amplified in an individual to drive changes in brain health and accelerate cognitive decline.

Recent Findings Currently, our cognitive health span does not match our life span. Age-related cognitive impairment and preventing and treating ARCI will require an in-depth understanding of the interrelated risk factors, including individual genetic profiles, that affect brain health and brain aging. Hypertension and cardiovascular disease are important risk factors for ARCI. And, many of the risk factors for developing hypertension, such as diabetes, smoking, stress, viral infection, and age, are shared with the development of ARCI. We must first understand the mechanisms common to the converging risk factors in hypertension and ARCI and then design person-specific therapies to optimize individual brain health.

Summary The understanding of the convergence of shared risk factors between hypertension and ARCI is required to develop individualized interventions to optimize brain health across the life span. We will conclude with a discussion of possible steps that may be taken to decrease ARCI and optimize an individual's cognitive life span.

Keywords Cognitive aging · Hypertension · Risk factors · COVID-19 · Precision aging

Introduction

Precision Aging® is the application of precision medicine to the identification of the individual risk profiles and genetic characteristics that link cognitive health span to life span. While there are many risk categories that affect brain and cognitive health, the effects of hypertension and cardiovascular disease on the development of age-related cognitive impairment (ARCI) and progression to Alzheimer's disease (AD) and AD-related dementias (ADRD) are well supported and have been recently reviewed [1•]. Importantly, many of the identified risk factors for the development of hypertension and cardiovascular disease are common to those identified for ARCI, AD, and ADRD [2••].

Previously, we have identified key drivers of brain health and disease that can be altered by the risk factors for ARCI [2••]. These drivers include brain inflammation [3, 4], compromised brain blood flow [5], increased neuropathology [6], and detrimental changes in synaptic function and synaptic connectivity [7]. Each of these drivers can be affected by known risk factors that ultimately accumulate and interact to alter neuronal function and cognition. The ultimate prevention and treatment of ARCI will require in-depth mechanistic

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understanding of how these common risk factors and risk categories interact to alter these drivers of brain health and disease.

According to the US Centers for Disease Control and Prevention and the American Heart Association [8, 9], key risk factors associated with the development of high blood pressure and secondary hypertension include chronic inflammatory diseases such as diabetes and obesity as well as environmental conditions such as high stress and smoking. An additional recent risk is contracting the SARS-COV-2 virus and complications from COVID-19 which include activation of cytokine release syndrome (CRS) which is known to result in the release of proinflammatory cytokines from macrophages and endothelial cells leading to extensive lung, heart, and vascular injury [10–12]. These risk factors are compounded by individual genetic profiles and age to increase the risk for developing hypertension. In turn, hypertension, in combination with the above listed risk factors, also results in an increased risk for cardiovascular disease and stroke [13].

Vascular contributions to cognitive impairment and dementia (VCID), AD, and ADRD significantly contribute to the 47 million people worldwide who suffer with dementia [14]. In addition, in the 87% of people over 65 years of age who are not demented [15], many of these individuals will experience ARCI that directly affects their quality of life and independence. This number is estimated to increase to over 130 million people by 2050. A number of studies have shown that risk factors for ARCI, VCID, and conversion to AD include hypertension, cardiovascular disease, diabetes, smoking, systemic inflammation, and stress [4, 16–22].

According to a 2017 report from the Alzheimer's Association [23], the cost of Alzheimer's disease (AD) and ADRD to the healthcare system is staggering with recent estimates for both paid and unpaid care costs for people in the USA by 2050 to exceed $1.1 trillion dollars. In addition to AD and ADRD, many older adults will also acquire age-related cognitive impairment (ARCI) that results in decreased quality of life, loss of independence, and productivity. The National Institute on Aging (NIA) has created a *National Plan to Address Alzheimer's Disease* in response to the 2011 National Alzheimer's Project Act. A key goal of the National Plan is to prevent and effectively treat Alzheimer's disease and ARCI by 2025. The 2019 update of this plan includes expanded support for research to identify the molecular and cellular mechanisms underlying the development of ARCI and ADRD. This review will provide an overview of the current understanding of the some of the shared molecular and cellular pathological mechanisms underlying specific risk categories common to both hypertension and ARCI including diabetes, smoking, stress, SARS-COV-2 infection, and age and how these common mechanism may be integrated, using a *Precision Aging*® model, to understand and affect the drivers of brain health and disease (Fig. 1).

