Examining the Impact of Stressors on Cardiovascular Disease, and the Relationship Between Cardiovascular Disease and Cognition

Nimanthi Ranatunga

Department of Psychology, The Ohio State University

Abstract

Background Cardiovascular disease (CVD) is a global health issue and a leading cause of death among Americans. Scientific research indicates that CVD and its risk factors may be influenced by stress, and are associated with deficits in cognitive functioning. Although risk for CVD has been measured using traditional risk factors, incorporating non-traditional risk factors may improve the performance of risk tools, and develop our understanding of more nuanced factors that can influence CVD.

Objective The present study, therefore, investigated how different experiences with stress (i.e., traumatic events and perceived stress) could impact CVD and its risk factors. We also examined the relationship between CVD, CVD risk factors, and cognition.

Methods Participants were 1092 adults (mean age = 54.91 years) from the Midlife in the United States (MIDUS) study. Stress was assessed using self-reported experiences with traumatic events and the Perceived Stress Scale (PSS). CVD risk was assessed using the general Framingham Risk Score (FRS) and experiences with angina. CVD was assessed using self-reported experiences with heart disease and TIA/stroke. Cognition was assessed using composite episodic memory and executive functioning scores from the Brief Test of Adult Cognition by Telephone (BTACT). Data were analyzed using Fisher's exact tests, logistic regressions, linear regressions, and Mann-Whitney U tests.

Results Both measures of stress were not significantly associated with CVD or its risk factors. Angina was not significantly associated with episodic memory or executive functioning composite measures. Higher risk scores were significantly associated with lower episodic memory composite measures but not with executive functioning composite measures. Heart disease was associated with poorer episodic memory but not with executive functioning. TIA/stroke was not associated with episodic memory or executive functioning.

Conclusions CVD and its risk factors have negative impacts on episodic memory and executive functioning, both of which are important in performing everyday activities. The present study demonstrates the need to create and target screening and preventative efforts to reduce the risk of poor cardiovascular health and cognitive impairment in the general population.

Introduction

Cardiovascular disease (CVD) is a global health issue. In 2020, approximately 19 million people died from CVDs (Tsao et al., 2022). This number is projected to reach 22.2 million by 2030 (Ruan et al., 2018). Scientific research indicates that cardiovascular disease and its risk factors are associated with deficits in cognitive functioning (Stampfer, 2006; Deckers et al., 2017). For example, CVD may lead to problems with memory, reasoning, and decision-making, and increases risk for development of vascular dementia (Venkat et al., 2015). There is a need, therefore, to understand what contributes to cardiovascular disease, and what the strongest measures of it are so that cognitive impairment can be prevented.

One way that cardiovascular disease can be measured is through acute cardiac events. Heart disease and stroke require particular attention because they were among the top five leading causes of death in 2016 (Benjamin et al., 2018). Many risk factors can contribute to cardiovascular disease, like an unhealthy diet, tobacco use, and physical inactivity (Hajar, 2017). Multiple risk factors should be assessed at a time because together, they increase one's risk for cardiovascular disease (D'Agostino et al., 2013). A tool that enables us to study the relationship between these factors and cardiovascular disease risk over time is the Framingham Risk Score

(FRS). This tool uses both modifiable (i.e., controllable) risk factors such as smoking tobacco, blood pressure, diabetes, and cholesterol/lipid levels, as well as non-modifiable risk factors such as age and sex. The FRS has been extensively used and has influenced clinical guidelines for cardiovascular disease all around the world (Bitton & Gaziano, 2010). Although risk for cardiovascular disease has traditionally been measured by the factors in the FRS, incorporating non-traditional risk factors may improve the performance of these tools. Angina, which is a chest pain, for example, is a non-traditional risk factor that has been demonstrated to be associated with higher rates of future cardiovascular events (Eisen et al., 2016).

Understanding these measures of cardiovascular disease and cardiovascular disease risk can be important in preventing cognitive impairment. For example, certain risk factors used in the FRS such as age, blood pressure levels, and diabetes are also risk factors for vascular dementia (Song et al., 2014). Patients who exhibit vascular dementia may experience deficits in memory, but more commonly with executive functioning (Lee, 2011). These are two cognitive functions, therefore, that are especially important to study. Heart disease and stroke, which were of interest to the present study, also have implications for cognition. Coronary heart disease has been shown to be associated with accelerated cognitive decline (Xie et al., 2019). Clinical stroke has been associated with poorer performance in multiple cognitive areas including executive function and episodic memory (Weinstein et al., 2014).

While the likelihood of experiencing chronic diseases like cardiovascular disease increases naturally as we age, it also increases through experiencing environmental events such as stress (Santosa et al., 2021). One way that stress can be experienced is through direct or indirect exposure to a traumatic event that involves actual or threatened death, serious injury, or sexual violence (5th ed.; DSM–5; American Psychiatric Association, 2013). Examples of traumatic events include experiencing physical assault, sexual assault, a natural disaster, combat, or a serious accident. Prior work has found associations between traumatic events and cardiovascular disease among a sample of middle-aged and older adults (Cao et al., 2021), and has highlighted the importance of studying lifetime trauma, as it may have a collective effect on health. Another way to conceptualize stress is perceived stress, which occurs when individuals evaluate the degree to which situations in their life are stressful (Katsarou et al., 2013). One study found that there was a 27% increased risk for coronary heart disease among individuals who had high perceived stress. Another study found higher levels of perceived stress to be associated with fatal stroke (Ohlin et al., 2004). Making a direct comparison between traumatic stress and perceived stress can therefore help us to understand which form of stress is most impactful for cardiovascular disease. Moreover, elucidating these relationships can help researchers develop intervention and preventative care methods to maintain cardiovascular health.

