The impact of cardiovascular diseases on neurocognitive performance: A review

Esteban Viruet-Sánchez[1], Ivette Mirles-Muñiz[1] & Orlando M. Pagán-Torres[1]

[1]School of Behavioral and Brain Sciences, Ponce Health Sciences University

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Abstract

Cardiovascular diseases (CVDs) are among the most prevalent conditions worldwide. During the last decades an increased number of studies analyzing the impact of CVDs on neurocognitive performance have emerged. The purpose of this article is to review the current literature detailing the impact of CVDs on neurocognitive performance. Our review is focused on the underlying neuropsychological aspect of this condition and addresses the structural and functional changes in the brain as described by various studies. We also focus on recent data showing how treating cardiovascular health can affect and individual's neurocognitive performance. The findings of this review suggest that patients with CVDs who have no history of stroke or dementia are at significant risk of experiencing cognitive decline. Furthermore, the majority of studies state that certain neurocognitive domains, such as attention and executive functioning, are the most affected by CVDs. We suggest integrating mental health professionals such as neuropsychologist and clinical psychologist into the CVDs treatment team to promote adherence and decrease maladaptive behaviors that can result in diminished neurocognitive performance in people with these conditions.

Palabras claves: cardiovascular diseases; neurocognitive performance; neurocognitive impairment; vascular cognitive impairment

Resumen

Las enfermedades cardiovasculares (ECV) se encuentran entre las condiciones más prevalentes a nivel mundial. Durante las últimas décadas, ha surgido un mayor número de estudios que analizan el impacto de las ECV en el rendimiento neurocognitivo. El propósito de este artículo es revisar la literatura actual que detalla el impacto de las ECV en el rendimiento neurocognitivo. Nuestra revisión se centra en el aspecto neuropsicológico subyacente de esta afección y aborda los cambios estructurales y funcionales en el cerebro, según lo describen diversos estudios. También nos centramos en datos recientes que muestran cómo el tratamiento de la salud cardiovascular puede afectar el desempeño neurocognitivo del individuo. Los hallazgos de esta revisión sugieren que los pacientes con ECV que no poseen historial de accidente cerebrovascular o demencia, tienen un riesgo significativo de experimentar deterioro cognitivo. Además, la mayoría de los estudios exponen que ciertos dominios neurocognitivos tales como la atención y el funcionamiento ejecutivo son los más afectados por las ECV. Sugerimos la necesidad de integrar a los profesionales de la salud mental tales como, los neuropsicólogos y psicólogos clínicos en el equipo de tratamiento de ECV para promover la adherencia y disminuir las conductas maladaptativas que pueden provocar una disminución del rendimiento neurocognitivo en las personas con dichas condiciones.

Keywords: Enfermedades cardiovasculares; desempeño neurocognitivo; deterioro neurocognitivo; deterioro cognitivo vascular

[1] Toda comunicación relacionada a este artículo debe dirigirse a la autora principal al siguiente correo electrónico: esteban.viruet7@gmail.com.

Introduction

According to the World Health Organization (WHO) (2017), CVDs were responsible for 17.9 million deaths in 2016; that amounts to 31% of global deaths. In addition, the American Heart Association (AHA) (2018) reported that CVDs was the 10th leading cause of death in the United States. Additionally, the AHA suggests that 80% of CVD-related deaths in the world are caused by heart attacks or strokes. Furthermore, CVDs have been identified as the leading causes of mortality among Hispanics and Latinos in the United States (Daviglus, Pirzada & Talavera, 2014).

The WHO (2017) has identified multiple behavioral risk factors for CVDs, such as using tobacco, having an unhealthy diet, being physically inactive, and excessive alcohol drinking. Furthermore, CVDs are linked to psychosocial influences that can impact or aggravate the general health of the organism (Brannon, Feist, & Updegraff, 2014). As we noted, this medical condition has reached epidemic proportions, causing major social, medical, and economic problems.

Evidence also suggest that, besides the impact it has on physical well-being of patients, CVDs may have neuropsychological consequences, such as neurocognitive impairment (Foley, 2011). The *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-5) (American Psychiatric Association, 2013) establishes that neurocognitive disorders exist on a spectrum of cognitive and functional impairment. The core feature of these disorders is acquired cognitive decline manifesting in at least one cognitive domain. There are different forms of neurocognitive impairment, including mild cognitive impairment (MCI), which is said to be the transitional stage from normal aging to dementia (Knopman & Petersen, 2014). This term was coined to describe a point between the cognitive changes that are associated with aging and the cognitive impairment that is an indication of dementia (Sadock, Sadock, & Ruiz, 2014).

Moreover, the recent literature suggests that the development of cognitive impairment associated with CVDs can be attributed to cerebrovascular irregularities (Gorelick et al., 2011). However, the cognitive impairment caused by or associated with vascular factors is more properly referred to as vascular cognitive impairment (VCI) (Hachinski et al., 2006). From mild MCI to full-blown dementia, VCI includes all those disorders that are linked to cerebrovascular diseases, no matter the mechanisms involved (Dichgans & Leys, 2017).

Nordlund and colleagues (2007) tried to determine the differences between MCI and VCI, suggesting that both conditions have characteristics that distinguish them from each other. These authors found that subjects with VCI performed more poorly in attention and executive functioning domains than did those with MCI. Additionally, the systematic review of Levine and Langa (2011), found that VCI is an important determinant of health status, quality of life and functional ability. Furthermore, it has been stated that cognitive problems in CVDs patients can affect their ability to benefit from treatment (e.g., medication management) (Alosco et al., 2012). Furthermore, VCI has been classified as the transitional stage from adaptive cognitive function to vascular dementia (VaD) (Rodríguez-García & Rodríguez García, 2015). As a syndrome, VaD is linked to dementia, and resulting in several pathologies, with evidence of CVDs being part of the diagnosis (Gorelick et al., 2011).

The future development of VaD in CVDs patients is highly probable, depending on the etiology of the CVDs (Kapasi & Schneider, 2016). The cognitive manifestations of VCI and VaD are similar to that of Alzheimer's disease (AD) (Korczyn, Vakhapova, & Grinberg, 2012). These three disorders share common risk factors, including age, obesity, physical inactivity, smoking, high blood pressure, and elevated cholesterol (Alonso et al., 2009; Stefanidis et al., 2018). In addition, a study found that about 50% of pre-mortem−diagnosed AD subjects displayed cerebrovascular pathologies, with only 30% displaying pure AD (Schneider, 2007). As manifestations of cognitive impairment, both VCI and VaD are characterized and induced by the presence of cerebrovascular conditions, such as cerebral small vessel disease, hypoxic ischemic encephalopathy, and stroke, among others (Rodríguez-García & Rodríguez-García, 2015).

Finally, these studies show the high incidence of poor neurocognitive functioning in individuals with CVDs has received more clinical attention in recent years, making this a critical topic of research. Studying the impact of CVDs on neurocognition may contribute to the understanding of the risk factors associated with the subsequent development of dementia and how this impairment can influence patient functionality and adherence to treatment, thereby threatening the life expectancy of the individual (Stanek et al., 2011). Our review is focused on the underlying neuropsychological aspect of this condition and addresses the structural and functional changes in the brain as described by various studies. Our review also focuses on recent data that despicts how treating cardiovascular health can affect an individual's neurocognitive performance.

Cardiovascular health, brain abnormalities, and functionality

Poor neurocognitive functioning has been consistently reported in individuals with CVDs (Stanek et al., 2009). According to Iazzo (2005), the heart is a muscle that has two functions: to collect oxygen-poor blood from different organs and tissues of the body, collect oxygenated blood from the lungs and pump it to all the organs and tissues of the body, including the brain. Therefore, it is evident that the heart is essential to brain function, as it pumps the blood that supplies the brain. Normal blood flow in the brain provides glucose and oxygen, which makes possible the elimination of heat and metabolic by-products. When this process does not work efficiently, the brain suffers radical metabolic changes resulting in physiological alterations (Cohen & Gunstad, 2010; Kapasi & Schneider, 2016; Selman & Winn, 2012). Furthermore, low cardiac output, endothelial dysfunction, and poor cardiac fitness have all been associated with neurocognitive impairment (Stanek et al., 2011).

To measure the cardiac function, it is often taken into consideration the cardiac output (CO), which quantifies the amount of blood existing in the heart (Constanzo, 2011; Jefferson, 2010). The brain receives about 15% of the CO, needing a constant supply of blood to sustain its neural functions (Constanzo, 2011). An acute or chronic alteration in CO leads to a change in cerebral blood flow (CBF), thus contributing to clinical brain injury (Jefferson, 2010; Ogawa et al., 2017; Ozdemir et al., 2013). Furthermore, CO may be affected by physical conditions that affect, primarily, left ventricle and right ventricle functions such as heart failure (HF) (Ghio et al., 2001).

HF is a condition in which the heart is unable to perfuse the body's organs, including the brain, with enough oxygenated blood (Sattar, 2011). HF may be described as being systolic or diastolic. According to Kasper et al. (2004), the distinction between these two forms of HF can be observed in the inability of the ventricles to contract normally and expel the blood needed to perfuse the organs (systolic failure) or to relax and fill (diastolic failure). Systolic failure can result in inadequate CO, which can cause weakness, fatigue, and other symptoms of hypoperfusion, while diastolic HF reveals itself with an elevation of filling pressures in the left ventricle and/or right ventricles (Kasper et al., 2004). There is a high prevalence of patients with systolic HF that suffer from cognitive dysfunction and dementia (Ampadu & Morley, 2015).

Studies have found that patients with HF often present signs of cerebral atrophy and infarcts (Stanek et al., 2009). Furthermore, HF patients exhibit changes in brain structure, presenting smaller gray matter volume, which has been linked to deficits in cognitive domains important for the instrumental activities of daily living (Almeida et al., 2012; Vogels et al., 2007). Some of the cognitive domains affected as a result of HF are attention, executive functioning, learning and memory recall, working memory, and psychomotor speed (Bauer, Johnson & Pozehl, 2011; Dardiotis, 2012). It is evident that these cardiovascular irregularities are highly associated with brain damage resulting in neurocognitive impairment.

Additionally, it has been reported that small and large cerebral blood vessels can suffer structural changes in the presence of CVDs, specifically atherosclerosis (Cohen et al., 2009; Wardlaw et al., 2013). For instance, these changes can result in cerebral small vessel disease (SVD). In cerebral SVD, ischemic lesions are located in small arteries that supply blood to the basal ganglia or to the deep white matter of the brain (Mandy et al., 2011). SVD is known as one of the most common causes of cognitive impairment and vascular dementia (Wardlaw et al., 2013), and it is frequently associated with vascular diseases such as hypertension and microvascular disease (Wardlaw et al., 2009).

Similarly, it has been found that patients with CVDs but with no prior history of stroke or brain disease also exhibit structural changes in brain anatomy (Cohen et al., 2009). A study implementing Magnetic Resonance Imaging (MRI), found that the brains of patients with poor cardiovascular health in the absence of strokes tend to have white matter hyperintensities (WMH; Cohen et al., 2009). WMH are white matter lesions in the brain appearing in T2- weighted images on MRI, which is a technique that enhances the detection of pathologic changes and small lesions (Blumenfeld, 2002; Debette & Markus, 2010; Tang, Chen, Zhang & Huang, 2014). Furthermore, a metanalysis of 46 studies reported that WMH are a significant indicator of future risk of stroke, cognitive decline and dementia (Debette & Markus, 2010).

In addition, Smith et al. (2011) found in their study that WMH are associated with executive dysfunction and memory impairment. Furthermore, a longitudinal study found that WMH were associated with an increased risk of clinical progression of cognitive decline and dementia in patients who had earlier made subjective complaints of cognitive decline (Benedictus et al., 2015). In addition, Tate and colleagues (2008), through neuroimaging techniques, found regional white matter abnormalities, specifically in the peri-ventricular and the central nuclei in the brain of patients either with CVDs or at risk of same concluding that these abnormalities were related to poor neurocognitive performance. These findings illustrate that several cardiac disorders can have an impact on brain structure and functionality, thus affecting cognitive domains.

Cardiovascular health and neurocognitive performance: Empirical findings

We conducted a narrative review in *PubMed, Google Scholar and Elsevier* between August 2018 to March 2019 to document the studies directed to explore the impact of CVDs on neurocognitive performance**.** The articles documented in this review must have been published in peer-review journals on English language. Also, the articles included in this review must be studies with quantitative design. To carry out the search in the data bases we used the following keywords: "*Neurocognitive Performance and Cardiovascular Health", "Neurocognitive Functioning and Cardiovascular Diseases",* and *"Myocardial Infarction and Neurocognitive Functioning*". We conducted the review in the data bases mentioned and then we proceed to analyze the titles and abstracts of each of the article to include the studies that accomplish the inclusion criteria. Moreover, we excluded doctoral dissertations and any kind of work that has not been published in a peer-review journal. At last, we proceed to expose and analyze the most recent findings about this topic and discuss the clinical implications for neuropsychology and health psychology. The studies were organized in the Table 1.

Stanek et al., (2009) postulated that cognitive impairment is a significant and frequent disability experienced by people who suffer from CVDs. The authors claimed that cognitive impairment occurs in about 80% of HF patients, stating that impairments in attention, executive function, memory, and psychomotor speed are common in this population. These findings suggest that CVDs can impact brain function and neurocognitive performance prior to stroke and dementia (Waldstein & Wendell, 2010). For instance, patients with CVDs but with no prior history of cerebrovascular abnormalities could experience neurocognitive impairment. According to Cohen and Gunstad (2010), this group represents the most accurate and "purest," in terms of examining the effects of CVDs on brain function. Since these types of patients have not experienced clinically evident prior strokes, changes in neurocognitive performance might be attributable to cardiovascular factors (Cohen & Gunstad, 2010).

A clear example of this is found in the meta-analysis performed by Stefanidis and colleagues (2018), which examined the effect of CVDs and its association with the increased risk of cognitive decline and dementia in patients with no clinical history of stroke. The authors found that, across studies, conditions such as atrial fibrillation and severe atherosclerosis were significant risk factors for the development of neurocognitive impairment. The neurocognitive performance of patients with CVDs without history of stroke or cardiac arrest is likely to be impaired in the areas of processing speed, psychomotor speed, focus and sustained attention, executive functions, learning efficiency, and memory retrieval (Cohen & Gunstad, 2010).

On the other hand, Jefferson and colleagues (2007) studied the association between systemic hypoperfusion and the performance of executive functions in a sample of 72 patients (aged 56 to 85 years old) with stable CVDs. The sample was stratified into two groups, patients with

CVDs and low CO and patients with CVDs and normal CO. In order to evaluate the cardiac function of the participants, echocardiograms were performed. Additionally, neuropsychological measures were administered to evaluate the neurocognitive performance of the participants. The results suggest that patients with poor CO did not exhibit significant impairment in their executive functioning. Low CO levels were associated with some degree of deterioration, but not in overall executive functioning.

Table 1: *Studies about cardiovascular diseases and neurocognitive performance*

Authors	Title	Publication Date	Design	Participants	Results
Jefferson, A. L., Poppas, A., Paul, R. H., & Cohen, R. A.	Systemic hypoperfusion is associated with executive dysfunction in geriatric cardiac patients	2007	Correlational	n=72	Findings suggest that reduced cardiac output is associated with poorer executive functioning among geriatric outpatients with stable cardiovascular disease, as the cognitive profile emphasizes a relationship between systemic hypoperfusion and problems with sequencing and planning. The executive dysfunction profile may be secondary to reduced blood flow to vulnerable subcortical structures implicated in frontal-subcortical circuitry.
Cohen, et al.	Vascular and cognitive functions associated with cardiovascular disease in the elderly	2009	Correlational	n=88	The results revealed two primary vascular components: one associated with cardiac function, the other with atherosclerotic burden/endothelial dysfunction. Both factors were significantly associated with cognitive function and white matter hyperintensities volume. Reduced systolic variability and increased intima media thickness were most strongly related to reduced attention, executive function, and information processing speed.
Okonkwo et al.	Longitudinal trajectories of cognitive decline among older adults with cardiovascular disease	2010	Longitudinal	n=172	There is measurable decline in neurocognitive function among patients with cardiovascular disease. This decline is linear in some cognitive domains and curvilinear in others and is not attributable to the normal aging process. Cardiac surgery, but not heart failure, significantly affects the trajectory of cognitive decline.

Okonkwo C., Cohen R.A., Gunstad J. & Poppas A.	Cardiac output, blood pressure variability, and cognitive decline in geriatric cardiac patients.	2011	Prospective	n=172	Cardiac output, systolic blood pressure variability, and diastolic blood pressure variability predicted decline in Attention-Executive-Psychomotor function. Specifically, lower cardiac output, reduced variability in systolic blood pressure, and increased variability in diastolic blood pressure were associated with a faster rate of decline in Attention-Executive-Psychomotor function. Mean resting systolic and diastolic blood pressure did not predict decline in Attention-Executive-Psychomotor function.
Alosco et al.	Cognitive Performance in Older Adults with Stable Heart Failure: Longitudinal Evidence for Stability and Improvement.	2014	Longitudinal	n=115	Latent class growth analyses revealed a three-class model for attention/ executive function, four-class model for memory, and a three-class model for language. The slope for attention/executive function and language remained stable, while improvements were noted in memory performance. Education and BDI-II significantly predicted the intercept for attention/ executive function and language abilities. The BDI-II also predicted baseline memory.
Liebel et al.	Cognitive processing speed mediates the effects of cardiovascular disease on executive functioning.	2017	Correlational	n=73	Cardiovascular disease (CVD) was significantly, negatively related to cognitive processing speed (CPS) (β = -.239, 95% CI [-.457, -.021]). CPS was significantly, positively related to an executive function (EF) composite score (β = .566, 95% CI [.368, .688]). CVD was significantly, negatively related to the EF composite score (β = -.137, 95% CI [-.084, -.211]). The indirect links from CVD to the individual measures of the EF composite score via CPS were all significant. CVD most adversely affected tasks of cognitive flexibility and inhibition indirectly through CPS.

Stephan et al.	Neuropsychological profiles of vascular disease and risk of dementia: implications for defining vascular cognitive impairment no dementia (VCI-ND).	2017	Cross-Sectional	n = 2,640	In the cross-sectional analysis, hypertension, peripheral vascular disease and coronary heart disease were not associated with cognitive impairment. Stroke was associated with impaired global Mini Mental State Examination (MMSE) and Cambridge Cognitive Examination (including memory and non-memory) scores. Diabetes was associated with impairments in global cognitive function (MMSE) and abstract thinking. In the longitudinal analysis, cognitive impairments were associated with incident dementia in all groups.

Nevertheless, authors found a significant correlation between systemic hypoperfusion and cognitive impairment in various executive functions. As the authors stated, these findings relating systemic hypoperfusion to poor executive function support past investigations that link cerebral hypoperfusion to the future evolution of VD.

Moreover, Cohen and colleagues (2009) used MRI to investigate the relationship between systemic vascular function, neurocognitive performance, and structural brain abnormalities, in a sample of geriatric outpatients who had treated, but stable, CVDs and no history of neurological illness. One of the several hypotheses of this study was that, relative to vascular function, significant associations would be observed for the domains of attention, executive functioning, and information processing speed. For their study, the authors recruited a total of 88 elderly patients (aged 56-85 years). All the participants had a documented history of CVDs. The investigators intended to measure attention and executive functioning using multiple validated neuropsychological measures. The test measures were grouped into five categories: global cognitive functioning, language functions, visual spatial abilities, learning and memory functions, and attention-executive-psychomotor functions. Their findings linked both CVDs and systemic vascular functioning to cognitive performance and structural brain abnormalities among participants. The study's results support current theories about the development of VCI in the absence of stroke and suggest that processing speed is the function most associated with systemic vascular irregularities.

However, another study found mixed results regarding the influence of CVDs on neurocognitive functioning. Okonkwo and colleagues realized a prospective study (2010) aimed to characterize the temporal course of changes in neurocognitive functioning in the presence of CVDs. The sample of this study consisted of a total of 172 older adults (55-85 years old) with CVDs. Several neuropsychological measures were administered to determine the neurocognitive trajectories of the participants across 36 months of follow-up. The results of this investigation suggest that declines in attention-executive-functioning-psychomotor speed were not significant across the sample. Furthermore, the subjects with a history of HF showed no significant trajectories of neurocognitive decline, though patients who had undergone cardiac surgery performed at lower levels.

Furthermore, Okonkwo and colleagues (2011) prospectively examined whether CO (specifically low) and other specific cardiovascular indices were associated to the longitudinal deterioration of several neurocognitive domains, such as executive function and attention. This study examined the same sample of 172 adults (55-85 years old) that the group's 2010 study did but deployed a different battery of neuropsychological measures. The results of this study suggest that low CO is significantly related to a later, faster decline in attention and executive functioning than is seen in those with higher CO. These results point out the importance of poor cardiac function as a predictor of later neurocognitive decline, and, finally, they support previous evidence indicating that low CO is associated with deficits in cognitive domains.

In addition, Alosco et al. (2014) conducted a longitudinal study with the purpose of evaluating the nature and manifestation of cognitive impairment in patients with HF over time. The authors reported that from 25% to 74% of patients with HF experience some form of cognitive impairment. Nevertheless, the specific patterns vary across studies. To address this problem, the authors examined the longitudinal trajectories of multiple cognitive domains in 115 older adults with HF. During a baseline assessment, participants completed demographic and psychosocial self-report measures, including the Beck Depression Inventory-II. Participants were also administered a brief neuropsychological test battery to assess specific domains, such as attention/executive function, memory, and language. The same procedures were repeated at 3-months and 12- months later. The results of the attention and executive function measures revealed that the participants remained stable over time. While the results of the memory domain measures revealed improvement across the study. However, additional analysis showed that HF patients with low educational levels and depressive symptomatology performed worse at baseline neuropsychological evaluation. Indeed, this study suggests that lower education level and greater depressive symptomatology are important risk factors for cognitive impairment in HF patients. The findings of this study indicated that the level of cognitive impairment in HF is not uniform and may be unique between individuals. In conclusion, cognitive impairment may be distinct across HF patients and affected by factors such as depression and education.

Recently, Stephan and colleagues (2017) conducted a population-based study to determine the neuropsychological profile (being both global and domain specific) of individuals with no dementia and vascular disorders (hypertension, peripheral vascular disease, coronary heart disease [CHD], diabetes, and stroke). An additional aim in this study was to evaluate the risk of two-year incident dementia in individuals with the mentioned vascular diseases and cognitive impairment. The authors randomly selected 2,640 individuals aged 65 or older. Participants were selected via two-phase screening procedure, after which they provided sociodemographic information, health status, functional ability, and a detailed cognitive evaluation.

The results revealed that the pattern of cognitive impairments varied across conditions, finding that hypertension, PVD, and CHD were not associated with impairment in any measure and further finding little evidence that these vascular conditions were associated with the risk of cognitive impairment. Moreover, patients with stroke performed significantly worse on orientation, language comprehension, learning memory, praxis, and perception. When assessing the risk of dementia, the authors found that individuals with CHD who presented impairments in memory, attention, calculation, and praxis were at greater risk of developing dementia. These results differ from those of the previously mentioned studies, in which conditions such as CHD were associated with cognitive impairment. The authors reiterated that this result could have been influenced by the methodological aspects of the study, which included the self-reported disease status, choice of cognitive test, and sample characteristics.

Another recent study, conducted by Liebel and colleagues (2017), aimed to study the consequent effects of CVDs on executive functions. The authors recruited a sample of 23 elderly individuals with CVDs for comparing the executive functioning of those people with a second group of 72 elderly individuals who did not have a history of cardiac events or a diagnosis of CVDs. The participants completed a battery of neuropsychological tests that were intended to evaluate the effects of CVDs on executive functions. The results of this study were statistically significant. The authors concluded that patients with CVDs revealed significant impairment in their executive functioning, compared to those without the condition. The patients with CVDs showed deterioration in executive functions, such as cognitive flexibility, inhibition, and phonemic and semantic fluency. These variabilities exist across the literature and indicate the necessity of further investigations about how CVDs can lead to diminished neurocognitive function.

Impact of cardiovascular health treatment on neurocognitive performance

The literature documented herein suggests that good cardiovascular health may increase the possibilities of preventing or postponing neurocognitive impairment (or mitigating if is present) in patients who suffer from CVDs. Physical and nutritional interventions as well as cardiac rehabilitation constitute part of the alternative remedies to treat and prevent cognitive decline in the presence of CVDs. Next, we will proceed to mention different studies that have attempted to contribute to the understanding of the mechanisms of CVDs and to the development of interventions that can reduce the impact of CVDs on neurocognitive performance.

In their study, Gunstad and colleagues (2005) claimed that patients who suffer from CVDs are at risk of presenting cognitive deficits long before the onset of stroke or dementia. The authors state that improving cardiovascular fitness may result in improved cognitive performance. In order to test this hypothesis, the authors investigated whether a cardiac rehabilitation (CR) program of 12 weeks would improve the neurocognitive performance of patients with CVDs. The study consisted of a total of 18 subjects that, at baseline, demonstrated poor neurocognitive functioning. All the participants underwent a 12-week CR program that included the monitoring of physical condition; education on nutrition, the psychological aspects of heart disease, and medication use; risk behavior modification; and aerobic exercise. Additionally, all the participants underwent neuropsychological assessment. The authors concluded that participants that underwent CR saw their neurocognitive performance significantly improved, specifically in the domains of attention and psychomotor speed. These results suggest that CR benefits not only the cognitive performance of patients with CVDs, but also can lead to a better quality of life in this population.

Aligned with this result, Stanek et al., (2009) aimed to examine the longitudinal cognitive functioning of patients who suffered from HF and other forms of CVDs. The authors hypothesized that the cognitive performance of patients with CVDs and who undergo medical stabilization and treatment for same would improve. The sample consisted of a total of 75 older adults (ranging in age from 53 to 84 years) with CVDs. The subjects underwent echocardiograms to evaluate their cardiac status and administration of a dementia rating scale to evaluate cognitive status. The results of this study demonstrated that subjects that underwent medical stabilization and treatment performed significantly well (compared to that performance on their previous neurocognitive evaluation), specifically, in this study, in the domains of attention and executive functioning. These results accentuate the pivotal role that controlling CVDs conditions can have in the neurocognitive performance of patients.

Netz et al. (2015) hypothesized that CVDs patients in CR that maintained physical activity would improve their neurocognitive performance. The study consisted of a total of 49 participants with CVDs, aged 60 and over. The participants were divided into high and low cardiovascular fitness groups. In order to examine and monitor the neurocognitive performance of the participants, the authors used neuropsychological testing. The results of this study showed that the subjects in the high cardiovascular fitness group performed significantly better across the neurocognitive domains than did those in the low cardiovascular fitness group. The patients in the high cardiovascular fitness group scored highest in the domains of attention and executive functioning.

Ngandu and colleagues (2015) carried out a randomized control trial that hypothesized that modifying vascular and lifestyle factors would result in neurocognitive improvement. The study consisted of a total sample of 2,654 participants, aged from 60 to 77 years old.

Individuals were screened and randomly assigned to intervention and control groups. The evaluation and intervention period lasted a total of 24 months. Both groups received regular health advice; the intervention group attended meetings with the study nurse and physician (for physical examination), received nutritional intervention, engaged in physical exercise training and cognitive training, participated in social activities, and learned how to manage metabolic and vascular risk factors. To examine the influence of the multi-domain intervention, the participants of this study underwent standard cognitive and neuropsychological testing. The results in this study suggest that simultaneous changes in several risk factors had a protective effect, which was reflected in neurocognitive status. Secondary outcomes showed that executive functioning and processing speed had improved from baseline. These findings illustrate that interventions directed at promoting healthier cardiovascular functioning are effective at improving the neurocognitive performance in patients with CVDs.

Conclusions

As documented, patients that suffer from CVDs have a significant risk of experiencing cognitive decline, which is a consistent finding across the literature. This review illustrates the empirical findings of the potential adverse impact that CVDs have (at both the structural and functional levels) on the brain and on neurocognitive performance. Furthermore, it was described the importance of CVDs treatments for neurocognitive performance.

As documented in the literature, patients suffering from poor cardiovascular health have changes in gray matter, small and large cerebral blood vessels and findings of WMH in their brain. In turn, these structural changes have been correlated with changes in neurocognitive functioning in this population.

The majority of the studies mentioned in this review agree that the attention and executive functioning are the most affected domains by the presence of CVDs. It has been stated that deficits in executive function (planning, problem solving, adapting behavior in response to changes in the environment) affect IADLs (Vaughan & Giovanello, 2010). This factor has been associated with the risk of a decline in functional health status. The occurrence of neurocognitive impairment in patients with CVDs may affect the ability of those individuals to adhere to treatment, cause them to not go to medical appointments, and have a negative impact on their general activities of daily living, making cognitive decline in the presence of CVDs an important topic of investigation.

As important as this area of research is, the unification of these topics in clinical practice has particular relevance for the advancement of knowledge and the treatment of these conditions. The information illustrated in our review, is consistent stating that patients with CVDs with neurocognitive impairment have the potential to benefit from alternative treatments that improve their neurocognitively functioning and consequently their daily and instrumental functioning.

This situation calls for the integration of different perspectives in multiple health-related fields, including medicine and neuropsychology. As mentioned above, a patient suffering from CVDs and who also has a neurocognitive impairment will probably have difficulties with the management of his or her medications and, consequently, with his or her overall health. Therefore, detecting, treating, and rehabilitating the neurocognitive aspect in this population could be beneficial not only to patients, but also to the treatment plans provided by cardiologists and other health service providers. An encouraging fact was reported by Rodriguez-Irizarry, Oliveras-Rentas, Olabarrieta-Landa and Arango-

Lasprilla (2018) in which they highlight that 11% of the referrals received by Puerto Rican neuropsychologists come from cardiologists. This data highlights that there is an interdisciplinary connection between neuropsychology and cardiology. Therefore, continuing to study and promote this topic can further solidify the collaboration bond of both disciplines, thus providing a more comprehensive service for patients.

Moreover, assessing the neurocognitive status of a patient with CVDs may help in predicting the future development of VaD or even AD, considering that this latter condition has been found to be etiologically influenced by vascular pathologies and common risk factors (Alonso et al., 2009; Kapasi & Schneider, 2016). In their Alzheimer's disease facts and figures (2019) report, The Alzheimer's Association established that conducting brief cognitive assessment in the primary care setting my help identify the earliest sings of cognitive decline in patients. They defined this procedure as a short evaluation aimed at detecting cognitive impairment conducted by a primary care practitioner (Alzheimer's disease facts and figures, 2019). The practitioner may do one or more of the following procedures: a) ask the patient directly about cognitive concerns, b) observe patient interactions and cognitive function directly during the visit, c) may seek input about cognitive function from the patients family or friends, d) take physical exams, medical history, and family history into account, and e) use one or more brief structured assessment tools to obtain objective measures of cognitive function.

The integration of clinical neuropsychologists and clinical psychologists in the treatment of CVDs could promote adherence to treatment and decrease maladaptive behaviors that may lead to complicate their physical conditions. This kind of multidisciplinary integration has been incorporated in a great variety of hospitals with positive results in the rehabilitation of patients (Jiménez et al., 2013). An integration of this nature is essential if patients are to successfully avoid risk behaviors that may lead to possible future neurocognitive complications caused by cardiovascular conditions.