Diabetes: a Key Risk Category for both Hypertension and Cognitive Dysfunction

Hypertension and type 2 diabetes (T2D) are often found in the same person, and there is considerable overlap in the etiology and disease mechanisms between hypertension and diabetes. Hypertension is found in nearly 30% of the adult population in the USA [24] and is present in over 78% of persons with diabetes [25]. In the Multi-Ethnic Study of Atherosclerosis (MESA) in over 3500 participants who were not hypertensive, those with diabetes and higher resting blood glucose levels were more likely to develop hypertension over the 4.7 years of the study [26]. In the USA, individuals with T2D are 2.5 times more likely to develop high blood pressure [27]. Likewise, a number of studies have shown that the presence of high blood pressure is an independent risk factor for the development of new-onset diabetes [6, 28]. In a study using meta-analysis from 4.1 million adults, individuals with a 20 mmHg higher systolic blood pressure had a 52% increase in developing diabetes [6].

The cellular and molecular mechanisms shared between hypertension and T2D include insulin resistance, increased activation of the renin-angiotensin-aldosterone system (RAAS), oxidative stress, and endothelial dysfunction [29, 30]. Insulin resistance and its associated hyperinsulinemia increases oxidative stress and reactive oxygen species (ROS) production via NADPH oxidase imbalance, which increases metabolic flux of the polyol (sorbitol) pathway and increases production of advanced glycation end products (AGE), acti133vation of protein kinase C, and others [31–33]. Likewise, increased RAAS activation, a well-known contributor to hypertension [34, 35], increases sympathetic outflow and increases vascular ROS and contributes to endothelial cell senescence, vascular aging [36••], and high blood pressure [30, 37, 38].

Sex differences in the role of diabetes in the development of hypertension and cardiovascular disease have been studied extensively over the last few decades [39], [40–43]. While both men and women exhibit age-related increases in blood pressure, premenopausal women have a lower incidence of hypertension than age-matched men [44, 45]. After the age of 55, hypertension incidence in women markedly increases with nearly 70% of women over 65 being diagnosed with hypertension in the USA [41]. In premenopausal women, it is thought that the presence of ovarian hormones affords protection to women against the development of cardiovascular disease and hypertension [46, 47]. The mechanisms underlying ovarian hormone protection have been suggested to include estradiol-induced increases in vascular endothelial nitric oxide production and vasodilation [48], improvement in endothelial function [49], and, in the case of hypertension, estrogen-induced central inhibition of sympathetic outflow [50, 51]. Importantly, this lower risk of hypertension in women under 55 is lost in the presence of T2D [43, 49, 52]. While

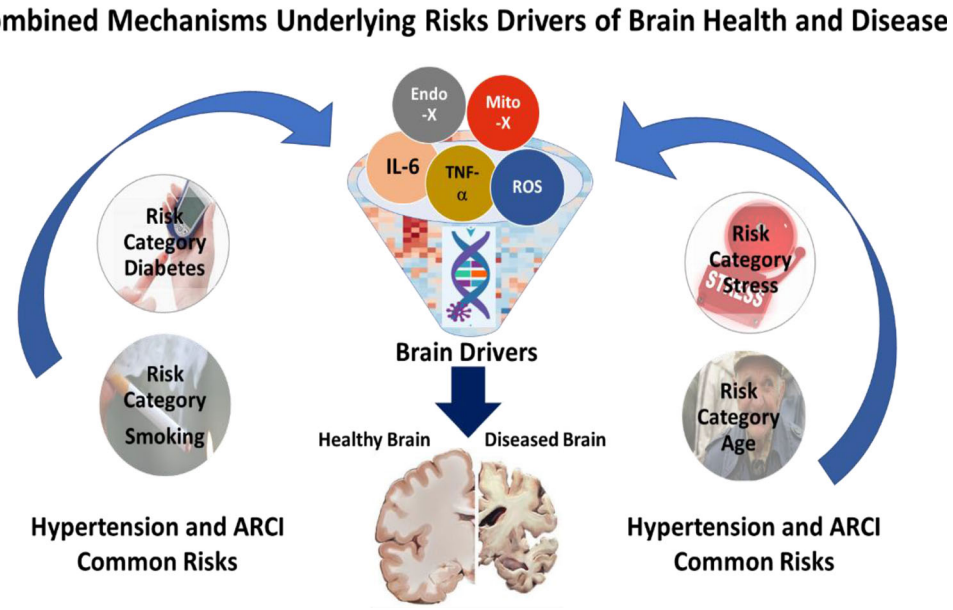


Fig. 1 Illustration of how the shared risk categories between hypertension and age-related cognitive impairment and some of their common mechanisms including inflammatory cytokines (e.g., IL6, TNFa), oxidative stress (ROS), mitochondria dysfunction (Mito-X), and endothelial cell dysfunction (Endo-X) are combined with an individual's genetic profile to result in a specific, *Precision Aging*® predicted, brain health profile (some images are derived and attributed to Creative Commons CCBY 4.0)

the specific mechanisms underlying why premenopausal women lose their protection in the presence of T2D, it has been suggested that the T2D-induced endothelial dysfunction overrides any protective effects of ovarian hormones [49].