In the present study, our first aim investigated the impact of stress on cardiovascular disease and cardiovascular disease risk in a sample of mid-life adults. Participants' experiences with traumatic events and their Perceived Stress Scale (PSS) score were used as measures of stress. Participants' experiences with heart disease and TIA/stroke were used as measures of cardiovascular disease. Their Framingham Risk Score and experience with angina were used as measures of cardiovascular disease risk. We hypothesized that both forms of stress would lead to a higher risk score and a higher likelihood of experiencing cardiovascular disease. Because cardiovascular disease has been shown to have strong implications for cognition, our second aim explored the relationship between cardiovascular disease, cardiovascular disease risk factors, and cognition, using composite measures of episodic memory and executive functioning. We hypothesized that individuals who had the presence of cardiovascular disease or had a higher risk score would have lower composite executive function and episodic memory scores.

Method

Participants

Data for these participants were taken from the Midlife in the United States Survey (MIDUS) dataset, a longitudinal study that began in 1995 conducted to understand biological, psychological, and social processes within the aging US population. Participants in the first wave of MIDUS completed a phone interview and a self-administered questionnaire. The second wave of MIDUS (MIDUS 2) was a 10-year follow-up visit from the first wave. This second wave included a sample of 592 African American participants from Milwaukee, Wisconsin. Data from additional MIDUS 2 projects were used; Cognitive data was collected through a short 20-minute cognitive assessment via phone (Brief Test of Adult Cognition interview; BTACT), and biomarker data was also collected.

The present study consists of 1,092 participants (57% female; Mean age = 54.91 years old, SD = 11.64) who had relevant demographic data (i.e., age, sex, education, race), stress metrics (i.e., answers on experience with traumatic events, Perceived Stress Scale score), biological markers (i.e., information related to average systolic blood pressure, blood pressure medication, smoking status, fasting blood glucose levels, HDL cholesterol levels, total cholesterol levels), and cognitive data (i.e., episodic memory and executive function composite scores). If participants were missing demographic information, both stress metrics, biomarker data, or cognitive data, they were excluded from analyses.

Measures

Traumatic Stressors

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) states that traumatic stress occurs when a person is exposed to actual or threatened death, serious injury, or sexual violence in one or more of the following ways: Direct exposure to the event, witnessing the event, learning that the traumatic event occurred to a loved one, or experiencing repeated and/or extreme exposure to details of the traumatic event (5th ed.; DSM–5; American Psychiatric Association, 2013). A sum of traumatic events was calculated from self-reported answers to questions about the following: Losing your home to a fire or flood, experiencing physical abuse, experiencing sexual abuse, experiencing combat, and experiencing a work accident. Only participants who expressed that the work accident was “very serious” were recorded as having experienced the event. This sum was dichotomized, so that participants who did not experience any traumatic events were a ‘0’, and participants that experienced at least one traumatic event were a ‘1’. This binary factor was used for analyses.

Perceived Stress

A 10-item version of the Perceived Stress Scale (PSS; Cohen et al, 1983) was used to gauge the degree to which respondents believed situations in their lives were stressful. Answers to each question ranged from 1-5. The scale was calculated by summing the responses to all questions, with answers ranging from (10-50). Higher values on the scale meant higher levels of stress.

Angina

Angina is a chest pain that results from reduced blood flow to the heart (Thom et al., 2006). Angina severity was measured using answers to questions from the Rose Scale (Rose, 1962). This scale was used in MIDUS, and has questions that ask about location, timing, and severity of chest pain (Shortridge et al., 2009). Based on the participant’s answers to these questions, they were assigned an angina severity rating between 0 and 3. A score of ‘0’ indicates that participants did not report any chest pain when walking uphill or in a hurry. A score of ‘1’ indicates that participants experienced chest pain when walking uphill but not when walking on a level plain at an ordinary pace. Those who experienced chest pain when walking on a level plain at an ordinary pace with no behavior changes have a score of ‘2’. A score of ‘3’ indicates that participants experienced chest pain when walking on a level plain at an ordinary pace, as well as behavior changes. A score of ‘6’ indicates that the participant did not meet the Rose criteria for angina. These scores were recoded so that higher scores reflected greater angina severity (A score of ‘6’ was coded to ‘0’, a score of ‘0’ was coded to ‘1’, etc.). These answers were then dichotomized for analyses, so that participants with a score of 0 were coded as ‘0’, and participants with scores of 1-4 were coded as ‘1’. These categories were used in analyses.

Framingham Risk Score

As mentioned previously, the Framingham Risk Score is a multivariable risk score that is comprised of several “traditional” risk factors for cardiovascular disease (i.e., age, systolic blood pressure based on whether one is taking blood pressure medication, total cholesterol levels, HDL cholesterol levels, whether one is diabetic, and whether one is a smoker). Information for these risk factors was taken from respondents’ answers to questions within MIDUS 2, and from lab data during the MIDUS 2 Biomarker visit. The Biomarker project is a part of the MIDUS 2 wave, and was completed by participants within four years of their MIDUS 2 interview.

Age was self-reported. The average of three different systolic blood pressure measures was used. To gauge their use of blood pressure medication, participants were asked several questions. They were coded as ‘1’ if they answered yes to currently taking blood pressure medication. They were coded as ‘2’ if they answered no to taking blood pressure medication, or no to any other questions on blood pressure medication. HDL cholesterol levels, total cholesterol levels, and fasting blood glucose levels were measured from a lipid panel. Fasting blood glucose levels at or above 126 mg/dl were coded as ‘1’, or a yes to having diabetes, and those below the level of 126 mg/dl were coded as ‘2’, or a no to having diabetes. Participants were coded as ‘1’ if they answered yes to being a current regular smoker. They were coded as ‘2’ if they answered no to being a current regular smoker, or if they answered no to any of the other questions on experiencing smoking or smoking regularly.

Participants were assigned point values based on their sex and answers to each of the risk factor questions (D’Agostino et al., 2008). The points for each of the questions were then summed to create a total number of points for each participant. This total value coincided with a specific 10-year risk percentage estimate for CVD.

Executive Functioning

The present study used the composite score of executive function derived from reported exploratory and confirmatory factor analyses of the subtests from the BTACT (Lachman et al., 2014). This executive function factor has been used in previous studies (Karlamangla et al., 2014; Hartanto et al., 2020) and is comprised of five cognitive measures regulated by executive functioning. These measures include working memory (Digits Backward), verbal fluency (Category Fluency), inductive reasoning (Number Series), processing speed (Backward Counting), as well as attention switching and inhibitory control from the Stop and Go Switch Task. The z-scores for all executive function measures were averaged to create the composite score, with higher scores indicating better executive functioning.

Episodic Memory

The present study used an episodic memory composite score, which was derived using confirmatory factor analysis. This episodic memory factor is comprised of the Word List Immediate and Word List Delayed. The z-scores for the episodic memory measures were averaged to create the composite score, with higher scores indicating better memory functioning.

Heart Disease

Participants self-reported if they had ever had heart disease. Dichotomous variables were used in our analyses.

TIA or Stroke

Similarly, participants were asked if they had ever had a TIA or a stroke. Dichotomous variables were used in our analyses.

Covariates

Age, sex, race, and education level were used as covariates in all analyses. Education was assessed as an ordinal variable, where respondents identified the highest degree of education they completed using the following categories: (1) No school/some grade school (1-6), (2) Junior high school (7-8), (3) Some high school (9-12, no diploma/no GED), (4) GED, (5) Graduated from high school, (6) 1 to 2 years of college (no degree yet), (7) 3 or more years of college (no degree yet), (8) Graduated from 2-year college, vocational school or assoc. degree, (9) Graduated from a 4- or 5-year college or bachelor's degree, (10) Some graduate school, (11) Master's degree, (12) PH.D., ED.D., MD, DDS, LLB, LLD, JD, or other professional degree. Race was self-reported.

Statistical Analyses

Descriptive statistics and frequencies were conducted and summarized for all variables on the final sample.

The first aim of this study investigated associations between stress and the cardiovascular variables. A Fisher's exact test was used to determine if there was a nonrandom association between experiencing traumatic events and having angina. This test was used rather than a chi-square test, because the cell of participants that did not experience traumatic events and did not have angina had an expected count of less than 5. Next, to examine whether there were significant differences in participants' Framingham Risk Score based on experience of traumatic events, a Mann-Whitney U test was conducted. A Fisher's exact test was used to determine if there was a nonrandom association between experiencing traumatic events and experiencing heart disease. This test was used rather than a chi-square test because the cell of participants that did not experience traumatic events but had heart disease had an expected count of less than 5. Another Fisher's exact test was used to determine if there was a nonrandom association between experiencing traumatic events and experiencing a TIA/stroke. This test was used rather than a chi-square test because the cell of participants that did not experience traumatic events but had a TIA/stroke had an expected count of less than 5. Next, a simple logistic regression was used to measure the effect of perceived stress on the likelihood that participants experience angina. In order to meet the linearity of the logit assumption and capture all non-linearity, higher order polynomial terms were added. A simple linear regression was used to measure the correlation between participants' perceived stress scores and their Framingham Risk Score. Covariates of age, sex, race, and education were added to the first model of the linear regression, and perceived stress was added to the second. Two logistic regressions were also run to measure the effect of participants' perceived stress levels on their experiences with heart disease and with TIA/stroke, respectively. For the logistic regression model between perceived stress and TIA/stroke, the linearity of logit assumption had to be met using higher order transformations.

The second aim of this study was to assess whether there was an association between the cardiovascular variables and cognitive measures (episodic memory and executive functioning). To examine whether there were differences in one's composite episodic memory and executive functioning scores based on angina experiences, two separate Mann-Whitney U tests were conducted. Two linear regressions were run to determine whether the risk score had a significant association with each of the composite scores. Covariates of age, sex, race, and education were added to the first model of each linear regression, and the respective cognitive measure was added to the second. To examine whether there were differences in the cognitive variables based on experiences with heart disease, two linear regressions were run. Covariates were added to the first model of the linear regression, and the respective cognitive measure was added to the second. Two linear regressions were also used to examine differences in the cognitive variables based on experiences with TIA/stroke.

Results

Sample Characteristics

Sample demographic characteristics and descriptive statistics are displayed in Table 1. The sample was primarily White (81.6%) and female (57.0%).

Association between Stress, Cardiovascular Disease, and its Risk Factors

Results from Fisher's exact test indicated that there was not a significant association between having experience with traumatic events and having angina (p = .376). The logistic regression model that tested the association between perceived stress scale score and presence of angina was statistically significant (χ^2 (18, N = 1089) = 68.19 p < .001). After controlling for all covariates, perceived stress significantly contributed to the model. However, after examining the distribution of values using a boxplot, the significance was in the opposite direction than anticipated; increased stress levels were associated with a decreased likelihood of having angina. Mean perceived stress scale scores were 26.329 for participants who did not experience angina and 21.777 for participants who did experience angina. Age was the only statistically significant covariate. A younger age, however, was associated with an increased likelihood of having angina.

Results from the Mann-Whitney U test indicated that there were no significant differences in Framingham Risk Score among the traumatic experience groups (U = 1914, *p* = .924). The simple linear regression that examined whether the risk score could be predicted based on participants' perceived stress scale score, demonstrated that, after adjusting for age, sex, race, and education, there was not a significant relationship (F(5, 1083) = 288.001, *p* = .091, R^2 = .571, R^2 change = .001). Age, sex, and education, however, were all significant predictors of the risk score. Older age and a lower level of education were associated with an increased risk score. Males, on average, had a higher risk score than females.

Fisher's exact tests indicated that there were not statistically significant associations between traumatic stress experience and heart disease (*p* = 1.00) or TIA/stroke (*p* = 1.00). After controlling for all covariates, the logistic regression model that tested the association between perceived stress score and experience of heart disease was statistically significant (χ^2 (18, N = 1084) = 133.981, *p* = < .001). Perceived stress did not significantly contribute to the model and was not associated with an increased likelihood of experiencing heart disease (*p* = .182). Age and sex were the only covariates that significantly contributed to the model. Older age was associated with an increased likelihood of having heart disease. Males had an increased likelihood of having heart disease compared to females. The logistic regression model that tested the association between perceived stress levels and experience of TIA/stroke was statistically significant (χ^2 (18, N = 1084) = 58.246, *p* = < .001). Perceived stress, however, did not significantly contribute to the model and was not associated with a significant increase in likelihood of experiencing a TIA/stroke (*p* = .909) (see Table 2). Age was the only covariate that significantly contributed to the model. Older age was associated with an increased likelihood of having experienced a TIA/stroke.

Association of Cardiovascular Disease and Risk Factors with Cognition

Results from the Mann-Whitney U test comparing participants' composite episodic memory value based on angina experience revealed that there were significant differences among angina groups (U = 27882, *p* = .01) (see Table 3). However, when comparing episodic memory composite means across groups, individuals who experienced angina had a higher mean than individuals who did not (see Table 4). Mean composite episodic memory scores were .08707 for participants who did experience angina and -.21772 for participants who did not experience angina. This direction of the relationship was opposite of what was expected. Similarly, the Mann-Whitney U test comparing participants' composite executive functioning value based on angina experience indicated significant differences (U = 24756, *p* < .001) (see Table 5). But, when comparing the means, individuals who had experienced angina had a higher executive functioning composite than individuals who did not (see Table 6). Mean composite executive functioning scores were .17561 for participants who did experience angina and -.26088 for participants who did not experience angina.

The simple linear regression that examined the relationship between the risk score for cardiovascular disease and composite episodic memory score, demonstrated that, after adjusting for age, sex, education and race, there was a significant relationship (F(5, 1086) = 56.86, *p* = .036, R^2 = .207, R^2 change = .003) (see Table 7), such that increased cardiovascular disease risk was associated with a lower composite episodic memory (see Figure 1). All covariates were significant predictors of composite episodic memory. Younger age and a higher education level were associated with higher composite episodic memory. Males, on average, had a lower composite episodic memory score than females. In addition, there was not a significant effect between risk percentage and executive functioning after adjusting for age, sex, education, and race ($F(5, 1086) = 81.85$, $p = .150$, $R^2 = .274$, change in $R^2 = .002$). All covariates, however, were significant predictors of composite executive functioning (see Table 8). Younger age and a higher education level were also associated with higher composite executive functioning. Females, on average, had a lower composite executive function score than males.

A linear regression indicated that heart disease was a significant predictor of composite episodic memory ($F(5, 1081) = 56.67$, $p = .024$, $R^2 = .208$, change in $R^2 = .004$) even after adjusting for covariates (see Table 9). All covariates were significant predictors of composite episodic memory, as previously mentioned. Similarly, a second linear regression demonstrated that heart disease was not a significant predictor of composite executive function ($F(5, 1081) = 81.24$, $p = .079$, $R^2 = .273$, change in $R^2 = .002$). All covariates were significant predictors, as previously mentioned (see Table 10).

The linear regression used to predict episodic memory given experience with TIA/stroke demonstrated non-significant results. TIA/stroke was not a significant predictor ($F(5, 1081) = 56.18$, $p = .098$, $R^2 = .206$, change in $R^2 = .002$). All covariates were significant predictors (see Table 11). Similarly, the second linear regression indicated that TIA/stroke was not a significant predictor of executive functioning ($F(5, 1081) = 81.55$, $p = .381$, $R^2 = .274$, change in $R^2 = .001$). All covariates, however, were significant predictors, and in an identical direction as previously mentioned (see Table 12).

Discussion

The present study examined how stress could impact cardiovascular disease, and the relationship between cardiovascular disease and cognition. We found that: 1) stress measured through exposure to traumatic events and perceived stress did not have significant associations with cardiovascular disease and its risk factors; 2) increased risk for cardiovascular disease assessed using the Framingham Risk Score was associated with poorer episodic memory; 3) experience with heart disease was associated with poorer episodic memory; and 4) experience with stroke/TIA was not associated with episodic memory or executive functioning.

Understanding different conceptualizations of stress is important, as each may have a different relationship with the development of cardiovascular disease (Gallo et al., 2014). Our results suggested that exposure to traumatic events did not have significant impacts on cardiovascular disease and its risk factors. These findings do not match what has been found in other studies. One study that examined the presence vs. absence of lifetime trauma exposure found that those exposed to trauma were more likely to report experiencing angina or heart failure (Spitzer et al., 2009). In addition, our study demonstrated that more chronic, perceived stress was not significantly associated with cardiovascular disease and its risk factors. These findings have been mixed in the literature. One study that measured the relationship between the PSS and adverse health outcomes following a heart attack found that moderate to high levels of perceived stress were associated with a greater likelihood of angina (Arnold et al., 2012). Another study that used the PSS did not find it to be a significant predictor of heart failure death or hospitalization (Alhurani et al., 2014).

The relationship between stress and cardiovascular disease may partially be due to inflammation that occurs within the body when stress is experienced. Inflammatory biomarkers such as interleukin 6 (IL-6) can be beneficial to the body at times of stress, as it helps to regulate the immune system and wound-healing processes (Fontes et al., 2015). However, chronically elevated levels of IL-6 may be detrimental to health (Fontes et al., 2015). These elevated levels of IL-6 may be responsible for and related to the development of cardiovascular disease (Zhang et al. 2018), traditional risk factors such as blood pressure and cholesterol (Patterson et al., 2010), angina (Biasucci et al., 1996), and have been present among samples exposed to trauma (Tursich et al., 2014). Experiencing traumatic events may lead to post-traumatic stress disorder (PTSD), which has also been shown to be associated with both IL-6 (Passos et al., 2015) and cardiovascular disease (Emdin et al., 2016; Akosile et al., 2018). Individuals with PTSD may have symptoms such as nightmares, feelings of numbness or social detachment, and avoid situations that remind them of the event they experienced (Coughlin, 2011). It is possible, therefore, that rather than the experience of traumatic events, it is the diagnosis of PTSD and presence of symptoms that have implications for cardiovascular disease and its risk factors. When assessing the relationships between the PSS score and our cardiovascular variables, we found that the average PSS score among our sample was only moderately high. It could be possible, therefore, that this level of stress was not high enough to have an impact on cardiovascular health and demonstrate a significant relationship (Alhurani et al., 2014).

Understanding cardiovascular disease and its risk factors is important, because they may contribute to cognitive decline and the development of Alzheimer’s or vascular dementia (Alonso et al., 2009). In our study, higher risk scores were significantly associated with lower composite episodic memory scores, which is in line with previous studies (Song et al, 2020; Dregan et al., 2013). Higher risk scores, however, were not associated with lower composite executive functioning scores. A previous study demonstrated that although risk factors were associated with deficits in multiple cognitive domains, none were associated with cognitive decline over a four-year period (Ganguli et al., 2014). This suggests that risk factors may lead to more static impairments within certain cognitive domains (i.e., cognitive deficits occur, but remain stable) rather than progressive impairments (i.e., cognitive decline) (Ganguli et al., 2014). This could have been a mechanism behind why the risk score was not associated with executive functioning.

In addition, our results did not demonstrate that the presence of angina led to lower composite episodic memory or executive functioning. We hypothesized that angina would be important to cognition, as it is a symptom of coronary heart disease (i.e., the leading cause of death worldwide) (Hermiz & Sedhai, 2022). It is, however, a complex symptom that can be influenced by multiple aspects such as physical exertion or stress (Boyette & Manna, 2022). Therefore, it may not be a measure of cardiovascular disease risk that is specific enough and diagnosed in a consistent manner (Timmis & Hemingway, 2007).

Our results demonstrated that TIA/stroke was not associated with episodic memory or executive functioning. The present study used a self-report variable that assessed all experiences with TIA/stroke, however, there are actually different kinds of strokes that can occur. Hemorrhagic strokes occur when a blood vessel in the brain bursts, whereas ischemic strokes occur when blood flow to the brain is blocked. Hemorrhagic strokes are generally more severe than ischemic strokes (Andersen et al., 2009). One study found that cognitive impairment occurred more in patients with hemorrhagic strokes rather than ischemic strokes (Renjen et al., 2015). Therefore, studying different stroke types may be a more effective way to assess cognitive impairment. Experiences with heart disease in the present study were shown to be associated with lower composite episodic memory, but not with executive functioning. Unlike the brain damage that can be caused by a stroke, it may be that cognitive impairment from heart disease is minor, and not sufficient enough to cause damage to the brain in a short period of time (Xie et al., 2019). Having a longitudinal design could have made cognitive impairments and/or decline more apparent (Xie et al., 2019).

This study has several strengths. First, the present study observed variables within a large, midlife sample that was more representative of the US population, making it more generalizable. Second, studying CVD experiences and measurable risk factors allows us to simultaneously assess the effect that both can have on cognitive health, helping us to indicate whether one measure is more useful for future preventative care methods than the other. Third, the present study assessed multiple risk factors at one time. Because the presence of each additional risk factor increases one's risk for CVD (D'Agostino et al., 2013), the decision to assess a comprehensive array of factors at one time provides insight into various pathways to the development of cardiovascular disease.

This study also has several limitations. First, for the purpose of this study, experiences such as losing a home to a fire or flood, and a "very serious" self-reported work accident were labeled as "traumatic events". These events, however, may be more nuanced examples of traumatic events, as the DSM-5 refers to an event as traumatic if one perceives their life to be in actual or threatened danger. Second, the use of telephones during the cognitive test may have hindered reaction times for one of the executive functioning components, the Stop Go Switch Task (Hughes et al., 2018). Finally, the present study was cross-sectional. Future studies could consider assessing these relationships longitudinally so that a more cause-and-effect relationship between variables can be proven.

In summary, we found that heart disease was associated with episodic memory but not executive functioning, and that TIA/stroke was not associated with cognition. We also found that the Framingham Risk Score was associated with poorer episodic memory but not associated with executive functioning, and that stress was not associated with cardiovascular variables. Future studies using longitudinal follow-up of these variables are needed. Cardiovascular disease is a global issue. It does not discriminate by age, sex, race, or income, and is expected to take the lives of 22.2 million individuals by the year 2030. Many types of CVD, however, are preventable, and monitoring risk factors such as the ones mentioned in this study are a strong way to prevent development of this burden. There is an intricate link between the heart and the brain. Cardiovascular disease and its risk factors have an impact on cognition, especially in areas related to memory and executive functioning, both of which are important components in performing everyday activities. The present study demonstrates the need to create and target screening and preventative efforts in order to reduce the risk of poor cardiovascular health and cognitive impairment in the general population.

Table 1. Demographic and health characteristics of the sample.

	N=1092
Age – Range (Mean)	34-83 (54.91)
Female	622 (57.0%)
Race	--
White	891 (81.6%)
Black and/or African American	159 (14.6%)
Native American or Alaska Native Aleutian Islander	13 (1.2%)
Asian	3 (0.3%)
Other	26 (2.4%)
Education	
Less than high school	50 (4.5%)
Graduated from high school or GED	242 (22.2%)
Some college no degree	237 (21.7%)
Associate's degree	81 (7.4%)
Bachelor's degree	233 (21.3%)
At least some graduate school	249 (22.8%)
Perceived Stress Scale – Range (Mean)	10-48 (22.05)
Experienced Traumatic Stress	259 (23.7%)
Experienced Angina	1025 (93.9%)
Experienced Heart Disease	124 (11.4%)
Experienced TIA/Stroke	44 (4%)
Framingham Risk Score – Range (Mean)	1-30 (10.64)

Executive Function Composite – Range (Mean)	-4.18 – 2.90(.148)
Episodic Memory Composite – Range (Mean)	-2.59 – 3.40(.068)

Table 2. Results of the logistic regression between PSS and TIA/stroke.

	B	**S.E.**	**Wald**	**df**	**Sig**	**Exp(B)**
Age	-0.095	0.015	39.707	1	<.001	0.909
Sex(1)	0.004	0.328	0	1	0.991	1.004
Perceived Stress Scale	-0.003	0.028	0.013	1	0.909	0.997
Race(Binned)	-0.438	0.436	1.011	1	0.315	0.645
Education(Binned)			1.769	3	0.622	
Education(Binned)(1)	0.609	0.562	1.174	1	0.279	1.839
Education(Binned)(2)	0.764	0.593	1.664	1	0.197	2.148
Education(Binned)(3)	0.483	0.597	0.653	1	0.419	1.621
Constant	8.511	1.379	38.089	1	<.001	4969.729

Note: Results demonstrate that scores from the PSS did not significantly contribute to an increased likelihood of experiencing a TIA/stroke, after adjusting for covariates.

Table 3. Results of the Mann-Whitney U test between angina and episodic memory.

Test Statistics	
	Episodic Memory Composite
Mann-Whitney U	27882
Wilcoxon W	30160
Z	-2.582
Asymp. Sig. (2-tailed)	.010

a. Grouping Variable: Presence of Angina

Note: Results demonstrate that there were significant differences in participants' episodic memory composite score based on presence of angina.

Table 4. Comparison of mean episodic memory composite scores based on angina category

Episodic Memory Composite Scores			
Presence of Angina	Mean	N	Std. Deviation
No	-0.21772	67	1.077836
Yes	0.08707	1025	0.905784
Total	0.06837	1092	0.919616

Note: Presence of angina was associated with a higher episodic memory composite.

Table 5. Results of the Mann-Whitney U test between angina and executive function

Test Statistics	
	Executive Function Composite
Mann-Whitney U	24756
Wilcoxon W	27034
Z	-3.831
Asymp. Sig. (2-tailed)	<.001

a. Grouping Variable: Presence of Angina

Note: Results demonstrate that there were significant differences in participants' executive function composite score based on presence of angina.

Table 6. Comparison of mean executive function composite scores based on angina category

Executive Function Composite Scores			
Presence of Angina	Mean	N	Std. Deviation
No	-0.26088	67	0.857463
Yes	0.17561	1025	0.906756
Total	0.14883	1092	0.909491

Note: Presence of angina was associated with a higher executive function composite.

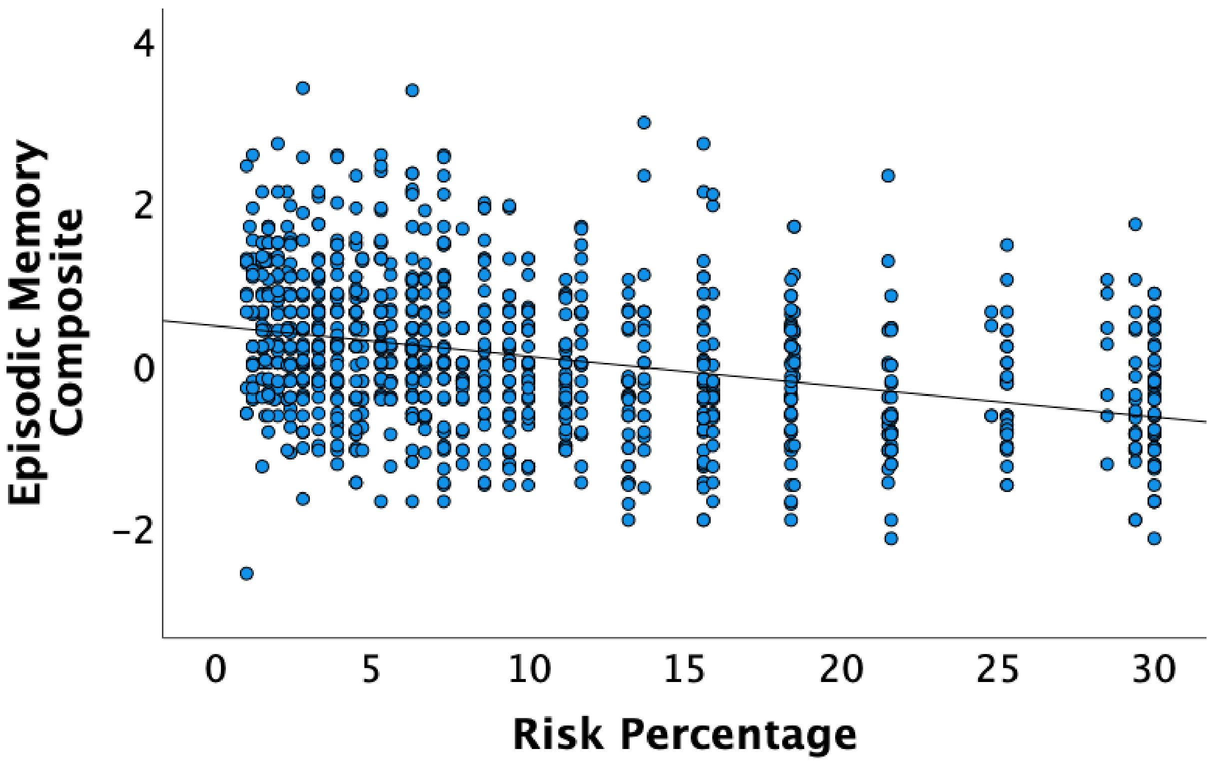

Figure 1. The relationship between FRS and episodic memory composite scores. A higher FRS was associated with a lower episodic memory composite score. Covariates of age, sex, education, and race were controlled for.

Table 7. Results of the linear regression between the FRS and episodic memory

Model		**B**	**Std. Error**	**Beta**	**t**	**Sig.**
1	(Constant)	-0.133	0.181		-0.739	0.46
	Age	-0.021	0.002	-0.262	-9.612	<.001
	Sex	0.54	0.05	0.291	10.709	<.001
	Education	0.078	0.01	0.213	7.799	<.001
	Race	-0.08	0.029	-0.074	-2.7	0.007
2	(Constant)	-0.121	0.18		-0.672	0.502
	Age	-0.017	0.003	-0.212	-5.81	<.001
	Sex	0.469	0.061	0.253	7.739	<.001
	Education	0.075	0.01	0.205	7.446	<.001
	Race	-0.079	0.029	-0.073	-2.68	0.007
	FRS	-0.009	0.004	-0.086	-2.099	0.036

Note: Results demonstrate that a higher FRS significantly predicted poorer episodic memory composite scores after adjusting for covariates.

Table 8. Results of the linear regression between the FRS and executive functioning

Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	1.167	0.171		6.833	<.001
	Age	-0.026	0.002	-0.338	-12.947	<.001
	Sex	-0.161	0.048	-0.088	-3.377	<.001
	Education	0.12	0.01	0.33	12.645	<.001
	Race	-0.176	0.028	-0.165	-6.306	<.001
2	(Constant)	1.175	0.171		6.88	<.001
	Age	-0.024	0.003	-0.305	-8.734	<.001
	Sex	-0.207	0.057	-0.113	-3.609	<.001
	Education	0.118	0.01	0.325	12.331	<.001
	Race	-0.175	0.028	-0.164	-6.293	<.001
	FRS	-0.006	0.004	-0.057	-1.442	0.15

Note: Results demonstrate that a higher FRS did not significantly predict poorer executive function composite scores after adjusting for covariates.

Table 9. Results of the linear regression between heart disease and episodic memory composite scores

Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	-0.137	0.181		-0.754	0.451
	Age	-0.021	0.002	-0.261	-9.535	<.001
	Sex	0.54	0.051	0.291	10.677	<.001
	Education	0.078	0.01	0.213	7.773	<.001
	Race	-0.078	0.029	-0.073	-2.657	0.008
2	(Constant)	-0.545	0.256		-2.129	0.033
	Age	-0.019	0.002	-0.242	-8.452	<.001
	Sex	0.525	0.051	0.283	10.337	<.001
	Education	0.077	0.01	0.21	7.675	<.001
	Race	-0.077	0.029	-0.071	-2.606	0.009
	Experience with Heart Disease	0.187	0.083	0.065	2.258	0.024

Note: Results demonstrate that having heart disease significantly predicted poorer episodic memory composite scores after adjusting for covariates.

Table 10. Results of the linear regression between heart disease and executive function composite scores

Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	1.132	0.172		6.594	<.001
	Age	-0.026	0.002	-0.333	-12.711	<.001
	Sex	-0.156	0.048	-0.085	-3.259	0.001
	Education	0.121	0.01	0.333	12.718	<.001
	Race	-0.175	0.028	-0.165	-6.291	<.001
2	(Constant)	0.831	0.242		3.434	<.001
	Age	-0.025	0.002	-0.319	-11.628	<.001
	Sex	-0.166	0.048	-0.091	-3.454	<.001
	Education	0.12	0.01	0.331	12.635	<.001
	Race	-0.174	0.028	-0.164	-6.252	<.001
	Experience with Heart Disease	0.138	0.078	0.048	1.756	0.079

Note: Results demonstrate that having heart disease did not significantly predict poorer executive function composite scores after adjusting for covariates.

Table 11. Results of the linear regression between TIA/stroke and episodic memory composite scores

Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	-0.135	0.181		-0.748	0.455
	Age	-0.021	0.002	-0.261	-9.56	<.001
	Sex	0.541	0.051	0.291	10.698	<.001
	Education	0.079	0.01	0.213	7.801	<.001
	Race	-0.084	0.03	-0.077	-2.826	0.005
2	(Constant)	-0.598	0.333		-1.797	0.073
	Age	-0.02	0.002	-0.251	-8.987	<.001
	Sex	0.54	0.05	0.291	10.699	<.001
	Education	0.078	0.01	0.213	7.777	<.001
	Race	-0.083	0.03	-0.076	-2.763	0.006
	Experience with TIA/Stroke	0.214	0.129	0.046	1.656	0.098

Note: Results demonstrate that having a TIA/stroke did not significantly predict poorer episodic memory composite scores after adjusting for covariates.

Table 12. Results of the linear regression between TIA/stroke and executive function composite scores

Model		**B**	**Std. Error**	**Beta**	**t**	**Sig.**
1	(Constant)	1.165	0.171		6.829	<.001
	Age	-0.026	0.002	-0.337	-12.882	<.001
	Sex	-0.155	0.048	-0.085	-3.25	0.001
	Education	0.12	0.01	0.33	12.636	<.001
	Race	-0.187	0.028	-0.173	-6.618	<.001
2	(Constant)	0.934	0.314		2.969	0.003
	Age	-0.026	0.002	-0.331	-12.389	<.001
	Sex	-0.155	0.048	-0.085	-3.253	0.001
	Education	0.12	0.01	0.33	12.617	<.001
	Race	-0.186	0.028	-0.172	-6.579	<.001
	Experience with TIA/Stroke	0.107	0.122	0.023	0.876	0.381

Note: Results demonstrate that having a TIA/stroke did not significantly predict poorer executive function composite scores after adjusting for covariates.

References

Akosile, W., Colquhoun, D., Young, R., Lawford, B., & Voisey, J. (2018). The association between post-traumatic stress disorder and coronary artery disease: a meta-analysis. *Australasian Psychiatry*, *26*(5), 524-530.

Alhurani, A. S., Dekker, R., Tovar, E., Bailey, A., Lennie, T. A., Randall, D. C., & Moser, D. K. (2014). Examination of the potential association of stress with morbidity and mortality outcomes in patient with heart failure. *SAGE Open Medicine*, *2*. https://doi.org/10.1177/2050312114552093

Alonso, A., Mosley, T. H., Gottesman, R. F., Catellier, D., Sharrett, A. R., & Coresh, J. (2009). Risk of dementia hospitalization associated with cardiovascular risk factors in midlife and older age: The Atherosclerosis Risk in Communities (Aric) study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *80*(11), 1194–1201. https://doi.org/10.1136/jnnp.2009.176818

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Andersen, K. K., Olsen, T. S., Dehlendorff, C., & Kammersgaard, L. P. (2009). Hemorrhagic and ischemic strokes compared. *Stroke*, *40*(6), 2068–2072. https://doi.org/10.1161/STROKEAHA.108.540112

Arnold, S. V., Smolderen, K. G., Buchanan, D. M., Li, Y., & Spertus, J. A. (2012). Perceived stress in myocardial infarction: Long-term mortality and health status outcomes. *Journal of the American College of Cardiology*, *60*(18), 1756–1763. https://doi.org/10.1016/j.jacc.2012.06.044

Benjamin, E. J., Virani, S. S., Callaway, C. W., Chamberlain, A. M., Chang, A. R., Cheng, S., Chiuve, S. E., Cushman, M., Delling, F. N., Deo, R., de Ferranti, S. D., Ferguson, J. F., Fornage, M., Gillespie, C., Isasi, C. R., Jiménez, M. C., Jordan, L. C., Judd, S. E., