Chapter 5

Cardiovascular Disease and Neurocognitive Function

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Cardiovascular (CV) diseases are the leading cause of morbidity and mortality in the USA and most Westernized nations [1, 2]. CV risk factors and diseases confer substantial increase in risk for ischemic and hemorrhagic stroke [3]. Yet, outside the context of clinical stroke, the brain is an under-recognized target organ of a spectrum of CV diseases. Although it has long been known that CV risk factors and diseases contribute to the development of vascular (previously known as multi-infarct) dementia, we now know that similar risk is conferred for Alzheimer's disease (AD) [4].

Recent research suggests that the patterns of cognitive impairment associated with vascular dementia (VaD) and AD may not be as etiologically distinct as previously assumed [5, 6]. Indeed, it is likely that most dementia is "mixed," with involvement of both vascular and neurodegenerative pathology [7, 8]. Accordingly, mounting evidence indicates a number of common pathways through which CV risk and protective factors may impact the development of both CV diseases and these major forms of dementia [9–12]. The paths connecting CV risk factors and diseases with dementia are likely multifold. That is, CV risk factors and diseases may directly or indirectly impact dementia pathology or these disease entities may only share similar risk factors.

Importantly, long before clinical manifestations of stroke or dementia are apparent, CV risk factors and diseases negatively impact the brain and neurocognitive function. Consistent with Hachinski's formulation of vascular cognitive impairment and its gradual progression [13], we have proposed that there is a continuum of neurocognitive and neurobiological impairment associated with increasingly severe manifestations of CV disease that, in some individuals, ultimately leads to a dementia and/or stroke [14]. This is a process that occurs across the life span.

In this chapter, we provide a broad overview of current knowledge pertaining to the relation of CV risk factors and diseases to dementia, neurocognitive function, and the brain. Here we are seeking breadth, rather than depth, of coverage in order to highlight complexities with respect to the interrelations among the risk factors and diseases of interest. Whenever possible, we refer to more detailed available reviews. Although we acknowledge the presence of mixed findings in most areas reviewed, here we highlight positive associations for ease of presentation. We first briefly review classification of CV risk factors and diseases. Next, in our review of neurocognitive function we follow roughly the natural history of CV disease pathogenesis and its linked treatments. While reading this chapter, it is critical to bear in mind that CV risk factors and diseases tend to aggregate among affected individuals. Further, pathologic alterations in the CV system often co-occur with dysfunction of the metabolic, renal, immune, pulmonary, and other physiological systems. In each section we seek to address the following questions as per our suggested research agenda [15]: (a) What domains of cognitive function are affected? (b) What are relevant vulnerability or resilience factors? (c) What are the mechanisms underlying the noted relations?

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Cardiovascular Disease Classification

To help ensure standardization of disease reporting, epidemiologists and clinicians in the USA and elsewhere typically classify CV and other diseases based on the International Classification of Diseases (ICD) codes published by the World Health Organization [16]. CV disease is part of the broadly defined diseases of the circulatory system (ICD-10 I00–I99, Q20–Q28). Many studies use the definitions initially adopted by the Framingham Heart Study which define CV disease as comprised of (1) coronary heart disease (CHD) (coronary death, myocardial infarction (MI), coronary insufficiency, and angina); (2) cerebrovascular disease (ischemic stroke, hemorrhagic stroke, and transient ischemic attack); (3) peripheral artery disease; and (4) heart failure [17, 18].

Using the broad ICD-10 definition, it is estimated that >80 million Americans have one or more types of CV disease, 73 million with hypertension, 16 million with CHD, 5.3 million with heart failure, and 5.8 million with stroke [1]. In addition, there is growing recognition of the importance of subclinical CV disease as assessed by a variety of noninvasive techniques (see below). These numbers quoted for prevalent CHD, stroke, and heart failure severely understate the burden of CV disease in the older adult population because much of the disease is subclinical. For example, electron beam tomography, a noninvasive technique to detect subclinical coronary artery calcification, an indicator of atherosclerotic plaque burden and CHD, showed that 38% of older adults in the Cardiovascular Health Study without any history of clinical CV disease had extensive coronary artery calcification (score >400) and 71% had evidence of subclinical atherosclerotic disease by low ankle–arm blood pressure index (ABI), major abnormalities on resting ECG, or internal carotid intima–media thickening on carotid ultrasound [19].

Cardiovascular Risk Factors and Neurocognitive Function

Traditional biomedical CV risk factors are well recognized, including hypertension, dyslipidemia, obesity, insulin resistance, and glucose intolerance. Newer biomarkers include measures of inflammation and oxidative stress, renal function, and homocysteine. Increased CV risk is conferred by a host of behavioral or lifestyle factors that include smoking, excessive alcohol consumption, poor diet, and physical inactivity. Some of these associations are complex and potentially nonlinear. It is increasingly recognized that various psychosocial and psychophysiological factors may also play a role in increasing CV risk. Here we examine relations of these biomedical (both traditional and new), behavioral, psychosocial, and psychophysiological CV risk factors to the brain, cognitive function, and dementia. However, first we begin with a description of two genetic polymorphisms that may link CV risk and dementia.

Genetics

At least two genotypes are known to be common to both CV disease and dementia. An association between the apolipoprotein E (*APOE*) *ε4* allele and AD has been widely replicated in the literature [20], and the *APOE* genotype is also a risk factor for dyslipidemia, atherosclerosis, cardiac disease, and stroke [21]. The *APOE* genotype impacts CV risk largely through its role in the modulation of lipid transport. However, the mechanism(s) by which the *APOE* genotype is associated with AD remains unknown. The *APOE* genotype may lead to dementia indirectly via its effects on lipid metabolism and CV disease, but it is likely that other mechanisms operate as well. Possibilities include effects of the *APOE* genotype on beta-amyloid deposition and/or differential antioxidant properties of the various allele combinations [12]. The *APOE ε4* alleles have also been associated with lower levels of cognitive performance, cognitive decline, and changes in brain morphology prior to dementia [22]. Another gene of interest is *MEOX2*, a known cerebrovascular gene. At least one study has identified a relation between low expression of *MEOX2* and AD neuropathology [23].

Traditional Biomedical Risk Factors

To date, the most available literature addresses the relations of traditional biomedical CV risk factors to brain

and cognitive outcomes. Here we examine hypertension, lipids, obesity, and glucose-related variables.

Hypertension/Antihypertensives

Hypertension is defined as a systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥90 mmHg, taking antihypertensive medicine, or having been told at least twice by a physician or other health professional that one has hypertension [18]. Applying this definition, about one-third of adults have hypertension. More than 90% of those affected have primary or idiopathic hypertension. About 10% have secondary hypertension where there are underlying diseases (such as renovascular disease) that cause hypertension. There is also growing awareness of the health importance of "prehypertension" defined as untreated systolic BP of 120–139 mmHg or untreated diastolic BP of 80–89 mmHg (and not having been told on two occasions by a health professional that one has hypertension) [18]. It is estimated that 37.4% of the US population >20 years of age has prehypertension [1]. Prehypertension markedly increases the risk for the development of overt hypertension and CV disease.

Hypertension has a major impact on morbidity and mortality. It is estimated that hypertension is associated with 5 years reduced overall life expectancy [24]. Yet, awareness of hypertension and adequate treatment and BP control in known hypertensives remains inadequate. Data suggest that perhaps 40% of all hypertensives do not meet their BP goals with resistant or difficult-to-control systolic hypertension being more common in older patients [25]. This is of major clinical importance as patients with poorly controlled hypertension are more likely to develop end-organ damage (e.g., heart failure, stroke, MI, and renal failure) and have a substantially higher long-term CV disease risk than patients with well-controlled BP.

It is well known that hypertension contributes significantly to the pathogenesis of stroke and VaD [1]. A growing literature links hypertension with AD as well [26, 27]. Evidence is strongest for a relation between midlife BP and development of AD, presumably due to the cumulative impact of long-standing hypertension [28]. In fact, several studies have suggested that midlife hypertension confers a similar degree of increased risk (approximately 3–4 times) for both VaD and AD [6, 29]. This heightened risk is thought to be primarily associated with hypertension's role in the pathogenesis of atherosclerosis [12].

Hypertension has been the most extensively studied of the traditional CV risk factors with respect to pre-stroke and pre-dementia cognitive performance (for review see [30]). The preponderance of early studies of the relation of BP to cognitive function contrasted the performance of those with diagnosed hypertension to persons with normal levels of BP (i.e., normotensives). Our review of those studies in 1991 suggested that hypertensives performed more poorly than normotensives particularly on tests of executive function, learning and memory, and attention [31]. More current case–control studies continue to document lowered levels of cognitive performance in hypertensives in age cohorts ranging from children to the elderly in these and other domains of function such as perceptuo-motor and motor performance and visuospatial abilities [32–34]. Moreover, indices of arterial stiffening, a major factor underlying BP elevation particularly in older adults, have been associated with lowered levels of cognitive function and prospective cognitive decline [35]. Recent work further suggests that the relation of BP to cognitive function is nonlinear and may be "J shaped" such that both high and low levels of BP are associated with lower levels of cognitive performance and cognitive decline [36–38].

Since 1993, a host of epidemiological investigations have shown that higher levels of BP are associated with lowered levels of cognitive function and cognitive decline [33]. The chronicity of lifetime exposure to high levels of BP is a particularly important determinant of poor prospective cognitive outcomes [39]. Further, higher BP at midlife predicts poorer cognitive performance during older age [40]. Although duration of hypertension is likely an important influence on cognitive outcome, this variable is notoriously difficult to capture adequately given that the disease may go undetected for lengthy periods of time [30].