Adults with T2D also have an increased risk of ARCI and ADRD [53–55]. There have been a number of studies that have shown and increased risk of mild cognitive impairment (MCI) in patients with diabetes with a high risk of conversion from MCI to dementia [56–58]. In a meta-analysis study, it has been shown that T2D is significantly associated with 56% increase of AD and 127% increase of VCID in diabetes patients [59]. Additionally, in a longitudinal study of 918 individuals over the age of 65 who were cognitively normal at baseline, following an 18-month follow-up, it was found that the risk of MCI attributable to diabetes was 8.8% for the whole entire sample [56]. Similarly, data from the English Longitudinal Study of Ageing (ELSA) investigated the association between HbA_{1c} levels and subsequent cognitive decline in 5189 participants over 50 years of age. This study reported that baseline HbA_{1c} levels were significantly associated with global cognitive, memory, and executive function, and over the 10 years of this study, a 1 mmol/mol increment in HbA_{1c} was significantly related to an increased rate of decline in global cognitive scores [60].

Many of the same cellular and molecular mechanisms that link diabetes to hypertension have also been implicated in the link between T2D and ARCI and ADRD [61]. Diabetes-induced hyperglycemia results in endothelial cell dysfunction and critically affects the integrity of the blood-brain barrier resulting in increased astrocyte metabolism and ROS production [62]. The increased ROS production stimulates a feed-forward cytokine cascade resulting in increased production of proinflammatory cytokines, microglia activation, and ultimately neuronal damage [63]. Hyperglycemia and resultant increases in ROS within the brain also result in neuronal mitochondrial dysfunction and increase in mitochondria oxidative stress [64, 65]. The neuronal mitochondrial stress results in further increases in inflammatory cascades including increases in TNFα, IL-1B, IL-6, and IL-8 [66]. Thus, diabetes-induced increases in brain ROS and inflammation are linked to changes in cognition and ARCI.

In summary, common cellular mechanisms underlying the risk factor of diabetes on hypertension and ARCI include increased systemic and central chronic inflammation including increases in systemic and brain levels of:

TNFα	Metabolic imbalance
IL-6	Endothelial dysfunction
ROS	Mitochondrial stress

Smoking: Common Mechanisms with Hypertension and Brain Health

Smoking of tobacco cigarettes and other tobacco products and their effects on blood pressure are the result of acute and chronic exposure of chemical factors and particulate matter found in tobacco. It has been known for decades that inhalation of tobacco smoke results in direct activation of sympathetic nerve activity in humans and increases catecholamine release from adrenergic nerve terminals [67–69]. In addition, long-term exposure to tobacco smoke alters autonomic nervous system control of blood pressure and attenuates the baroreceptor reflex, thus allowing for unrestrained increase in sympathetic activation by cigarette smoke [69]. Long-term use of tobacco cigarettes is also known to stimulate lung

afferent C-fibers via inflammation-induced activation of transient receptor potential (TRP) channels which in turn increase cardiac sympathetic activity [70, 71].

Tobacco smoking also is known to result in endothelial dysfunction and decrease flow-mediated dilation and increase inflammation and oxidative stress [72–74]. The endothelial dysfunction is thought to be related to tobacco smoke that induced increased in mitochondrial oxidative stress [75] and inhibition of mitochondrial respiration [76]. In recent study in mice, exposure to cigarette smoke impaired endothelium-dependent vasodilation, increased superoxide production, induced SOD2 hyperacetylation, and reduced expression of endothelial nitric oxide [75]. It is thought that these combined cellular effects of tobacco smoke together contribute to endothelial oxidative stress that impaired blood vessel relaxation and high blood pressure. Smoking is also known to result in increases in chronic inflammation in the vasculature and increases in cell adhesion molecules both of which increase risk of hypertension and cardiovascular disease [77]. Increases in levels of IL-6 and soluble ICAM-1 and MCP-1 have consistently been shown to be significantly associated with tobacco smoking [78–82]. Smokers in the Framingham Heart Study had soluble ICAM-1 levels 25% higher than nonsmokers [83].

The effects of chronic tobacco smoking on cognitive function have been examined in a number of studies with most showing a clear relationship between current smoking and cognitive function [84–87]. In a study of 5705 participants from the Rotterdam study, the relationship between smoking and cognitive function was examined over a 5.5 year period [88]. These investigators reported that smoking is related to a decline in global cognition among older adults In a review by Durazzo and colleagues [89] of large nonindustry-related cohort studies, the generally accepted conclusion is that long-term smoking results in an approximately 70% increased risk for developing Alzheimer's disease.