Some of the limitations presented in the preparation of this review was the heterogeneity in the literature on which are the specific neurocognitive domains that are affected in this type of patients. In addition, another limitation we found was the limited amount of scientific literature on the Hispanic/Latino population with CVDs and their neurocognitive status (Delgado-Derio, Vásquez-Vivar, Orellana- Pineda, Reccius-Meza, Donoso- Sepúlveda & Behrens-Pellegrino, 2008; Romero, López, Velez, & Ortiz, 2013).

This limitations give rise to a series of recommendations that could expand our knowledge on this topic, among those: 1) Develop studies on the neuropsychological profile of different Hispanic/Latino populations with CVDs, 2) conduct studies that illustrate the impact of CVDs isolated from major vascular factors in different cultures in order to understand the nature of this condition on neurocognitive functioning, 3) and finally, we suggest that future prospective studies focus on specific clinical manifestations or conditions under the umbrella of cardiovascular diseases. This will allow a deeper understanding of the variability in neurocognitive functioning between the various cardiovascular conditions.

In conclusion, empirical evidence suggests revealed through empirical literature reveal that patients with CVDs may suffer neurocognitive difficulties. These findings suggest the importance to evaluate these patients neuropsychologically. This will allow the detection of existing deficits and as a result, to refer these patients to professionals who can help them through reliable treatments to maximize the physical and mental health of this population.

Declaration of interest.

The authors report no conflicts of interest. The authors are responsible for the content and writing of this manuscript.

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References

Alzheimer's Association. (2019). Alzheimer's disease facts and figures. *Alzheimers & Dementia*, *15*(3), 321–387. doi: 10.1016/j.jalz.2019.01.010

Almeida O. P., Garrido G. J., Beer C., Lautenschlager N. T., Arnolda L., & Flicker L. (2012). Cognitive and brain changes associated with ischaemic heart disease and heart failure. *European Heart Journal, 33*(14), 1769-1776. doi: 10.1093/eurheartj/ehr467

Alonso, A., Jacobs Jr., D. R., Menotti, A. Nissinen, A., Dontas, A., Kafatos, A., & Kromhout, D. (2009). Cardiovascular risk factors and dementia mortality: 40 years of follow-up in the Seven Countries Study. *Journal of the Neurological Sciences*, *280*(1-2), 79-83. doi: 10.1016/j.jns.2009.02.004

Alosco, M. L., Garcia, S., Spitznagel, M. B., van Dulmen, M., Cohen, R., Sweet, L. H., Josephson, R., Hughes, J.,

Rosneck, J., … Gunstad, J. (2013). Cognitive performance in older adults with stable heart failure: longitudinal evidence for stability and improvement. *Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition*, *21*(2), 239-56. doi: 10.1080/13825585.2013.818616

Alosco, M. L., Spitznagel, M. B., Cohen, R., Sweet, L. H., Colbert, L. H., Josephson, R., . . . & Gunstad, J. (2012). Cognitive impairment is independently associated with reduced instrumental ADLs in persons with heart failure. *The Journal of Cardiovascular Nursing*, *27*(1), 44-50. doi: 10.1097/JCN.0b013e318216a6cd

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Ampadu, J., & Morley J. E. (2015). Heart failure and cognitive dysfunction. *International Journal of Cardiology*, *178*, 12-23. doi: 10.1016/j.ijcard.2014.10.087

Bauer, L. C., Johnson, J. K., & Pozehl, B. J. (2011). Cognition in heart failure: an overview of the concepts and their measures. *Journal of the American Academy of Nurse Practitioners*, *23*(11), 577-585. doi: 10.1111/j.1745-7599.2011.00668.x

Benedictus, M. R., van Harten, A. C., Leeuwis, A. E., Koene, T., Scheltens, P., Barkhof, F., . . . & van der Flier, W. M. (2015). White matter hyperintensities relate to clinical progression in subjective cognitive decline. *Stroke*, *46*(9), 2661-2664. doi: 10.1161/STROKEAHA.115.009475

Blumenfeld, H. (2002). *Neuroanatomy through clinical cases*. Sunderland: Sinauer Associates.

Biesbroek, J. M., Kuijf, H. J., van-der Graaf Y., Vincken K. L, Postma A., Mali W. P., . . . & Geerlings, M. I. (2013). Association between subcortical vascular lesion location and cognition: a voxel-based and tract-based lesion-symptom mapping study. *PLoS ONE, 8*(4), e60541. doi:

10.1371/journal.pone.0060541
Biesbroek, J. M., Weaver, N. A., Hilal, S., Kuijf, H. J., Ikram, M. K., Xu, X., . . . & Chen, C. P. (2007). Impact of strategically located white matter hyperintensities on cognition in memory clinic patients with small vessel. *PLoS ONE, 11*(11), e0166261. doi: 10.1371/journal.pone.0166261
Brannon, L., Feist, J., & Updegraff, J. A. (2014). *Health psychology: An introduction to behavior and health* (8th ed.). Boston, MA: Cengage Learning.
Cohen, R. A., & Gunstad, J. (2010). *Neuropsychology and cardiovascular disease*. Oxford, England: Oxford University Press.
Cohen, R. A., Poppas, A., Forman, D. E., Hoth, K. F., Haley, A. P., Gunstad, J., . . . & Gerhard-Herman, M. (2009). Vascular and cognitive functions associated with cardiovascular disease in the elderly. *Journal of Clinical and Experimental Neuropsychology, 31*(1), 96- 110. doi:10.1080/13803390802014594
Constanzo, L. S. (2011). *Fisiología* (4th ed.). Barcelona, Spain: Elsevier España S.A.
Benjamin, E. J., Virani, S. S., Callaway, C. W., Chamberlain, A. M., Chang, A. R., Cheng, S., . . . & Muntner, P. (2018). American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. *Circulation*, *137*(12), e67-e492. doi: 10.1161/CIR.0000000000000558
Dardiotis, E., Giamouzis, G., Mastrogiannis, D., Vogiatzi, C., Skoularigis, J., Triposkiadis, F., & Hadjigeorgiou, G. M. (2012). Cognitive impairment in heart failure. *Cardiology Research and Practice*, *1*, 1-9. doi: 10.1155/2012/595821
Daviglus, M. L., Pirzada, A., & Talavera, G. A. (2014). Cardiovascular disease risk factors in the Hispanic/Latino population: lessons from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Progress in cardiovascular diseases, 57*(3), 230-236.
Daviglus, M. L., Pirzada, A., & Talavera, G. A. (2014). Cardiovascular disease risk factors in the Hispanic/Latino population: lessons from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Progress in cardiovascular diseases, 57*(3), 230-236.
Debette, S., & Markus, H. S. (2010). The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *Bmj, 341*, c3666.
Delgado-Derio, C., Vásquez Vivar, C., Orellana Pineda, A., Reccius Meza, A., Donoso Sepúlveda, A., & Behrens Pellegrino, M. I. (2008). Rendimiento cognitivo en pacientes chilenos con cardiopatía coronaria y factores de riesgo cardiovascular. *Revista de Neurología, 46*, 24-29. doi: https://doi.org/10.33588/rn.4601.2007454
Dichgans, M., & Leys, D. (2017). Vascular Cognitive Impairment. *Circulation Research*, *120*(3), 573-591.doi: 10.1161/CIRCRESAHA.116.308426
Duering, M., Gonik, M., Malik, R., Zieren, N., Reyes, S., Jouvent, E., . . . & Dichgans, M. (2013). Identification of a strategic brain network underlying processing speed deficits in vascular cognitive impairment. *Neuroimage, 66*, 177-183. doi: 10.1016/j.neuroimage.2012.10.084
Foley, J. (2011). A comprehensive update on the neuropsychology of cardiovascular disease. *Journal of Clinical and Experimental Neuropsychology, 33*(6), 718-720. doi:10.1080/13803395.2011.583541
Ghio, S., Gavazzi, A., Campana, C., Inserra, C., Klersy, C., Sebastiani, R., . . . & Tavazzi, L. (2001). Independent and

additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *Journal of the American College of Cardiology, 37*(1), 183-188. doi: 10.1016/S07351097(00)01102-5

Gorelick, P. B., Scuteri, A., Black, S. E., DeCarli, C., Greenberg, S. M., Iadecola, C., . . . & Seshadri, S. (2011). Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. S*troke*, *42*(9), 2672-2713.doi: 10.1161/STR.0b013e3182299496

Gunstad, J., Macgregor, K. L., Paul, R. H., Poppas, A., Jefferson, A. L., Todaro, J. F., & Cohen, R. A. (2005). cardiac rehabilitation improves cognitive performance in older adults with cardiovascular disease. *Journal of Cardiopulmonary Rehabilitation, 25*(3), 173-176.

Hachinski, V., Iadecola, C., Petersen, R. C., Breteler, M. M., Nyenhuis, D. L., Black, S. E., . . . & Leblanc, G. G. (2006). National Institute of Neurological Disorders and Stroke–Canadian stroke network vascular cognitive impairment harmonization standards. *Stroke*, *37*(9), 2220-2241.doi: 10.1161/01.STR.0000237236.88823.47

Iazzo P.A. (2005). *Handbook of cardiac anatomy physiology and devices*. New Jersey, Humana Press Inc.

Jefferson, A. L. (2010). Cardiac output as a potential risk factor for abnormal brain aging. *Journal of Alzheimer's Disease, 20*(3), 813-821. doi 10.3233/JAD-2010-100081

Jefferson, A. L., Poppas, A., Paul, R. H., & Cohen, R. A. (2007). Systemic hypoperfusion is associated with executive dysfunction in geriatric cardiac patients. *Neurobiology of Aging, 28*(3), 477-483. doi: 10.1016/j.neurobiolaging.2006.01.001

Jiménez, J., Rivera, D., Benítez, P., Tarrats, H., & Ramos, A. (2013). Integrating Mental Health Services into a General Hospital in Puerto Rico. *Journal of Clinical Psychology and Medical Settings, 20*(3), 294-301. doi: 10.1007/s10880-012-9352-x

Kapasi, A., & Schneider, J. A. (2016). Vascular contributions to cognitive impairment, clinical Alzheimer's disease, and dementia in older persons. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1862*(5), 878-886. doi: 10.1016/j.bbadis.2015.12.023

Kasper, D. L., Fauci, A. S., Hauser, S. L., Longo, D. L., Jameson, J. L., & Loscalzo, J. (2004). *Harrison's principles of internal medicine* (16th ed.). New York, NY: McGraw-Hill Education.

Knopman, D. S.,&Petersen, R. C. (2014). Mild Cognitive Impairment and Mild Dementia: A Clinical Perspective. *Mayo Clinic Proceedings, 89*(10), 1452-1459.

Korczyn, A. D., Vakhapova, V., & Grinberg, L. T. (2012). Vascular dementia. *Journal of the Neurological Sciences*, *322*(1-2), 2-10. doi: 10.1016/j.jns.2012.03.027

Leto, L. & Feola, M. (2014). Cognitive impairment in heart failure patients. *Journal of Geriatric Cardiology,* 11(4), 316-328. doi: 10.11909/j.issn.1671-5411.2014.04.007

Levine, D. A., & Langa, K. M. (2011). Vascular Cognitive Impairment: Disease Mechanisms and Therapeutic Implications. *Neurotherapeutics, 8*(3), 361-373. doi.org/10.1007/s13311-011-0047-z

Liebel, S. W., Jones, E. C., Oshri, A., Hallowell, E. S., Jerskey, B. A., Gunstad, J., & Sweet, L. H. (2017).

Cognitive processing speed mediates the effects of cardiovascular disease on executive functioning. *Neuropsychology, 31*(1), 44-51. doi:10.1037/neu0000324

Lourenco, J., Serrano, A., Santos-Silva, A., Gomes, M., Afonso, C., Freitas, P., . . . & Costa, E. (2018). Cardiovascular risk factors are correlated with low cognitive function among older adults across europe based on The SHARE Database. *Aging and Disease, 9*(1), 90-101. doi:10.14336/ad.2017.0128

Netz, Y., Dwolatzky, T., Khaskia, A., & Dunsky, A. (2015). Cardiovascular Fitness and Neurocognitive Performance among Older Adults in the Maintenance Stage of Cardiac Rehabilitation. *Israel journal of Psychiatry and Related Sciences, 52*(3), 55-63.

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., . . . & Kivipelto, M. (2015). A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomized controlled trial. *The Lancet, 385*(9984), 2255-2263. doi: 10.1016/S0140-6736(15)60461-5

Nordlund, A., Rolstad, S., Klang, O., Lind, K., Hansen, S., & Wallin, A. (2007). Cognitive profiles of mild cognitive impairment with and without vascular disease. *Neuropsychology, 21*(6), 706-712. doi: 10.1037/0894-4105.21.6.706

Ogawa, Y., Iwasaki, K., Aoki, K., Shibata, S., Kato, J., & Ogawa, S. (2007). Central hypervolemia with hemodilution impairs dynamic cerebral autoregulation. *Anesthesia and Analgesia, 105*(5),1389-1396. doi: 10.1213/01.ane.0000281910.95740.e4

Okonkwo, O. C., Cohen, R. A., Gunstad, J., & Poppas, A. (2011). Cardiac Output, Blood Pressure Variability, and Cognitive Decline in geriatric cardiac patients. *Journal of Cardiopulmonary Rehabilitation and Prevention, 31*(5), 290-297. doi: 10.1097/HCR.0b013e318220a817

Okonkwo, O. C., Cohen, R. A., Gunstad, J., \ Tremont, G., Alosco, M. L., & Poppas, A. (2010). Longitudinal trajectories of cognitive decline among older adults with cardiovascular disease. *Cerebrovascular Diseases, 30*(4), 362-373. doi: 10.1159/000319564

Ozdemir, O., Soylu, M., Durmaz, T., & Tosun, O. (2013). Early haemodynamic changes in cerebral blood flow after cardiac resychronisation therapy. *Heart, Lung and Circulation, 22*(4), 260-264. doi: 10.1016/j.hlc.2012.10.009

Rodríguez-García, P. L., & Rodríguez-García, D. (2015). Diagnóstico del deterioro cognitivo vascular y sus principales categorías. *Neurología, 30*(4), 223-239. doi: 10.1016/j.nrl.2011.12.014

Rodríguez-Irizarry, W., Oliveras-Rentas, R., Olabarrieta-Landa L., & Arango-Lasprilla J. (2018). La práctica de la neuropsicología en Puerto Rico: implicaciones para la certificación de la especialidad. *Revista Iberoamericana de Neuropsicología, 1*(1), 45-62.

Romero, L. M. C., López, I. E. N., Vélez, C. D., & Ortiz, J. P. (2013). Tamizaje de deterioro cognitivo leve en adultos mayores con enfermedad cardiovascular en un Hospital Nacional de Chiclayo, Perú. *Revista Médica de Risaralda, 20*(1), 14-19.

Sadock, J. E., Sadock, V. A., & Ruiz, P. (2014). *Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry* (11th ed.). Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Sattar, H. (2011). *Fundamentals of Pathology* (1st ed.). Chicago, IL: Pathoma LLC.

Schneider, J. A., Arvanitakis, Z., Bang, W., & Bennett, D. A. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*, *69*(24), 2197-2204. doi:10.1212/01.wnl.0000271090.28148.24

Selman, W. R., & Winn, H. R. (2012). Cerebral blood flow. *Neurosurgical Focus*, *32*(2), doi: 10.3171/2011.12.FOCUS1135

Smith E.E., Salat D.H., Jeng J., McCreary C.R., Fischl B., Schmahmann J.D. (2011). Correlations between MRI white matter lesion location and executive function and episodic memory. *Neurology, 76*(17),1492–1499. doi: 10.1212/WNL.

Stanek, K. M., Gunstad, J., Paul, R. H., Poppas, A., Jefferson, A. L., Sweet, L. H., . . . & Cohen, R. A. (2009). Longitudinal cognitive performance in older adults with cardiovascular disease. *The Journal of Cardiovascular Nursing, 24*(3), 192-197. doi:10.1097/jcn.0b013e31819b54de

Stanek, K. M., Gunstad, J., Spitznagel, M. B., Waechter, D., Hughes, J. W., Luyster, F., . . . & Rosneck, J. (2011). Improvements in cognitive function following cardiac rehabilitation for older adults with cardiovascular disease. *International Journal of Neuroscience*, *121*(2), 86-93. doi: 10.3109/00207454.2010.531893

Stefanidis, K. B., Askew, C. D., Greaves, K., & Summers, M. J. (2018). The effect of non-stroke cardiovascular disease states on risk for cognitive decline and dementia: A systematic and meta-analytic review. *Neuropsychology Review*, *28*(1), 1-15. doi:10.1007/s11065-017-9359-z

Stephan, B. C. M., Minett, T., Muniz-Terrera, G., Harrison, S. L., Matthews, F. E., & Brayne, C. (2017). Neuropsychological profiles of vascular disease and risk of dementia: implications for defining vascular cognitive impairment no dementia (VCI-ND). *Age and ageing*, *46*(5), 755-760.

Tang, M. Y., Chen, T. W., Zhang, X. M., & Huang, X. H. (2014). GRE T2∗-weighted MRI: principles and clinical applications. *BioMed research international*. Retrieved by: http://dx.doi.org/10.1155/2014/312142 doi:10.1155/2014/312142

Tate, D. F., Jefferson, A. L., Brickman, A. M., Hoth, K. F., Gunstad, J., Bramley, K., . . . & Cohen, R. A. (2008). Regional white matter signal abnormalities and cognitive correlates among geriatric patients with treated cardiovascular disease. *Brain Imaging and Behavior, 2*(3), 200-206. doi:10.1007/s11682-008-9032-5

Vaughan, L., & Giovanello, K. (2010). Executive function in daily life: Age-related influences of executive processes on instrumental activities of daily living. *Psychology and Aging, 25*(2), 343-355. doi: 10.1037/a0017729

Vogels, R. L., Oosterman, J. M., van Harten, B., Gouw, A. A., Schroeder-Tanka, J. M., Scheltens, P., . . . & Weinstein, H. C. (2007). Neuroimaging and correlates of cognitive function among patients with heart failure. *Dementia and Geriatric Cognitive Disorders*, *24*(6), 418-423. doi: 10.1159/000109811

Wardlaw, J. M., Doubal, F., Armitage, P., Chappell, F., Carpenter, T., Muñoz-Maniega, M. S., ... & Dhillon, B. (2009). Lacunar stroke is associated with diffuse blood–brain barrier dysfunction. *Annals of Neurology, 65*(2), 194-202. doi:

10.1002/ana.21549

Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., . . . & Dichgans, M.; STandards for ReportIng Vascular changes on Euroimaging (STRIVE v1). (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet Neurology, 12*(8), 822-838. doi: 10.1016/S1474-4422(13)70124-8

Waldstein, S. R., Wendell, C. R., Hosey, M. M., Seliger, S. L., & Katzel, L. L. (2010). Cardiovascular disease and neurocognitive function. In C. L. Armstrong & L. Morrow (Eds.), *Handbook of medical neuropsychology: Applications of cognitive neuroscience* (pp. 69-99). New York, NY: Springer Science + Business Media. doi.org/10.1007/978-1-4419-1364-7_5

World Health Organization. *Cardiovascular diseases*. (17 May 2017). Retrieved from: http://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-