A number of vulnerability and resilience factors may moderate associations of high (or low) blood pressure or hypertension to cognitive function and decline [30]. Vulnerability to the potential cognitive consequences of hypertension is most pronounced at younger ages [41], among those with lower levels of education [42], in women [43], among those with *APOE e4* alleles [44, 45], and in hyperinsulinemic,

diabetic, or obese persons [46–48]. The latter findings suggest that the cumulative impact of more than one CV risk factor may be multiplicative rather than additive. In addition, within hypertensives those with uncontrolled BP display the most pronounced cognitive difficulties [49, 50].

Various neurobiological mechanisms may underlie hypertension–cognition relations [30, 51]. These include neurophysiological factors such as reduced regional or global cerebral blood flow or metabolism, disruption of the blood–brain barrier, endothelial dysfunction, or other aspects of cellular dysfunction, all of which have been associated with hypertension. Neuroanatomical findings in hypertension include increased cerebral white matter disease, silent brain infarction, and brain atrophy, in addition to macrovascular disease.

Prospective investigations generally indicate better cognitive outcomes for those taking antihypertensive medication than untreated hypertensives [52]. Results of double-blind, placebo controlled trials of antihypertensives have yielded complex and conflicting findings [53] with similar numbers of studies suggesting positive, negative, or no impact. Our work and results of a recent meta-analysis suggest that whereas select measures of verbal memory appear to benefit from antihypertensive agents, measures of learning and perceptuo-motor speed may show decrement [54, 55].

Lipids/Statins

Dyslipidemia encompasses a range of disorders of lipoprotein lipid metabolism that include both abnormally high and low lipoprotein concentrations and abnormalities in the composition of these lipoprotein particles. Dyslipidemias are clinically important because of their role in the pathogenesis of CV disease. In clinical practice, a lipid or cholesterol panel commonly measures total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Higher levels of LDL-C promote atherosclerosis, whereas higher levels of HDL-C are in part protective against atherosclerosis. Higher levels of TG are associated with increased risk for atherosclerosis, but controversy remains as to whether elevated TG concentrations are independently causal in atherosclerosis. The consensus treatment guidelines [56] for the management of dyslipidemia are continually being reevaluated and these guidelines have made the target lipoprotein concentrations more stringent for individuals with CV disease.

Epidemiological and clinical trial data suggest that the optimal concentration for LDL-C may be <100 mg/dL or even as low as 70 mg/dL for some high-risk patients with known CHD. The optimal concentration for the protective HDL-C may be >60 mg/dL. Desirable levels for TG are below 150 mg/dL, and perhaps as low as 80 mg/dL. The initial therapy for dyslipidemia usually consists of therapeutic lifestyle interventions that include diets reduced in saturated fat and cholesterol and increased in fiber and complex carbohydrate content, weight loss, and regular aerobic exercise. In many patients with hyperlipidemia at risk for CHD, therapeutic lifestyle intervention does not effectively lower LDL-C to within the target range. Several classes of drugs are available to treat hyperlipidemia. Statins (HMG-CoA reductase inhibitors) are the most commonly used lipid-lowering agents. Other pharmacologic agents include fibrates, niacin, bile acid sequestrants (resins), and ezetimibe.

To date, relatively few studies have examined the relation between lipid levels and dementia [10, 12, 57]. This paucity is surprising, given the established role of the *APOE* genotype in lipid metabolism and its association with dementia [57]. Studies have demonstrated significant and nonsignificant relations of both high levels of total and LDL-C and low levels of HDL-C with increased risk of dementia [58–61]. Similar to hypertension, the evidence is strongest for an effect of midlife dyslipidemia [62, 63]. Proposed mechanisms linking lipid levels with dementia include atherosclerosis, *APOE* genotype, modulation of beta-amyloid protein, and oxidative stress [11, 12].

Among dementia- and stroke-free persons, levels of total serum (or plasma) cholesterol have been examined in relation to cognitive function in cross-sectional and longitudinal investigations [63, 64]. Several cross-sectional studies of young to middle-aged adults have found that lower levels of total cholesterol are associated with higher scores on various indexes of IQ (e.g., the vocabulary subtest of the Wechsler scales). Yet, some have noted worse performance on tests of processing speed and visuoconstructional ability among those with relatively lower levels of cholesterol [64]. These findings led Muldoon and colleagues to hypothesize that higher cholesterol levels may be

associated with lower levels of crystallized intelligence, thus perhaps reflecting less exposure to health literacy, whereas higher cholesterol may predict better fluid intelligence. Recent data from the Framingham Heart Study revealed similar relations of lower levels of cholesterol to poorer performance on measures of abstract reasoning, attention/concentration, executive function, and word fluency [65].

In contrast to these findings, a number of epidemiological investigations have revealed associations of higher total or LDL cholesterol with lower levels of performance [63], or relations of higher HDL-cholesterol with better performance [66], on cognitive screening measures. Further, and similar to the BP literature, higher levels of cholesterol during middle age may be predictive of lower levels of cognitive function at older ages [67]. Higher total cholesterol has also been related to cognitive decline or impairment [64, 68]. However, Swan and colleagues reported *less* prospective decline in perceptuo-motor speed as a function of higher cholesterol levels [69]. Further, those with decreasing total cholesterol levels after midlife had greater cognitive difficulty in late life [67]. Elderly subjects with frailty and reduced muscle mass (sarcopenia) often have reduced nutritional parameters, low cholesterol levels, and cognitive impairment further complicating studies on the relation between cholesterol levels and neurocognitive function. As in the BP literature, the possibility of nonlinear relations of cholesterol to neurocognition requires exploration.

Biological mechanisms linking high versus low cholesterol levels to cognitive function may differ. As reviewed by Muldoon and colleagues [64], cholesterol is an important constituent of neuronal and glial membranes and of myelin sheaths. It provides structural integrity, modulates membrane fluidity, and is important for synaptic function, neurotransmission, and the transport of nutrients to the brain. Brain lipids are indeed vulnerable to serum lipid levels. Cholesterol is also a precursor of steroid hormones (e.g., estrogen) involved in brain function. Therefore, it is possible that lower levels of cholesterol may negatively impact the brain's microstructure and function. Further, cholesterol may act as an antioxidant. Yet, higher levels of cholesterol play a major role in the development of atherosclerosis, which may lead to macrovascular disease and associated structural and functional changes in the brain prior to stroke. In addition, in vitro studies have suggested that increased cholesterol levels may lead to increased formation of beta-amyloid from amyloid-precursor protein [70]. The relation of the *APOE* polymorphism to cholesterol is beyond the scope of this chapter [see 64] but this association could be pertinent to cognitive decline and dementia.

Statin use may be related to lesser prospective decline in cognitive performance [71]. Results of investigations of the impact of statin administration have yielded mixed findings. Whereas most have noted no significant impact on cognitive function, others have found small detrimental relations to performance on tests of attention or a failure to show the practice effects evidenced by a placebo control group [72].

Obesity

Overweight is defined as a body mass index (BMI) of 25–29.9 kg/m^2 and obesity as a BMI of $\geq$30 kg/m^2. The degree of obesity is often further broken down into subcategories: a BMI of 30–34.9 kg/m^2 is classified as class 1 obesity, 35–39.9 kg/m^2 is classified as class 2 obesity, and >40 kg/m^2 as morbid obesity. A BMI less than 18.5 kg/m^2 is underweight, and a BMI of 18.5–24.9 kg/m^2 is considered normal. BMI is an easily measurable index of overweight and obesity. Other adiposity measures such as waist circumference, waist to hip ratio, assessment of total body fat by DEXA scan, and measurement of intra-abdominal and subcutaneous fat by CT scan may correlate more strongly with metabolic abnormalities that could mediate the association between obesity and CHD. These findings lead many to advocate the inclusion of measures of body fat distribution such as waist circumference in conjunction with measurement of BMI. An increased waist circumference (>102 cm in men and >88 cm in women) is used as a measure of central obesity and is included in the definition of the metabolic syndrome [73]. Some also advocate use of the waist–hip ratio of >0.95 and >0.88 for men and women, respectively, as index of abdominal obesity [73, 74].

Obesity is associated with increased morbidity and mortality, particularly in younger persons. There may be a "U-" or a "J-shaped" relation between BMI and mortality in older adults [75]. Recent Framingham data demonstrate that greater BMI is predictive of first CHD

event (angina, MI, or cardiac death) and first cerebrovascular event (stroke, transient ischemic attack, and stroke-related death) [76]. There is strong evidence that weight loss in overweight and obese individuals reduces risk factors for diabetes and CV disease.

Although the obesity–dementia literature appears mixed at first glance [10], ostensibly conflicting findings are likely explained by the decreased validity of adiposity measurement in the elderly, as well as the increased rate of adiposity decline immediately before dementia onset [77, 78]. Taking these methodological issues into consideration, the bulk of the research supports a relation between obesity and dementia (AD, VaD, and all-cause) [79]. Central obesity at midlife may be an especially potent risk factor [80]. Proposed mechanisms include endocrine dysregulation (e.g., hyperinsulinemia, abnormal leptin levels), inflammation, and enhancement of other CV risk factors.

Results of a rapidly growing number of case–control or cross-sectional investigations have shown relations of obesity (and sometimes overweight) to lower levels of cognitive performance in non-demented, stroke-free cohorts ranging from children to older adults following adjustment for correlated risk factors such as hypertension and diabetes [81, 82]. Affected measures typically include executive function and memory. Age interactions have been explored but not noted [83]. Examining participants from the Framingham Study [48], Elias and colleagues reported associations of obesity to executive function and memory in men only. These investigators also reported a significant cumulative effect of obesity and hypertension on several memory measures. Our group has reported significant interactions of BMI (or waist circumference) with BP level [47]. Those with higher BMI and BP showed diminished performance on tests of motor speed and manual dexterity, and executive function (i.e., response inhibition). Recent prospective data indicated that midlife central obesity, in conjunction with hypertension, was associated with decreased executive function and visual memory 12 years later [84]. The relation between central obesity and cognitive function is diminished after adjustment for physical activity [85].

In contrast, Kuo [86] recently found that overweight persons performed better than normal weight persons on tests of reasoning and visuospatial speed of processing. Obese persons were also better than normal weight individuals on the latter measure. Leanness has also been related to lower Mini-Mental State Examination (MMSE) scores in the elderly [87]. Sturman [88] reported nonlinear associations of BMI to cognitive function. It has been posited that relations of lower BMI to lesser cognitive performance, particularly among older adults, may in part reflect weight loss that is apparent prior to the diagnosis of AD.

Jagust [89] has reviewed potential mechanisms linking obesity to the brain. These include metabolic, inflammatory, vascular, degenerative, and lifestyle (e.g., exercise) factors. Increased BMI and WHR have been associated with temporal lobe or hippocampal atrophy [89], greater overall brain atrophy [90], and greater white matter disease [89]. There is some suggestion that the frontal lobes may be particularly affected [91].

Central obesity may also negatively affect the brain via neuroendocrine disturbances such as hypercortisolemia and low levels of sex steroid and growth hormones [92]. Both central and total obesity have been associated with other hormonal abnormalities such as hyperleptinemia (i.e., high serum levels of leptin – a hormone that plays a major role in fat metabolism), which has known central effects [93]. These hormonal abnormalities have been related to enhanced sympathetic nervous system activity [92, 93] that may promote silent cerebrovascular disease [78, 80]. Both central and total obesity have also been associated with enhanced proinflammatory factors [79, 80]. Sweat [94] recently found that C-reactive protein was associated with decreased frontal lobe function among overweight or obese women (but not men). Obesity may also operate, in part, via correlated CV risk factors such as the metabolic syndrome.

Diabetes, the Metabolic Syndrome, Glucose, Insulin

CV diseases are highly comorbid with diabetes mellitus. Further, CV risk factors commonly aggregate in a pattern known as the metabolic syndrome which is characterized by glucose intolerance, insulin resistance, central adiposity, dyslipidemia (here characterized by increased TG and decreased HDL-C), and hypertension. There is a strong association between the metabolic syndrome and atherosclerosis. The National

Cholesterol Education Program Adult Treatment Panel III (ATP III) definition has been most commonly used [56, 72]; metabolic syndrome is diagnosed when ≥3 of the following five risk factors are present: (1) fasting plasma glucose ≥100 mg/dL; (2) HDL-C ≤40 mg/dL in men or ≤50 mg/dL in women; (3) triglycerides ≥150 mg/dL; (4) waist circumference ≥102 cm in men or ≥88 cm in women; and (5) BP ≥130 mmHg systolic or 85 mmHg diastolic or drug therapy for hypertension. Those with the metabolic syndrome are at increased risk of developing diabetes mellitus.

Diabetes is characterized by high levels of glucose in the blood. Approximately 7% of adults in the USA are known to have diabetes, with an additional 6 million people having undiagnosed diabetes [95]. Criteria for diagnosing diabetes include either a fasting glucose level higher than 126 mg/dL (>7 mmol/L) on two occasions; random (non-fasting) blood glucose level >200 mg/dL (>11 mmol/L) and accompanied by the classic symptoms of increased thirst, urination, and fatigue; or glucose level >200 mg/dL at 2 h during an oral glucose tolerance test [95]. Levels between 100 and 126 mg/dL (6.1–6.9 mmol/L) are referred to as impaired fasting glucose or prediabetes. Diabetes can be caused by too little insulin, resistance to insulin, or both. There are two main forms of diabetes: type 1 diabetes mellitus, previously known as insulin-dependent diabetes, childhood diabetes, or also known as juvenile diabetes, is characterized by loss of the insulin-producing beta cells of the islets of Langerhans of the pancreas leading to a deficiency in insulin secretion. Type 2 diabetes, previously known as adult-onset diabetes, is the most common type of diabetes and accounts for >90% of all cases of diabetes mellitus and is characterized by variable degrees of insulin deficiency and resistance. Morbidity from diabetes involves both macrovascular (atherosclerosis) and microvascular disease (retinopathy, nephropathy, and neuropathy). The therapeutic goals are the alleviations of symptoms of hyperglycemia and aggressive CV risk factor intervention to reduce end-organ damage.

A number of reviews highlight the evidence linking diabetes with dementia [10, 12, 96, 97]. One comprehensive meta-analysis of 25 prospective studies found a 1.6-fold greater risk of future dementia for individuals with diabetes, compared to those without diabetes [98]. Diabetes-associated cerebrovascular disease may mediate the relation [98]. There is also evidence to support detrimental effects of hyperinsulinemia and glucose intolerance on cerebral structure and function, consistent with dementing processes [99].

Prior to dementia, relations of both type 1 and type 2 diabetes to lower levels of cognitive function are well documented (for reviews, see [99–101]). Type 1 diabetes has been associated with difficulties in attention, learning and memory, visuospatial abilities, and perceptuo-motor and motor speed. Associations are most pronounced among those with an age of onset between 4 and 6 years, perhaps via detrimental effects of hyperglycemic episodes on the developing brain [99, 100]. Among type 1 diabetic adults, poor metabolic control is a critical predictor of cognitive difficulties [99]. Findings have been mixed regarding the impact of episodes of hypoglycemia. Although a recent large prospective study found long-term decline in motor speed and psychomotor efficiency among type 1 diabetics, other cognitive functions were not affected [102].

Case–control studies of type 2 diabetes report the most pronounced impact on tests of learning and memory [99]. Also affected are measures of attention, psychomotor speed, and problem solving. Age interactions suggest a greater impact of type 2 diabetes on cognitive function in older than middle-aged adults [99]. Type 2 diabetes has also been associated with cognitive decline, with duration of disease an important predictive factor [103].

Outside the context of frank diabetes, investigations have shown relations of the metabolic syndrome to cognitive function, often using cognitive screening measures [104]. Impaired or increased fasting glucose has been associated with decreased cognitive performance including memory [105]. Hyperinsulinemia has been related to lower levels of cognitive function [46, 106], and insulin resistance has been associated with cognitive decline [107].

Biological mechanisms linking diabetes to cognitive difficulties are thought to be largely independent of comorbid CV risk factors and diseases. As reviewed by Ryan [99], chronic hyperglycemia may be associated with the development of advanced glycosylated end products – oxidation products that are found in senile plaques and neurofibrillary tangles, which are characteristic of AD pathology. Hyperglycemia may increase aldose reductase activity and protein kinase C activity, each of which may negatively impact basic cellular and neuronal functions.

Hyperinsulinemia is also thought to impact brain function perhaps via modulation of synaptic activity. Diabetes may alter blood–brain barrier structure and function thus allowing the passage of toxic substances [108] and has been associated with cortical brain atrophy [109].

Biomarkers

The use of commonly measured and established risk factors (e.g., cholesterol levels, BP, smoking status) does not fully explain the risk of developing CV disease. Therefore, there is a great deal of interest in whether the measurement of new metabolic parameters (biomarkers), particularly chemicals associated with myocardial cell damage, left ventricular dysfunction, renal failure, endothelial dysfunction, and inflammation, can increase the ability to predict CV disease independently of established risk factors. For example, a recent study demonstrated that the combination of N-terminal pro-brain natriuretic peptide, troponin I, cystatin C, and C-reactive protein (CRP) improved the risk stratification for CV disease death in older men beyond an assessment that was based on the established risk factors of age, systolic BP, use of antihypertensive treatment, total cholesterol, HDL-C, use of lipid-lowering medications, diabetes, smoking status, and BMI [110]. From a clinical prospective, the addition of a combination of biomarkers could add substantial prognostic information on the risk of morbidity and mortality from CV disease, leading to more targeted prevention and intervention approaches. However, caution must be applied to extending the risk of disease at a population level using combinations of biomarkers to predict risk in a given person due to the marked overlap of distribution of values for a given biomarker between those with and without the disease [111].

Inflammation

Blood-based biomarkers of systemic inflammation including CRP, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) have been extensively studied as correlates of CV disease. CRP, an inflammatory marker, is widely regarded as a risk factor for CV disease [112]. In contrast, epidemiologic studies have yielded mixed results about the relations between dementia and inflammatory markers [12]. There is some evidence suggesting that a relation exists between inflammatory markers at midlife and AD. For example, participants with higher midlife CRP in the Honolulu–Asia Aging Study had a twofold increased risk of developing AD over 25 years of follow-up [113]. Taken together, limited findings imply that inflammation causes neuronal dysfunction consistent with enhanced risk of dementia. Inflammation may also be associated indirectly with dementia outcomes because of its role in promoting atherosclerosis and potentially because of effects on brain atrophy, with higher levels of IL-6 correlating with hippocampal gray matter atrophy in middle-aged adults [114].

Studies in various community-based samples of older adults have generally found that higher levels of inflammatory biomarkers predict greater decline in cognition during follow-up, with IL-6 generally a stronger predictor than CRP [115–120]. In those studies where multiple domains of function were assessed, higher levels of inflammation correlated best with declines in nonverbal memory [120], immediate verbal recall, and orientation [118]. Significant interactions of inflammation with the metabolic syndrome [119] and the *APOE ε4* genotype [120] on cognitive decline have also been reported.

Several large population-based studies have examined the cross-sectional and longitudinal association of inflammatory markers with radiographically defined vascular disease of the brain, with some conflicting results. For example, among older community-dwelling stroke-free adults, higher IL-6 levels were associated with a greater likelihood of having MRI-defined brain infarcts or white matter hyperintensities, whereas associations of CRP and these outcomes were modest and generally not significant [121]. Among dementia-free elderly in the Rotterdam Scan Study, CRP was associated with both prevalent periventricular and subcortical white matter lesions and the progression of these lesions over 4 years, but not with prevalent or incident lacunar infarction [122]. In contrast, no relations between CRP and either silent lacunar infarcts or white matter hyperintensities were found in community-based studies of older [123] or stroke-free middle-aged and elderly subjects [124]; the latter study also reported no significant associations

of CRP with progression of white matter lesions over 6 years.

Oxidative Stress

Cellular dysfunction from cumulative free radical-mediated injury may contribute to several conditions of aging; the aging brain may be particularly susceptible. Numerous studies have reported associations between biomarkers of oxidative stress and clinical syndromes of cognitive dysfunction, including primarily mild cognitive impairment (MCI) and AD. The majority of these studies have used a case–control design with healthy age-matched controls. For the most part, these studies have not accounted for differences between subject groups in important comorbidities (CV disease, hypertension) which are also related to oxidative stress and dementia or MCI. However, a link between oxidative stress and dementia is supported by studies in autopsy brain tissue [125], and in experimental animal models where increased tissue expression of peroxidation end products and decreased antioxidant capacity were observed.

Few studies have examined the association between oxidative stress and cognitive function prospectively. For example, among older community-dwelling adults, Berr et al. reported that those with cognitive decline (defined by change in MMSE score) had higher levels of lipid peroxides and lower levels of antioxidants at baseline [126]. Biomarkers of lipid peroxidation have also been associated with MRI-defined white matter disease in older adults [127]. Prior studies have not examined associations of oxidative stress biomarkers with different domains of cognitive function in non-demented individuals.

The association of oxidative stress or reduction–oxidation imbalance with cognitive decline and overt cognitive impairment has implications for potential preventive interventions. If these associations are causal, then increasing antioxidant capacity could potentially protect against cognitive decline. Two large randomized clinical trials testing antioxidant supplementation with beta carotene [128] or vitamin E [129] have yielded conflicting results. Among older women free of CV disease, vitamin E supplementation resulted in no difference in longitudinal decline in general cognition, verbal memory, and language fluency [129]. In contrast, long-term beta-carotene supplementation among older male physicians resulted in modestly higher scores (compared to placebo) on tests of general cognitive function and verbal memory but not category fluency [128]. Because inflammation and oxidative stress are interrelated pathophysiological processes and are also related to established CV risk factors such as dyslipidemia, it is possible that there is a cumulative effect of these factors on neurocognitive dysfunction. However, in most epidemiologic studies, inflammatory and oxidative biomarkers have been considered as "independent" risk factors; few prior studies have examined potential multiplicative effects of these factors on cognition.

Biomarkers of Chronic Kidney Disease (CKD)

Kidney disease is an extremely common comorbidity which affects nearly one in five elderly in the USA [130] and which frequently coexists with other conditions known to affect brain function, namely hypertension, diabetes, and cardiac diseases. Biomarkers of kidney disease include abnormally high urinary protein or albumin excretion, which represents an alteration or injury to the normal filtration barrier, and elevations of circulating small molecules (creatinine, cystatin C, urea nitrogen), which are normally freely filtered by the kidney. Studies in patients with end-stage renal disease on maintenance dialysis showed that nearly one-third had clinically significant cognitive impairment, as defined by a MMSE score of <24 [131] or by large deficits in two or more domains of cognitive function [132]. In the latter study, one-quarter of dialysis patients had a history of prior stroke as compared to 9% of age-matched controls, suggesting a possible role for cerebrovascular disease in explaining the excess impairment.

More recent studies have examined the cross-sectional associations of mild-to-moderate kidney disease and neurocognitive function, noting poorer performance on various cognitive tests including those assessing executive function and verbal learning and memory [133]. Utilizing large epidemiologic studies, authors have reported cross-sectional associations of decreased neurocognitive function with poorer renal filtration function among older adults [134, 135], younger and middle-aged adults [136], and postmenopausal women [137]. In the latter study, significantly poorer performance in CKD was observed

for tests of general cognition (MMSE) and attention/concentration, but not on tests of verbal fluency or verbal recall. Three longitudinal studies have examined the association of kidney disease with incident cognitive dysfunction or dementia. Among community-dwelling older adults in the Cardiovascular Health Cognition Study, elevated serum creatinine and elevated urinary albumin excretion were associated with an increased risk of incident dementia; associations were generally stronger for vascular-type versus Alzheimer's type dementia [138, 139]. In an analysis of data from the Health, Aging, and Body Composition Study, incident cognitive dysfunction [defined by a low or declining Modified Mini-Mental State (3MS) Exam score] was 30 and 80% more likely in older individuals with mild and moderate severity kidney disease, respectively [134].

Homocysteine

Homocysteine (Hcy) is an amino acid that is influenced substantially by diet. In high concentrations, Hcy has direct and indirect neurotoxic effects in vitro. High plasma levels of Hcy have been associated with increased risk of CV disease. Circulating Hcy levels can be reduced by diet and vitamin supplementation (e.g., B_6, B_{12}, folic acid) permitting testing of the hypothesis that Hcy is not simply a correlate of brain disease or dysfunction but rather a causative risk factor. Numerous observational studies conducted in diverse patient populations have found cross-sectional associations between higher Hcy and worse performance on tests involving different cognitive domains; associations have generally been greater among the elderly than among middle-aged individuals [140, 141]. Among prospective studies of Hcy and rate of cognitive decline, most but not all [142] have reported a positive association, and Hcy has also been associated with the risk of incident dementia independent of other known risk factors [143–145].

In contrast to this wealth of observational data, interventional trials have shown inconsistent effects of lowering Hcy on the rate of cognitive decline. Among the two largest randomized clinical trials in older individuals with hyperhomocysteinemia, one study – among healthy elderly – found no effect on the change in cognition over 2 years [146]. Another study – among 850 participants followed for 3 years – found a significantly slower rate of decline for tests of psychomotor speed, information processing speed, and memory [147]. Therefore, although Hcy levels seem to correlate with cognitive function, its role as a causative factor in cognitive decline remains uncertain.

Behavioral Risk Factors

Behavioral or lifestyle risk factors for CV health and brain health may operate in part through their known associations with traditional CV risk factors and biomarkers. Associations of psychosocial and psychophysiological factors with CV disease have also been noted. In general, factors with known associations with stroke [148] have also shown relations to cognitive difficulties prior to stroke (or dementia).

Smoking

Smoking, a significant risk factor for CV disease, has been examined as a correlate of dementia and AD. Early case–control studies revealed inverse relations between tobacco consumption and cognitive impairment, citing nicotine as an agent that protected from cholinergic deficit and subsequently enhanced information processing and attention. However, more recent prospective studies (which appropriately adjusted for confounding variables such as education) found that smoking either was associated with increased risk or had a null effect on dementia outcomes [11, 149]. Results of a recent meta-analysis concluded that smokers have increased risk of dementia and cognitive decline [150]. Selective mortality in which smokers are at increased of dying prematurely from CV disease and cancer may confound studies of the relation between smoking and dementia.

A recent review suggests pre-dementia associations of smoking status with cognitive decline particularly on measures of verbal memory and processing speed [151]. Further, smoking during middle age has been related to poor cognitive outcomes in older age [152]. Potential mechanisms include oxidative stress, inflammation, and other CV risk factors, CAD and

CHD [151]. Importantly, prenatal exposure to smoke and sidestream smoke (resulting in higher blood cotinine – a metabolite of nicotine – levels) is related to lowered levels of cognitive performance in children [151]. Neuroimaging findings include increased white matter hyperintensities, silent brain infarction, and brain atrophy among smokers [151].

Alcohol

Numerous observational studies reveal that moderate amounts of alcohol consumption are associated with decreased risk of hypertension, CV events, and dementia [7, 13, 58, 149]. Wine seems to demonstrate especially protective effects [149]. Although alcohol appears to be a protective factor in both CV and cognitive health, it should be noted that excessive drinking has been associated with risk of dementia [12, 149]. Observational studies support consumption of $\leq$1 alcoholic drink per day for women and $\leq$2 for men to reduce the risk of CVD disease and dementia while minimizing adverse affects of alcohol [57].

Reviewed elsewhere [154], alcoholism has well-known and potent negative effects on cognitive function that lead to a particular dementia profile. Outside the context of frank alcoholism, associations between alcohol consumption and cognitive function have been complex and nonlinear (thus paralleling alcohol's relation to stroke [155]). In that regard, U- or J-shaped relations have been noted, with moderate levels of alcohol consumption associated with better cognitive performance [156, 157]. In some studies, this relation has only been noted among women but across measures of complex attention, perceptuo-motor speed, learning and memory, problem solving, and executive function [158, 159]. Moderate alcohol intake in middle age has been associated with better cognitive outcomes in older age [160]. It has been noted that some abstainers may have previously been heavy drinkers.

Diet/Antioxidants

Dietary factors, such as consumption of saturated fats, have been associated consistently with CV disease and insulin resistance [11]. Although this association suggests an indirect link between diet and dementia, little research has examined a direct link [11, 12]. It remains unclear whether antioxidant consumption is effective in the prevention of CV disease [11], but several agents show promise in the delay or prevention of AD [161]. These agents include aged garlic extract, curcumin (a component of turmeric), melatonin, resveratrol (found in the skin of red grapes), *Ginkgo biloba* extract, green tea, β-carotene, vitamin C, and vitamin E [11, 12, 161]. Mechanisms for this relation include decreased oxidative damage to sensitive brain tissue, as well as possible vascular benefit [12]. Although findings are mixed, some studies suggest that higher levels of dietary intake of antioxidants (vitamin E, C, carotene) and supplements of these nutrients have also been associated with less cognitive decline in the elderly [162]. Protective effects of dietary poly- and mono-unsaturated fatty acids have also been noted [163]. Conversely, diets high in saturated fat have been associated with cognitive decline [164]. Dietary intake of omega-3 fatty acids has been associated with greater corticolimbic gray matter volume [165].

Physical Activity, Exercise

As noted previously, several studies cite relations among obesity, CV disease, and dementia. It is known that physical activity reduces CV disease risk through its impact on numerous CV risk factors, including obesity. Thus, it is intuitive that several studies note an inverse relation between physical activity and dementia [11]. An epidemiologic study revealed that engaging in activity (strenuous enough to cause breathlessness and sweating) 2–3 times/week for 20–30 min was associated with decreased risk of dementia even after adjustments for risk factors including locomotor disorders, *APOE* genotype, vascular disorders, smoking, and alcohol consumption [166]. These results suggest that mild-to-moderate exercise may reduce risk of dementia even in genetically susceptible individuals.

Prior to dementia, there is compelling evidence for an association between higher levels of aerobic fitness or exercise and better cognitive function [167, 168]. Results of a meta-analysis indicate the most potent association between aerobic fitness training and improvements in executive-control functions such as coordination, inhibition, scheduling, planning, and

working memory [169]. Further, exercise has demonstrated associations with neuroplasticity in animal models and in humans [167, 168].

Psychosocial Risk

Various psychosocial factors have demonstrated prospective relations to CV risk factor and disease outcomes [170, 171] including stroke [172, 173]. For example, depression is a potent predictor of CV morbidity and mortality. Anxiety, anger and hostility, and other measures of negative emotionality also predict poor CV outcomes. Stress has been associated (albeit inconsistently) with CV outcomes, social support with better outcomes, and lower socioeconomic (SES) with worse outcomes. Each of these factors may be associated with brain outcomes, in part, by promoting or attenuating CV risk. However, another interesting possibility is that of common genetic and/or neurobiological vulnerability among select factors. For example, McCaffery has reported substantial common genetic comorbidity for depression and coronary artery disease [174].

Relations of depression to diminished cognitive function and dementia are well documented, and these disorders may be linked, in part, via inflammatory mechanisms [175]. There is also some support for the relations of other psychosocial factors like anxiety, hostility, social support, and SES to lower levels of cognitive function. It is an interesting new area of research to examine such "upstream" variables and their potential relations to brain outcomes via CV disease or by promoting the psychophysiological disturbances described below.

Psychophysiological Risk

Autonomic Nervous System

Autonomic nervous system dysregulation, including stress-induced CV responses, has been associated with increased risk of CV disease. Several indices of autonomic (i.e., sympathetic and parasympathetic) nervous system dysregulation have been examined in relation to cognitive performance and the brain. Increased BP variability (assessed by 24 h ambulatory monitoring) has been associated with poorer performance on several tests of cognitive function in elderly hypertensives [176] and a sample of older adults [177]. In two samples, we have reported that independent of resting clinic BP and other potential confounders, systolic and diastolic BP reactivity was associated with diminished performance on tests of attention, immediate and delayed verbal memory, and/or executive function (i.e., response inhibition) [178, 179]. We therefore suggested that enhanced stress-induced BP reactivity may be a biobehavioral risk factor for decreased cognitive performance.

Stress-induced BP reactivity is a stable dimension of individual differences, and BP responses evoked in laboratory settings show generalizability to daily life [180]. It is possible that repeated episodes of BP reactivity might have a negative impact on the brain and therefore cognitive function. With respect to plausible biological mechanisms, greater stress-induced BP reactivity has been associated with incident stroke [181]. Enhanced BP reactivity has also been related to carotid atherosclerosis and its progression and silent cerebrovascular disease [182, 183]. Similarly, various other BP indexes of autonomic dysregulation have been associated with silent cerebrovascular disease. In elderly hypertensives, both extreme nocturnal dippers (nocturnal BP fall $\geq$20%) and non-dippers had significantly greater prevalence of silent brain infarction than did dippers [184]. In addition, older, predominantly normotensive, adults with greater BP variability on ambulatory monitoring had the highest severity ratings of white matter disease [185]. Enhanced BP responses to orthostatic manipulation have been associated with a greater prevalence of silent brain infarction in elderly hypertensives [186]. We have hypothesized that repeated episodes of stress-induced BP responses during daily life may enhance cerebrovascular damage by inducing periods of cerebral hypoperfusion or vasospasm, perhaps due to compromised autoregulatory capacity in older adults [183].

Hypothalamic–Pituitary–Adrenocortical (HPA) Axis

Study of the relation of HPA axis functioning to brain and cognition has focused largely on cortisol – disruption of which is associated with increased CV

risk. Numerous investigations have revealed associations between higher resting cortisol levels and lowered levels of cognitive performance, particularly on tests of learning and memory [187–189]. It has also been noted that stress-induced cortisol elevations are associated with decreased learning and memory performance [190]. Consistent with this pattern of association, high levels of cortisol have been associated with hippocampal damage [191]. Results of longitudinal studies suggest that cumulative exposure to high and increasing levels of cortisol is associated with decreased hippocampal volumes and decline in attention, memory, and executive function [187, 188]. This suggests that detrimental effects of cortisol on the brain may extend to the frontal lobes [188]. McEwen and colleagues [192] have more generally hypothesized that repeated perturbations across a number of physiological systems (e.g., neural, endocrine, immune) – known as allostatic load – are associated with decreased cognitive function and cognitive decline.

Functioning of the hypothalamic–pituitary–gonadal (HPG) axis also bears important relations to the brain and cognitive function. Although space limitations preclude us from reviewing this literature here, the reader is referred to reviews by Sherwin on the relations of estrogen, testosterone, and hormone therapy to the brain [193, 194]. These hormones should receive further consideration in studies of CV risk, disease, and cognitive function given their potential protective (e.g., estrogen) or risk-promoting (e.g., testosterone) relations to various CV endpoints.

Summary

The preceding sections cite evidence linking numerous CV and stroke risk factors with select cognitive impairment, as well as with both VaD and AD. Cerebral hypoperfusion is thought to be particularly important to the ultimate development of dementia. De la Torre has suggested that CV risk factors may operate through a critically attained threshold of cerebral hypoperfusion which triggers a series of cerebromicrovascular changes including increased oxidative stress and impaired nitric oxide activity, pathogenic processes that then promote AD and VaD [195]. Although further research is necessary, early interventions (both pharmacologic and non-pharmacologic) to address modifiable risk factors may help prevent or delay the onset of dementia [196, 197]. Health-care providers may utilize history of CV risk factor burden as an additional means of identifying individuals at increased risk for all-cause dementia.

Among stroke- and dementia-free samples, relevant literature has also demonstrated relations of a multitude of CV risk factors to lower levels of cognitive function. The risk factors span multiple levels of analysis including traditional biomedical risk factors, newer biomarkers, and behavioral, psychosocial, psychophysiological factors. It is critical to remember the potent interrelations among these variables, and that they may exert a cumulative negative impact on cognitive outcomes. For example, the cumulative negative impact of CV risk factors has been demonstrated in several studies using compilations based on the Framingham Stroke Risk Factor Profile [198]. Variability is noted in terms of the domains of neurocognitive function most affected by different risk factors, and surprisingly little is known about relevant vulnerability and resilience factors.

We and others have discussed that, among persons without stroke or dementia, the effect sizes noted in studies of CV risk and cognitive function range from small to large, thus indicating heterogeneity of effects and the likelihood of effect modification. The clinical significance of the reduced levels of cognitive performance in relation to the CV risk factors is yet to be determined. It is not typical in this body of literature to see reference to frank impairment or dementia. However, we have suggested that even small or subtle differences that fall within the range of "normal" performance, such as the difference between above average and average scores, may be perceived as significant at an individual level and could impact role or daily functioning. This is an area in great need of investigation.

We have further suggested that these subtle associations present the first manifestations of the impact of CV risk on the brain and cognitive function. Because these correlates are seen in children and young adults, and because midlife risk factors predict late-life cognition, it is critical to intervene aggressively with risk factor profiles early in the life course. Otherwise, CV risk factors tend to develop into CV diseases which

appear to have an even greater negative impact on cognitive function.

Cardiovascular Diseases and Neurocognitive Function

In contrast to the CV risk factor literature, relatively few studies are available on the relations of CV diseases to neurocognition. Here we discuss cardiac conduction disturbances, subclinical and clinical manifestations of CV disease, heart failure, and several common treatments for these diseases.

Cardiac Arrhythmias, Cardiac Arrest

The cardiac arrhythmias comprise disorders of heart rhythm. Three of the most common and clinically important cardiac arrhythmias are atrial fibrillation (AF), ventricular tachycardia (VT), and ventricular fibrillation.

The prevalence of AF is about two million, with a lifetime risk of about 20% [1]. During AF, the heart's two upper chambers (the atria) beat chaotically and irregularly, and their contractions are not coordinated with the contractions of the ventricles. The irregular and often rapid heart rate compromises cardiac output and reduces systemic blood flow. These events can result in symptoms of heart palpitations, shortness of breath, and weakness. AF increases risk of developing blood clots that may lead to stroke. Paroxysmal (transient or episodic), persistent, and permanent AF all increase the risk of stroke by two- to threefold and may be responsible for about 15–20% of all strokes. Treatments for AF include medications and procedures that attempt to either reset the heart rhythm back to normal (cardioversion) or control the rapidity of the cardiac rate. Patients with AF are anticoagulated to prevent blood clots and emboli.

VT is defined as three or more successive beats of ventricular origin at a rate greater than 100 beats/min. VT that lasts more than 30 s is called sustained ventricular tachycardia. The hemodynamic consequences of VT depend largely on the presence or the absence of myocardial dysfunction. VT is also dangerous because it can degenerate and become ventricular fibrillation.

Ventricular fibrillation is the uncoordinated, often very rapid ineffective contractions of the ventricles caused by chaotic electrical impulses. In ventricular fibrillation, no blood is pumped from the heart, so it is a form of cardiac arrest that may be fatal unless treated immediately. Indeed the overwhelming majority of sudden cardiac deaths (estimated at about 325,000 per year) are thought to be from ventricular fibrillation. The most common cause of ventricular fibrillation is inadequate blood flow to the heart muscle due to coronary artery disease, as occurs during a heart attack. Ventricular fibrillation is a medical emergency. Cardiopulmonary resuscitation (CPR) must be started as soon as possible, followed by defibrillation. Antiarrhythmic drugs help maintain the normal heart rhythm.

Reviewed by Mead [199], some studies have found a higher prevalence of AF among patients with diagnosed dementia, whereas others have not. Cross-sectional comparisons of patients with AF and those with normal sinus rhythm suggest decreased performance on tests of memory, attention, cognitive composites, and the Mini-Mental State Examination (MMSE) [199]. A prospective study found no association between AF and future cognitive performance. However, this finding was based on only 17 participants with diagnosed AF.

AF is thought to be related to cognitive dysfunction via correlated CV risk factors, cardiogenic brain embolism, and decreased cerebral blood flow [199, 200]. The presence of silent brain infarction, mainly in cortical regions, is twice as likely among those with AF as those without [199]. Knecht and colleagues reported lower levels of learning and memory, attention, and executive function in conjunction with increased hippocampal atrophy in AF patients [201].

Ventricular fibrillation has been studied in the context of resuscitated cardiac arrest. Early case studies suggested a potent negative impact of cardiac arrest on the brain and neurocognition, with reports of isolated amnesia and extensive damage to the hippocampal regions presumably due to abrupt hypoxia and ischemia [200]. More recent investigations confirm that cognitive deficits may be severe, but suggest that these deficits are not isolated to memory, but rather extend to motor and executive functions [202].

Important predictors of subsequent cognitive difficulties include delay in the start of CPR and the need for advanced cardiopulmonary life support [203]. Some recovery of function has been noted in 3 months following cardiac arrest, but pronounced residual deficits typically remain [202]. The cognitive consequences of cardiac arrest have been attributed to diffuse and sudden ischemic–hypoxic injury [202, 204]. Because these are typically persons with preexisting cardiac disease, the mechanisms discussed in prior and future CV risk factor and disease sections are also likely operative.

Subclinical Cardiovascular Disease

A growing literature supports associations between subclinical, or presymptomatic, CV disease and cognitive function. Advantages of examining subclinical disease states are multifold [205–207]. Subclinical disease can typically be measured quickly, painlessly, and noninvasively. Numerous confounds in the study of CV disease are also dramatically reduced by examining preclinical disease states. It is well known that CV diseases tend to cluster together, and highly comorbid conditions and risk factors (e.g., CAD, diabetes, obesity) become less difficult to account for adequately in nonclinical populations. Third, subclinical measures allow us to predict future CV (and thereby neurocognitive) risk in currently asymptomatic individuals, providing ample opportunity for early intervention. Lastly, relations between subclinical CV disease and cognition provide support for the idea of a continuum of CV disease-related cognitive impairment. If CV-associated decrements in cognitive function are proportional to the degree of underlying CV disease, relations between subclinical CV disease and cognitive function would be expected to be smaller in magnitude than relations between frank CV disease and cognitive function.

At least four subclinical disease states, including atherosclerosis, arterial stiffness, endothelial dysfunction, and left ventricular hypertrophy, have been linked with decrements in concurrent cognitive function and/or prospective cognitive decline. Each of these subclinical diseases is associated with increased risk of various symptomatic CV diseases and/or mortality, above and beyond standard CV risk factors [205, 208–211].

Atherosclerosis

Atherosclerosis is a known contributor to the development of VaD because of its involvement in cerebral ischemia and stroke [26, 212]. Evidence also indicates that atherosclerosis, as well as subclinical markers of atherosclerosis, are associated with both current AD and prospective risk for AD [10, 11, 212]. The mechanisms whereby atherosclerosis contributes to AD are unclear, although oxidative stress, inflammation, and immune responses have been suggested as possible players. Further, the atherosclerosis–dementia relation appears to be strongest among *APOE ε4* carriers [213].

The most frequently studied indices of subclinical atherosclerosis are carotid intima–media thickness (IMT) and plaque, a more advanced form of atherosclerotic disease. IMT, a measure of arterial wall thickness, has been used as a surrogate measure for generalized atherosclerotic disease [214–216]. Overall, current evidence supports a cross-sectional association between carotid atherosclerosis and cognitive function across at least seven population-based samples [217–224], two CV disease samples [225, 226], and another sample at risk for CV disease [227]. Specifically, significant associations between increased carotid IMT and diminished cognitive function have been found across a number of cognitive domains, including global cognitive function, attention, psychomotor speed, verbal memory, nonverbal memory, language, verbal fluency, inductive reasoning, and mental flexibility. Importantly, not all cross-sectional studies have identified a relation between carotid atherosclerosis and cognition [218, 228]. Furthermore, conclusions regarding the most affected cognitive domains are currently premature, given that each domain has not been examined with sufficient frequency.

Longitudinal research linking carotid atherosclerosis with prospective cognitive decline is more limited. Several studies have identified longitudinal relations in population-based samples [229–231], but these associations were largely restricted to performance on brief cognitive screening measures such as the Modified Mini-Mental State (3MS) Examination and the Digit Symbol Substitution Test. One more comprehensive study that examined carotid IMT and cognitive decline found no evidence to support a longitudinal association [232]. In contrast, our group noted decline on several memory tests as a function

of greater carotid IMT [233]. Studies have also found evidence for a carotid IMT–cognition relation in AD or stroke patients [234–236], but these findings are limited to highly select populations.

Arterial Stiffness

Two common markers of arterial stiffness, pulse pressure (PP) and pulse wave velocity (PWV), are considered indicators of subclinical CV disease [207, 237]. Pulse pressure, computed as the difference between systolic and diastolic BP values, is viewed as a surrogate marker of arterial disease, whereas PWV is regarded as a direct measure of arterial stiffness [238]. PWV is measured between two locations in the arterial tree; carotid and femoral peripheral sites are typically utilized to provide a measure of aortic stiffness.

Both high and low PP predict incident AD and overall dementia [239]. In an examination of participants in the Maine–Syracuse Study [240], greater PP was associated with lower levels of performance on a global composite of cognitive function and specific measures of verbal concept formation, attention, perceptuo-motor speed, and visuoconstructional ability. In another recent study, high PP was associated with diminished performance on a cognitive screening measure among older adult participants in the Third National Health and Nutrition Examination Survey [241]. Cross-sectional evidence also links high PWV with diminished cognitive function. Individuals with dementia or MCI have been found to have higher PWV values than cognitively intact participants [242], and PWV has been found to correlate inversely with MMSE performance among individuals referred for memory deficit [243], even among those without overt vascular disease [244].

Growing evidence also suggests an association between arterial stiffness and cognitive decline that is independent of BP level. Scuteri and colleagues [245] found an association between higher baseline PWV and MMSE decline among participants with memory complaints. Expanding upon these findings, Waldstein and colleagues [35] examined longitudinal relations of PP and PWV to multiple domains of cognitive function among non-demented, stroke-free participants in the Baltimore Longitudinal Study of Aging. Increasing levels of PP were significantly related to prospective decline on tests of verbal learning, nonverbal memory, working memory, and a cognitive screening measure over up to 11 years of follow-up. Similarly, persons with higher baseline PWV exhibited prospective decline on tests of verbal learning and delayed recall, nonverbal memory, and a cognitive screening measure. In contrast, an examination of Rotterdam Study participants failed to identify a significant association between PWV and incident dementia or cognitive decline over two time points [246].

Endothelial Dysfunction

Endothelial function represents an important component of vascular health and contributes to the maintenance of vascular homeostasis [247]. Disruptions in vascular homeostasis, mediated by endothelial dysfunction, can precipitate atherogenesis and other harmful vascular events such as transient ischemia, plaque rupture, thrombosis, and infarction. Brachial artery flow-mediated dilatation (FMD), measured as the magnitude of arterial dilatation after an induction of forearm ischemia, is a commonly used marker of endothelial function [207, 248]. Specifically, the temporarily high blood flow following forearm ischemia triggers the release of nitric oxide (NO), a powerful vasodilator. NO release is reduced in the presence of endothelial dysfunction, thereby resulting in a reduced brachial artery FMD. Lower values of brachial artery FMD thus indicate poorer endothelial function.

Relatively little research has directly examined the relation between brachial artery FMD and cognitive function. In a study of geriatric outpatients with CV disease, Cohen and colleagues [226] demonstrated consistent associations between increased brachial artery FMD and lower levels of performance on measures of attention, executive function, and psychomotor speed. Consistent with the pattern of impairment typically observed in vascular disease [249, 250], significant associations were not identified among other domains tested, including language ability, memory, and visual–spatial function. Brachial artery FMD has also been associated with structural brain indices as measured by magnetic resonance imaging (MRI). In the aforementioned study, brachial artery FMD was significantly associated with reduced whole brain volume, but not extent of white matter disease. In contrast, in another sample of older adults with CV disease

[251], brachial artery FMD was significantly associated with the latter, but not the former index.

Left Ventricular Hypertrophy

Increased left ventricular mass, or left ventricular hypertrophy (LVH), can be assessed noninvasively via echocardiography. The extent of LVH is often, but not always, a reflection of the cumulative impact of another symptomatic or asymptomatic CV disease, such as hypertension, on the myocardium over time [252]. Despite its recognition as a measure of subclinical CV disease among otherwise healthy individuals [205], limited research has examined LVH in relation to cognitive function. Among elderly participants in the Helsinki Aging Study, LVH was present more often in individuals with cognitive impairment or dementia than cognitively intact participants [253]. Furthermore, baseline LVH predicted decline in MMSE performance over 5-year follow-up. Using data from the Framingham Offspring Study, Elias and colleagues [252] identified a significant cross-sectional relation between LVH and performance on cognitive tests assessing verbal concept formation, verbal memory, and visual–spatial memory and organization. However, these relations were significantly attenuated following statistical adjustment for BP, treatment for hypertension, other vascular risk factors, and prevalent CV disease. These latter covariates may therefore mediate the relation between LVH and cognitive function.

Mechanisms

Researchers have proposed a number of mechanisms through which subclinical CV disease may directly or indirectly affect cognitive function. The subclinical measures described above have been associated with various CV risk factors, including demographic, metabolic, immunologic, and lifestyle factors, which in turn have been associated with lower levels of cognitive function [205, 254–257]. However, relations of subclinical CV disease to cognition are unlikely to be due solely to these shared risk factors [35, 207]. Other hypothesized mechanisms include a common genetic vulnerability, chronic cerebral hypoperfusion, micro- and macro-cerebrovascular diseases, and other associated structural brain changes, such as cortical atrophy [226, 239, 242, 251]. It should be noted that subclinical disease states often co-occur and may act additively or synergistically in the prediction of diminished cognitive function [205]. The possibility thus exists that one subclinical disease may mediate another subclinical disease's effects on the brain and cognition, potentially in combination with other mediating variables.

Coronary Heart Disease (CHD)

CHD is the leading cause of death in the USA [1]. Manifestations include stable angina, acute coronary syndromes, myocardial infarction, heart failure, sudden death, and silent ischemia. More than one million people have a MI each year, and many more are hospitalized for angina. Of patients with acute MI, based on ECG and biomarkers, approximately two-thirds have a non-ST segment elevation myocardial infarction (MSTEMI) where they have an increase in their cardiac isoenzymes (creatine kinase MB, or tropin) and an absence of persistent ST segment elevation on their ECG, and approximately one-third have ST segment elevation MI (STEMI) accompanied by increase in their cardiac isoenzymes.

Treatment of patients with stable angina is targeted to prevent MI and reduce or relieve symptoms. An "ABCDE" approach is advocated: aspirin and antianginal therapy; beta-adrenergic antagonists and blood pressure control; cholesterol-lowering agents and cigarette-smoking cessation; diet; and exercise. Invasive intervention with coronary angioplasty, stenting, and by coronary artery bypass grafting (CABG) is indicated in subsets of CHD patients.

Reviewed by Vingerhoets [258], a history of MI has been associated with concurrent dementia across several investigations. Non-demented cardiac patients have been described as exhibiting dysfunction on tests of memory, fine motor control, and orientation [259]. Cardiac patients assessed prior to CABG surgery have displayed decreased word fluency, manual dexterity, verbal learning, and psychomotor speed, with performance similar to persons with carotid stenosis [258]. Others have similarly found cognitive impairment in pre-surgical coronary patients [260]. Prospective investigations have reported relations between several

diagnoses of vascular disease such as CHD and MI with lower levels of future performance on cognitive screening measures [261, 262].

Vingerhoets [258] has proposed several mechanisms linking MI with cognitive dysfunction. These include the presence of systemic vascular disease that leads to cardiac and cerebrovascular insufficiency, brain infarction due to cardiogenic embolism, acute or chronic hypoxia due to impaired myocardial function that leads to decreased cerebral perfusion, and post-MI depression. CHD has been associated with brain atrophy [263] and white matter lesions on MRI [264].

Coronary Artery Bypass Grafting (CABG)

A common cardiac surgery used to treat advanced coronary artery disease (CAD), CABG surgery involves bypassing diseased portions of the coronary arteries using healthier segments of noncardiac blood vessels [265]. CABG may be performed with or without cardiopulmonary bypass (CPB), in which a pump takes over heart and lung function during the operation to permit surgery on a non-beating heart [266]. Despite its effectiveness for reducing angina, stabilizing ventricular function, and prolonging life, evidence suggests that CABG surgery may have unforeseen adverse effects on the brain and cognition [267–270].

Both short- and long-term changes in cognitive function have been observed following CABG surgery. In a seminal, though highly debated [271–276] study, Newman and colleagues [277] found incidence of post-surgical cognitive decline from baseline to be 53% of patients at hospital discharge, 24% at 6 months postsurgery, and 42% at 5-year follow-up.

Short-term cognitive deficits (appearing <1 month postoperatively) in post-CABG patients are now well recognized, with reported incidences varying considerably from study to study (33–83%) depending on the patient population studied, number and type of neuropsychological tests utilized, interval between surgery and testing, and criteria used to define cognitive decline [278–280]. These short-term effects may include decrements across a number of domains of cognitive function, including memory, psychomotor speed, executive functions, and visuoconstructional abilities [270]. Memory and concentration complaints are the most frequently self-reported cognitive changes, though these findings are not always corroborated by neuropsychological data [270, 281].

Long-term deficits are less understood. At least two studies have detected an initial cognitive recovery period ensuing the aforementioned early cognitive decline, followed by a later period of cognitive decline up to 5 years postsurgery [265, 282]. Across studies, motor and psychomotor speeds appear to be the most vulnerable cognitive domains, but nonsignificant findings and significant effects for other cognitive domains have also been identified [270, 276, 283–286]. These discrepancies are likely a function of the numerous methodologic differences across studies; Selnes and colleagues [270] describe the prevailing pattern as consistent with cognitive changes observed in patients with mild subcortical vascular disease.

The presumed neurobiological underpinnings of post-CABG cognitive changes remain a topic of debate [267, 270, 287–289]. The occurrence of cerebral microemboli (particularly during cannulation, manipulation of the aorta, and cardiotomy suction) and cerebral hypoperfusion during surgery has received the most attention as possible mechanisms linking CABG with its cognitive sequelae. Other potential contributing factors include anesthesia, peri- and postoperative AF, medications, systemic inflammation, depression and/or anxiety, and patient characteristics such as age, genetic factors, other cerebrovascular disease risk factors (e.g., hypertension, diabetes), and preexisting cerebrovascular disease.

Peripheral Arterial Disease

Peripheral arterial occlusive disease (PAD), a subtype of peripheral vascular disease (PVD), results from atherosclerosis of the arteries that supply the lower extremities (i.e., abdominal aorta, iliac, femoral, popliteal, tibial). PAD affects approximately 16% of adults over the age of 55, including 10% asymptomatic PAD (stage I), 5% intermittent claudication (stage II), and 1% chronic leg ischemia (stages III–IV), and is a major cause of disability among older individuals [290]. Revascularization may be utilized in stage III or IV PAD (i.e., necrosis or gangrene), and stage IV disease may necessitate limb amputation. Because it is a diffuse atherosclerotic disease, PAD is associated with comorbid atherosclerosis of the coronary and carotid

arteries [291]. Risk for atherosclerotic events such as MI, PAD, and stroke clusters among individuals [292–294].

Reviewed by Phillips [295], several early investigations examined patients with PVD as control subjects in studies of the impact of vascular surgeries (e.g., carotid endarterectomy, CABG surgery) on cognitive function [296–298]. Results of these studies suggested that patients with PVD displayed mild neuropsychological dysfunction [296, 297] or showed similar cognitive function as patients with carotid disease [298].

Comparing PVD amputees and non-amputees with mild to moderate claudication to healthy control subjects and atherothrombotic stroke patients, Phillips et al. [299] found that PVD patients performed more poorly than healthy controls on tests of attention, psychomotor speed, executive functions, visual memory, and visuospatial ability. Furthermore, the performance of the PVD patients was typically quite similar to that of the stroke patients.

Our research group found that PAD patients performed significantly more poorly than hypertensives and normotensives, but better than stroke patients, on seven tests of nonverbal memory, concentration, executive function, perceptuo-motor speed, and manual dexterity [14]. These findings were independent of age, education, and depression scores. Eight to sixty-seven percent of PAD patients displayed impaired performance (<5th percentile of normotensive controls) on the seven aforementioned cognitive tests. We concluded that the findings suggested a continuum of cognitive impairment associated with increasingly severe manifestations of cardiovascular disease.

In the population-based Rotterdam Study, Breteler et al. [217] found that individuals having an ankle–brachial index (ABI) <0.90 (diagnostic of PVD) displayed poorer performance on the MMSE than patients with greater ABIs. The presence of PVD, as assessed by ABI, has also been associated with cognitive decline on the MMSE and a test of perceptuo-motor speed particularly among individuals having an *APOE* e4 allele [229, 232].

Several direct and indirect mechanisms may link PAD to cognitive difficulties and have been reviewed (see [14, 295]). In that regard, risk factors for atherosclerosis are generally the same for all arterial systems and include dyslipidemia, diabetes, hypertension, and smoking. These risk factors have all been related to structural abnormalities on MRI that reflect microvascular disease, macrovascular disease, brain atrophy, and diminished cerebral perfusion. Next, atherosclerosis in the carotid arteries, which is often comorbid with PAD, has been related to decreased cognitive performance perhaps by indirectly reducing cerebral perfusion. Generalized atherosclerosis may also be related to cognitive dysfunction via increased microemboli. Studies that have conducted neuroimaging in patients with PAD have found increased white matter disease and brain atrophy [300, 301]. In the Rotterdam Study, mean ABIs were significantly lower in patients with white matter lesions on MRI [301].

Heart Failure/Heart Transplantation

Heart failure (HF) is a syndrome where there are structural or functional cardiac disorders that impair the ability of the left ventricle to fill with or eject blood. It is characterized by specific clinical symptoms, such as dyspnea and fatigue, and signs on physical examination, such as fluid retention [302]. The prevalence of HF has been increasing and is projected to double within 40 years, despite improvements in CV mortality rates over recent decades [302, 303]. This pattern is a product of the rapidly aging population and the increasing prevalence of HF with advancing age. Heart transplantation is a treatment option considered for patients with end-stage HF [304].

Diminished cognitive function in HF has been the subject of several recent comprehensive reviews [303, 305–307]. One systematic review and meta-analysis of 2,937 HF patients and 14,848 controls identified a pooled odds ratio for cognitive impairment of 1.62 (CI: 1.48–1.79, $p < 0.0001$) among individuals with HF [303]. The pattern of impairment associated with HF appears to be diffuse; affected domains include attention, concentration, memory, language, psychomotor speed, and executive function [307–309]. These decrements in cognitive function are associated with an increased risk of hospital readmission, disability, and mortality among HF patients [306, 310, 311]. There is mixed, and very limited, evidence regarding the cognitive consequences of heart transplantation [308]. Although some studies show postsurgical improvement in cognition [312, 313], others show evidence

to the contrary [314, 315], and numerous methodologic weaknesses preclude strong conclusions [308]. Post-transplant neuropsychological function is thus an important area for future study.

The neuropathological mechanisms underlying cognitive changes associated with heart failure remain unclear, and relevant mechanistic research is lacking [307]. The primary hypotheses involve multiple cardiogenic emboli and cerebral hypoperfusion associated with insufficient cardiac output [303]. Given that the brain receives a large relative proportion of cardiac output [308], the latter hypothesis appears highly plausible as a contributing factor. However, other cardiovascular risk factors and disease states (e.g., ischemic heart disease, cerebrovascular disease, hypertension, hypotension, AF, diabetes, lifestyle factors) are common among HF patients, and these factors may contribute directly to the observed cognitive changes [303, 305, 316]. Furthermore, fatigue, depression, medication side effects, and other neurological complications are prevalent in HF and carry independent neuropsychological implications [308].

Summary

Although relatively few investigations are available, there is compelling evidence of an association between various CV diseases and pronounced neurocognitive dysfunction. Studies in this area frequently refer to frank cognitive impairment (as compared to normative standards or control subjects) or report dementia prevalence. Patterns of performance differ somewhat across the diseases described, but frequently include tests of executive function, motor or perceptuo-motor speed, attention, and memory.

Discussion

CV disease is a complex biopsychosocial phenomenon that likely yields lifelong impact on brain structure and function and, ultimately, cognitive function. We have suggested that there is a multilevel interplay among numerous factors that may serve as proximal and distal mediators of these associations. As noted in Fig. 5.1, genetic risk may operate through any of the subsequent levels to impact brain and cognition. Genetic risk may be expressed in neurobiological manifestations that are present even prior to the appearance of CV risk factors or disease pathology. Genetics and neurobiology may predispose to various behavioral, psychosocial, and psychophysiological factors that have known associations with CV risk factors and diseases. All of these factors may have independent influences on brain structure and function and cognitive performance or may operate through different meditational pathways. Although we have drawn a linear model for the sake of simplicity, it is critical to note the likelihood of multidirectional associations including interrelations among factors at any given level. Although, to our knowledge, tests of this model are unavailable, we have provided reviews of literature that help us to construct possible conceptual linkages.

Here, we have provided brief overviews of the relations of numerous CV risk factors, CV diseases, and their treatments to neurocognitive function. We have highlighted positive findings in order to illustrate possible patterns of associations. Although findings in each area are indeed mixed, we suggest that the preponderance of evidence points to robust associations.

Much more work is needed to clarify the specific neurocognitive tests that are most sensitive to the various CV risk factors and diseases (and associated vulnerability and resilience factors). We have suggested previously that test batteries should provide adequate coverage of major domains of cognitive function. Although there is typically pressure to reduce such data for analysis by factor analysis or conceptual clusters, we prefer to analyze univariate tests to maximize information. Just as it is less informative to interpret a WAIS Verbal or Performance IQ than its individual subscales, there is a substantial loss of information when using factor or composite scores. In clinical neuropsychological assessment, one uses all information available to determine patterns of performance.

In particular, there remains a great need to incorporate more extensive neurocognitive measures into epidemiological investigations, which most commonly use measures such as the MMSE, 3MS, and Short Portable Mental Status Questionnaire to measure "cognitive function." These measures are not optimal in tracking trajectories of domain-specific cognitive decline in healthy individuals and have psychometric limitations [317].

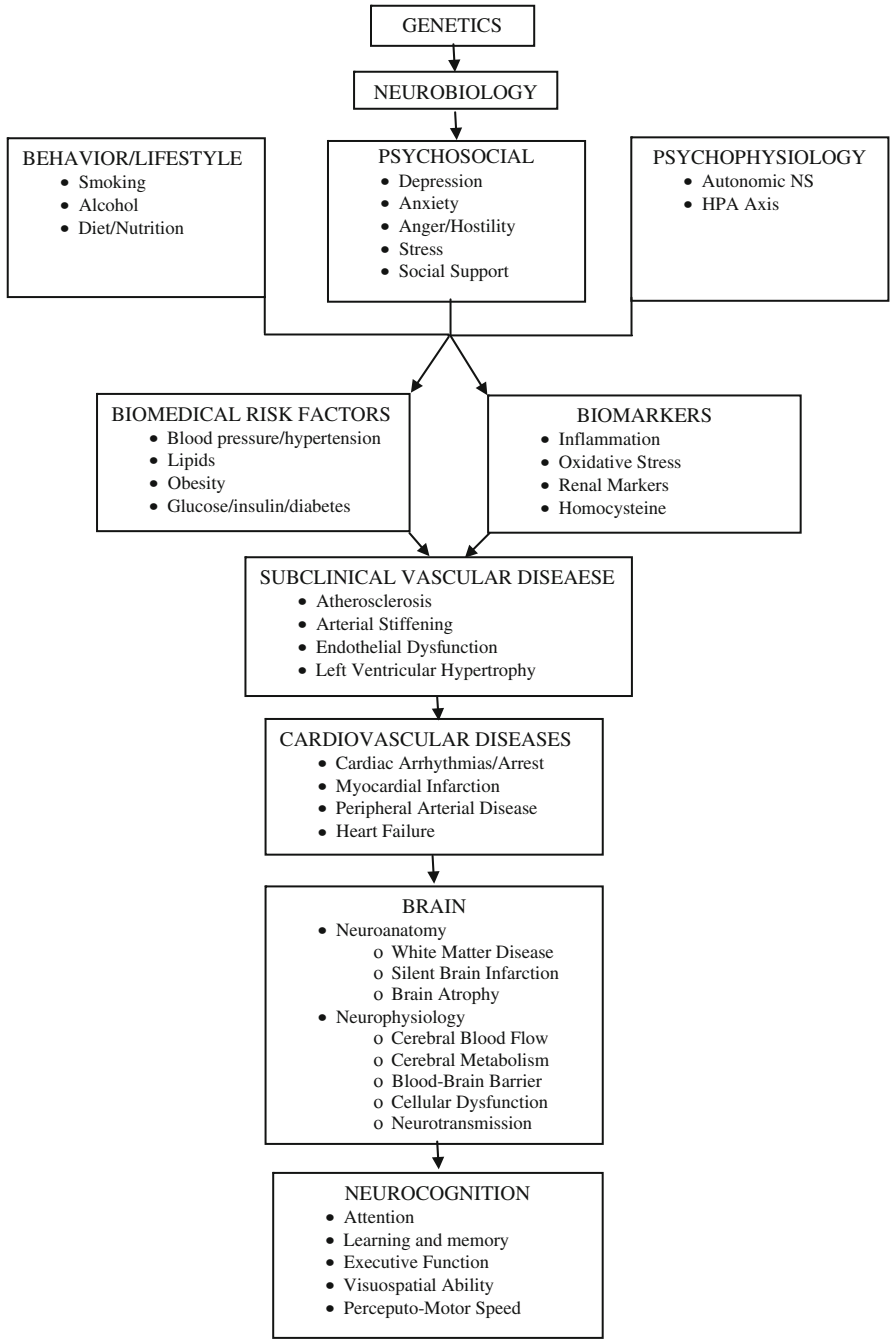

Fig. 5.1 Potential proximal and distal mediators of the relations of CVD risk factors and diseases to neurocognitive function

We did not have space to discuss the methodological adequacy of the research in this area. Studies are quite variable with respect to adequacy of design, sample size and characteristics, measurement with respect to both CV and neurocognitive variables, consideration of adjustment variables, and study exclusions. Particularly many studies of CV disease and cognition are fraught with the methodological problems noted above, in addition to the challenges of assessing respective contributions of multiple comorbidities.

There is little research examining the mechanisms underlying relations between CV risk factors or diseases and neurocognition. When possible, investigators should include both cognitive and neuroimaging measures in the same study and examine direct tests of mediation. In addition to traditional MRI and PET methodologies, newer imaging methods such as amyloid and tau imaging should also be employed.

There is generally a paucity of research on the daily life impact of cognitive difficulties related to CV risk factors or diseases. A review is beyond the scope of this chapter. However, work to date suggests associations with quality of life, physical function (e.g., gait, balance, risk of falls), daily function, disability, and frailty. This is another area in great need of investigation.

Despite the need for further research in each of the areas reviewed, we do have enough evidence to suggest that the relation of CV risk factors and diseases to brain and cognitive outcomes begins very early in life. Further, there appears to be a continuum of cognitive impairment associated with increasingly severe manifestations of cardiovascular disease. Accordingly, early and aggressive efforts at prevention and intervention are critical to the maintenance of "brain health" and cognitive function across the life span.

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