In addition to the cardiovascular/pulmonary effects of smoking, there are studies suggesting that the cellular mechanisms that are involved in chronic smoking effects on heart, blood vessel, and lung damage are also involved in the deleterious effects on brain function and cognition [90]. In studies of younger adults with no overt other diseases, smoking has been shown to decrease performance in measures of executive function, learning and memory, attention, and processing speed [91]. A number of studies have shown that long-term cigarette smoking is significantly associated with decreases in gray and white matter volume and density [92, 93], as measured by magnetic resonance imaging (MRI). In a longitudinal study of 1451 persons over 60 years of age, MRI was used to examine the effects of smoking on hippocampal volume and morphology [94]. In this study, both men and women smokers showed larger rates of hippocampal atrophy as compared with age-matched nonsmokers suggesting that smoking is a major factor in brain aging.

The cellular mechanisms underlying smoking-related morphological brain changes and related cognitive decline include decreases in protective antioxidants [95, 96],increased brain levels oxidative stress [89], and increased inflammatory cytokines and chemokines all of which affect brain health and disease [2]. In a study of older adult smokers with normal cognition, smoking was found to be significantly associated with increases in cerebrospinal fluid levels of F2-isoprostane, a known biomarker of oxidative stress.

Thus, common cellular mechanisms of the risk factor of smoking on both hypertension and ARCI include increased oxidative stress and increased circulating and brain inflammatory cytokines including:

IL-6	ICAM-1
TNFα	MCP-1
ROS	Endothelial dysfunction

Chronic Stress: Common Mechanisms in Hypertension and Brain Health

Stress is generally thought to encompass the physiological and emotional responses to various types of either external or internal stimuli [97]. These stimuli can be short-term representing acute stressors or long-term, cumulative stressors representing chronic stress. Chronic stressors can include work-related stress, social isolation, socioeconomic stress as well as physical stress including physical, psychological, or traumatic injury or exposure to biological, chemical, or radiological hazards. The presence of chronic toxic stress from which an individual is unable to adapt to or overcome contributes to the cumulative physiological dysregulation and ultimate decline of multiple physiological systems including cardiovascular function, glucose regulation, and neurological functions [98, 99].

Chronic stress is a major risk factor for the development of hypertension [100] and related cardiovascular disease [101, 102]. With regard to blood pressure, both acute and chronic stress are known to activate the sympathetic nervous system to release norepinephrine from sympathetic nerve terminal that cause vasoconstriction and activate the hypothalamic-pituitary-adrenal axis (HPA). Activation of the HPA results in the release of corticotrophin-releasing factor (CRF) from neurons in the paraventricular nucleus which, in turn, results in an increase in adrenocorticotropic hormone (ACTH) release from the anterior pituitary as well as release of catecholamines and glucocorticoids from the adrenal gland and release of the mineralocorticoid aldosterone [40]. Continuous activation of the HPA axis results in long-term damage to blood vessel endothelial cells due to sustained sheer stress. Such damage results in increased endothelial cell production of

inflammatory cytokines such as IL-6, C-reactive protein (CRP), IL-8, PAI-1 [103, 104], and ROS leading to alterations in vascular tone, vascular remodeling, and the development of atherosclerosis [105–107].

The effects of stress and elevated glucocorticoids on brain health were recently reviewed [108•], [109] and have been studied extensively over the last four decades beginning with the seminal paper out of Bruce McEwen's lab showing binding of corticosterone in the hippocampus [110]. Animal studies in rodents have shown that exposure to prolonged, elevated glucocorticoids impairs learning and memory [111], increases neuronal loss in the hippocampus, and decreases neurogenesis in the dentate gyrus [111]. Studies in humans have confirmed that elevated corticosteroids are inversely associated with memory impairments and decreases in hippocampal volume [112]. The mechanism underlying the cognitive effects of prolonged stress and elevated glucocorticoids is thought to be related to their actions on brain cytoplasmic glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs). Upon ligand activation, these receptors undergo conformational changes resulting in nuclear translocation and activation of glucocorticoid response elements that in turn modify gene expression [113]. The role of GRs and MRs on long-term memory formation and information retrieval involves modulation of hippocampus glutamate neurotransmission, MAPK signaling pathways, CREB phosphorylation, and phosphorylation of synaptic proteins [114]. In some studies, mild acute stress-induced increase in GR activation has been shown to facilitate long-term memory consolidation and is dependent on the temporal relationship between stress events and learning [115]. However, other studies have shown that high levels of psychological stress or high doses of cortisol lead to impairment of learning and memory tasks [116]. This suggests that the relationship between memory performance of complex cognitive tasks to stress is an inverted U-type relationship [117] with the ideal stress/memory relationship found at the peak of the U-type curve decreasing upon continuation of high chronic stress.

In summary, the cellular mechanisms underlying chronic stress effects on both hypertension and cognitive function include increased endothelial cell production of inflammatory cytokines such as:

IL-6	PAI-1
CRP	ROS
IL-8	Mitochondrial dysfunction

COVID-19: Common Mechanisms with Hypertension and Brain Health

Recent studies have shown that high blood pressure is the most common comorbidity observed in COVID-19 patients and COVID-19 patients with hypertension have significantly worse disease and death rates vs non-hypertensive patients [11, 118–120]. In an early study out of China from data on nearly 2000 COVID-19 hospitalized patients, approximately 15% also exhibited hypertension [121]. In a second study of 1590 COVID-19 patients with a mean age of 49 years, 17% reported hypertension, and of these patients, 32% were likely to have severe COVID-19 disease compared with 12.6% non-hypertensives with severe disease [118]. Importantly, it is also known that age is the most common risk factor for both severe COVID-19 and hypertension. Initial studies out of China have shown that older adults are particularly susceptible to SARS-CoV-2 with individuals over 60 years of age accounting for 81% of the deaths in China [11]. The fatality rate in individuals increases with age with case-fatality rates (CFR) of 14.8% in patients over 80, 8.0% in patients between 70 and 79, and 3.6% in patients between 60 and 69 [11, 121].

The mechanisms underlying the relationship between hypertension and COVID-19 have been suggested to involve the SARS-CoV-2 virus binding to the angiotensin-converting enzyme 2 (ACE2) receptor. This enzyme ACE2 receptor is highly expressed in the kidney, endothelium, lung, brain, and heart and interacts with the spike protein(s) of SARS-COV-2 [122]. Thus, ACE2 is a functional receptor for SARS-COV-2 and serves as an entry point into epithelial and endothelial cells expressing ACE2, such as the mucosa of the respiratory and gastrointestinal tract, as well as vascular endothelial cells. Patients diagnosed with COVID-19 who are admitted into the hospital generally have pneumonia and abnormal chest imaging, and complications include acute respiratory failure, acute respiratory distress syndrome (ARDS), and acute myocardial injury. Recent reports suggest that ARDS appears to be a significant predictor of mortality and a COVID-19-induced "cytokine storm" is thought to be involved in morbidity and mortality [123]. Initial COVID-19-related published studies from Chen et al. reported out on the clinical and immunological characteristics of 41 patients diagnosed with COVID-19 in Wuhan, China [11]. In this study, the authors reported that all 41 patients had pneumonia and a common complication included ARDS (29%) and cardiac injury (12%). Both ICU and non-ICU patients showed increases in IL-6, IL-7, IL-8, IL-9, IL-10, TNFα, and VEGF as compared with healthy adults. In addition, patients requiring ICU admission had higher concentrations of GCSF, MCP1, MIP1A, and TNFα than did those not requiring ICU admission.

A number of laboratories across the world are working to develop treatment for COVID-19 and vaccines against SARS-COV-2. Many of these approaches involve developing blockers of the ACE2 virus binding site [122, 124–126].

However, while blockade of ACE2 has been shown to block entry of SARS viruses into cells [122], blockade of the ACE2 enzyme will also block the well-known anti-inflammatory tissue protective effects of ACE2 and its essential role in the generation of the protective peptide angiotensin 1–7 (Ang-(1–7). The ACE2 enzyme is a key regulator of lung, heart, vascular, kidney, and brain function and an important component of the well-known renin-angiotensin-system (RAS) [127]. It has become recognized that RAS involves two separate enzymatic pathways that provide a physiological counterbalance of two related peptides acting at distinct receptors. The well-described ACE-AngII-AT1R system is thought to be physiologically opposed and balanced by the ACE2-Ang-(1–7)-Mas system [128–130]. Functionally, these two separate enzymatic pathways of RAS are thought to be involved in balancing reactive oxygen species (ROS), nitric oxide (NO) production, and inflammation in peripheral tissues and in the brain [127, 131]. It has been suggested that a potential adjunct therapy for COVID-19 patients might be the replacement of Ang-(1–7) in COVID-19 patients with a Ang-(1–7) peptide memetic [35] that would be expected to decrease the inflammatory storm and rebalance the ACE2-Ang-(1–7)-Mas system and thereby lead to a decrease in mortality in severe COVID-19 patients.

There are similar risk factors between patients with severe COVID-19 and patients at risk for AD, ADRD, and VCID. These include age, inflammation, diabetes, hypertension, hypercholesterolemia, and pulmonary and cardiac disease [16–18, 132]. Early published reports out of China show evidence of neurological manifestations in COVID-19 patients [133]. In the 214 patients studied, neurological symptoms were sorted into three primary categories: (1) central nervous system (CNS) symptoms or diseases (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy), (2) peripheral nervous system (PNS) symptoms (hypogeusia, hyposmia, hypoplasia, and neuralgia), and (3) skeletal muscular symptoms. Severe disease patients (41.1%) possessed additional risk factors of hypertension (36.3%), fever, and cough, and 45.5% had neurological manifestations. It has been suggested that the CNS complications in COVID-19 may be due to ACE2 expression in the CNS and PNS [134] and the dissemination of SARS-CoV-2 virus either across the cribriform plate or through damaged cerebral vascular endothelial cells, thus leading the viral binding to ACE2 and subsequent budding and neuronal inflammation and damage [135].

In summary, some of the cellular mechanisms that are common to the effects of COVID-19 on both hypertension and cognitive function include increases in:

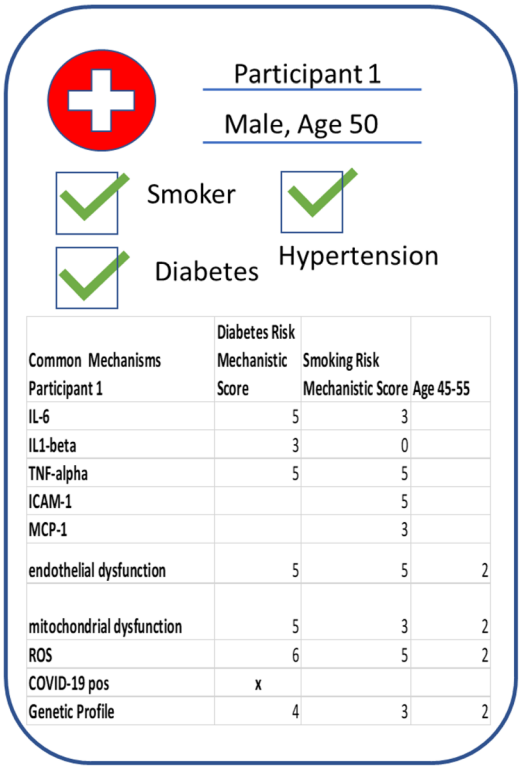
TNFα	MCP1
IL-6	ROS
GCSF	Endothelial dysfunction

Age: Common Mechanisms with Hypertension and Brain Health

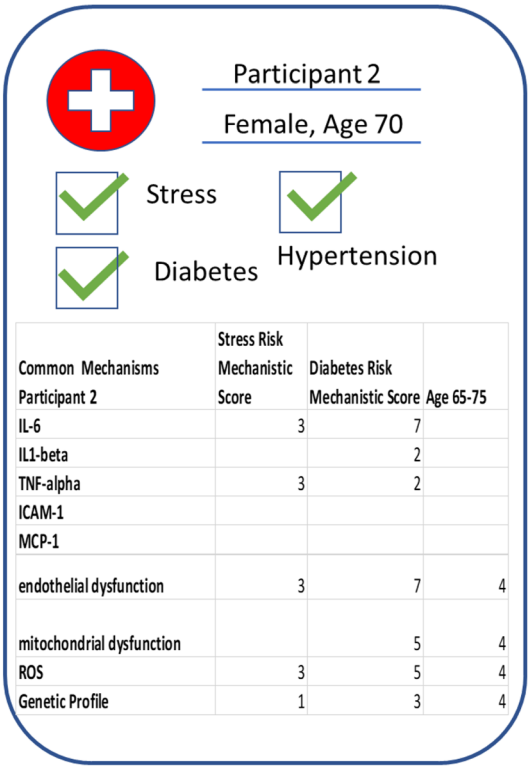
According to the American Heart Association, the risk for hypertension increases in increased age, and the prevalence of high blood pressure is 26% in persons between 20 and 44 compared with 78% among those greater than 65 years of age [136]. Vascular aging and related hypertension encompass progressive pathological remodeling of the vascular system resulting in decreased vascular wall elasticity, increased fibrosis, perivascular inflammation, and vascular calcification [137, 138]. The vascular endothelial cells, which are critical to vascular homeostasis and the regulation of vascular tone, are known to change with increasing age. The role of endothelial cell senescence in age-related vascular function has been recently covered in an excellent review out of the Sowers lab at the University of Missouri [36••]. Similar to other cell types, vascular endothelial cells (ECs) undergo changes with age, and the senescence of the ECs is known to occur when these cells stop dividing and undergo significant phenotypic changes including alterations in cytoskeletal structure, increased cell apoptosis, decreased nitric oxide release, and elevated inflammation [139]. The structural and functional changes that occur with vascular senescence lead to increased arterial stiffness and the loss of the ability of EC to induce vasorelaxation and ultimately an increased risk for hypertension, particularly systolic hypertension and cardiovascular disease [140].

The cellular mechanisms underlying EC senescence and loss of new EC are thought to include a number of mechanism that affect cellular growth and replication, and these include increases in oxidative stress and ROS [141]; increases in vascular inflammation; activation of NF-kappa B; and increases in IL-6, IL-8, TNF-alpha, and activated NLRP3 inflammasome [142, 143].

The common cellular mechanisms of hypertension and aging have been reviewed by Buford [144]. The described vascular health triad—chronic low-grade inflammation, chronic increases in oxidative stress, and hypertension—contributes together to create a feed-forward cascade of continual endothelial dysfunction which feeds the increases in inflammatory cytokines and reactive oxygen damage and chronic hypertension [145]. In addition to the age-related EC senescence and associated inflammatory cascades, age-related hypertension has also been linked to changes in insulin-like growth factor (IGF-1) and microvascular rarefaction [146]. Microvascular rarefaction is the reduction in the number of arteriolar and capillary networks that comprise the resistance vessels in the cerebral cortical vascular bed [147]. Microcirculatory rarefaction results in an increase in vascular resistance and decreases oxygen delivery, and in the brain, there is an increase in white matter lesions and loss of cerebral circulation autoregulation [148]. Decreases in microvascular density are significantly



Common Mechanisms Participant 1	Diabetes Risk Mechanistic Score	Smoking Risk Mechanistic Score	Age 45-55
IL-6	5	3	
IL1-beta	3	0	
TNF-alpha	5	5	
ICAM-1		5	
MCP-1		3	
endothelial dysfunction	5	5	2
mitochondrial dysfunction	5	3	2
ROS	6	5	2
COVID-19 pos	x		
Genetic Profile	4	3	2



Common Mechanisms Participant 2	Stress Risk Mechanistic Score	Diabetes Risk Mechanistic Score	Age 65-75
IL-6	3	7	
IL1-beta		2	
TNF-alpha	3	2	
ICAM-1			
MCP-1			
endothelial dysfunction	3	7	4
mitochondrial dysfunction		5	4
ROS	3	5	4
Genetic Profile	1	3	4

Fig. 2 An illustrative example for how the *Precision Aging*® approach might be used to derive an individual brain driver signature. Shown is the fictional data from 2 individuals with very different risk "report cards." Both have hypertension that is managed but have different additional risk factors that affect brain health. Due to the convergence of the underlying cellular mechanism that drives the risk categories of diabetes, smoking, stress, sex, and age, the combined scores for levels of IL-6, IL-1beta, TNA-alpha, ICAM-1, MCDP-1, ROS, endothelial dysfunction, and mitochondrial dysfunction can be measured and assigned a unique value for each individual in accordance with age, sex, and the extent of the concomitant disease (e.g., diabetes) and levels of risk exposure (e.g., years smoking or stress level)

associated with increased peripheral resistance and the onset of hypertension [149, 150]. Factors that are known to modulate vascular and endothelial growth and thus vascular rarefaction included vascular endothelial growth factor (VEGF), growth hormone (GH), and insulin-like growth factor-1 (IGF-1). With regard to endothelial cell function and hypertension, IGF-1 has been shown to promote EC cell function and capillary density [151], [36••], and an age-related decline in IGF-1 is significantly associated with an increased risk for hypertension [146, 152].

Age has long been known to be the primary risk factor for cognitive impairment. Age is a convenient proxy for a wide array of cellular and molecular mechanisms that underlie ARCI. These include mitochondrial dysfunction [153], oxidative stress and increased ROS production, decreased brain lysosomal function [154], decreased levels of synaptic proteins such as neuronal pentraxin 2 [155], and increased brain inflammation and microglia activation as well as changes in cerebral perfusion and brain oxygenation [156].

Changes in endothelial cell function and their role in brain blood flow autoregulation have been suggested to be involved in age-related changes in cognitive function [1]. In studies of cerebral blood flow using perfusion MRI and internal carotid ultrasound in individuals over 75 years of age, cerebral blood flow was found to be reduced in healthy older adults compared with healthy young adults (approximately 28 years of age), and decreases were significantly associated with increasing levels of cognitive dysfunction [157•]. These age-related changes in cerebral blood flow were also related to decreases in circulation of NO bioavailability.

The role of systemic and brain inflammation in aging and its effect on cognitive function have been the focus on many investigations and recent reviews [158], [159••]. In older subjects with chronic inflammatory diseases such as heart failure, increases in circulating levels of proinflammatory cytokines have been shown to result in decreases in cognitive function [160–162]. Increases in circulating levels of TNF-alpha, IL-6, and CRP have all been significantly associated with age-related memory impairment and executive function [132, 163–166].

In summary, some of the cellular mechanisms that are common to the effects of aging on both hypertension and cognitive function include increases in:

IL-6	Endothelial senescence
IL-8	Activated NLRP3 inflammasome
TNFα	Mitochondrial dysfunction

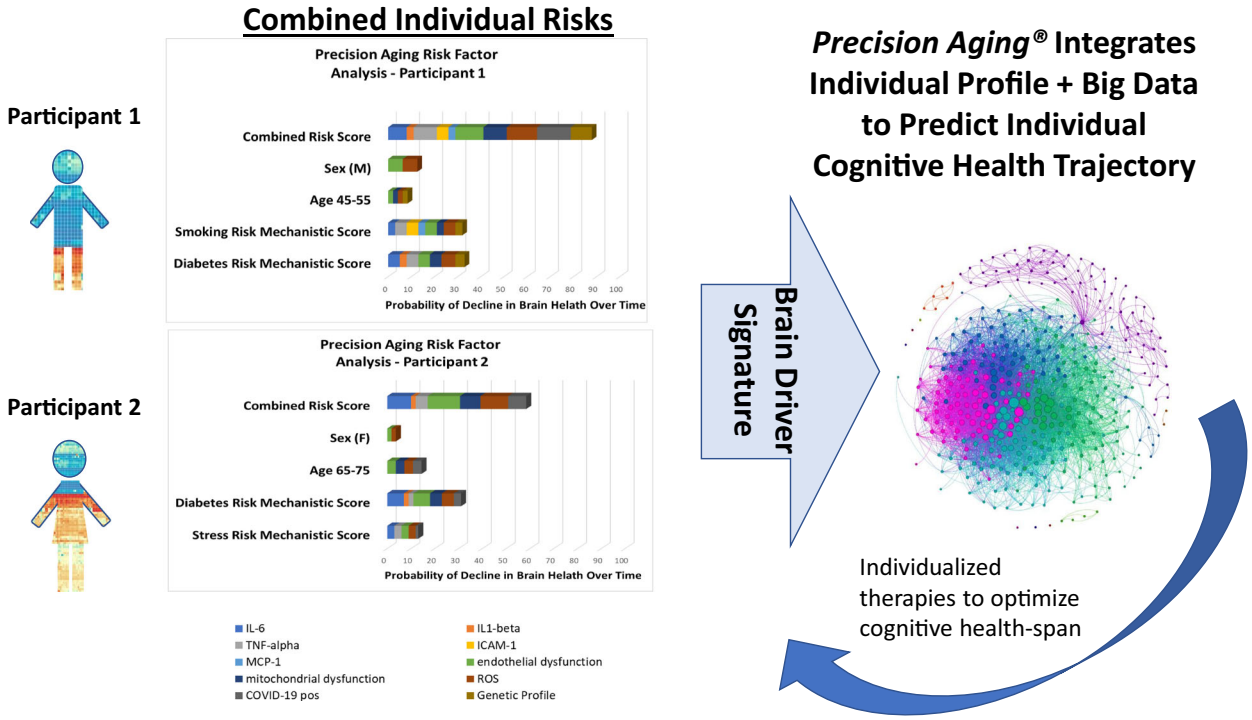


Fig. 3 Illustration of how the data from the risk factor report cards are combined to create an individualized brain driver signature. *Precision Aging*® then combines this individual profile risk score with large, big data sets to predict an individual cognitive health trajectory. Specific individualized interventions could then be created to optimize an individual's cognitive health span

Perspectives

The goal of matching one's cognitive health span to their life span requires detailed integration of data regarding an individual's specific risk factors and the underlying cellular and genetic mechanisms driving brain and cognitive health. It is clear that both hypertension and ARCI are influenced by similar risk factors and share mechanistic underpinnings. These mechanisms converge and are amplified to predict an individual's cognitive aging trajectory.

In order to design and ultimately prescribe individual interventions to optimize cognitive health span, we are informed by examples given by Precision Medicine and individualized cancer therapeutics. Precision Medicine, with regard to cancer, uses the genetic information in an individual's tumor to define the treatment path. With *Precision Aging*®, we suggest that one can use not only an individual's specific genetic risk profile for factors that contribute to cognitive aging but also risk profiles and combined cellular mechanistic scores related to factors such as smoking, diabetes, stress, age, and sex to establish an individualized brain health trajectory.

Figure 2 is an illustrative example of risk factor score report cards from 2 different participants. Mechanisms measured include IL-6, IL1-beta, TNF-alpha, ICAM-1, MCP-1, ROS, endothelial dysfunction, and mitochondrial dysfunction. Participant 1 is male and under 60 years of age with managed hypertension. But he is also a chronic smoker and has unmanaged diabetes and tested positive for COVID-19. His common mechanism scores and genetic profile scores are combined to create a total risk score. This can be compared with participant 2 who is female and 70 years of age who also has managed hypertension. Her common mechanism scores include scores for stress and managed diabetes that are combined to create a unique total risk score. Combined Risk Score is illustrated in Fig. 3.

As illustrated in Fig. 3, we can conceivably combine an individual's scores for each of the key cellular mechanism to create a "Combined Risk Score" that defines an individual's brain driver signature. *Precision Aging*® then compares this profile risk score with a large, normative database to predict an individual's cognitive health trajectory. Specific individualized interventions could then be created to optimize an individual's cognitive health span.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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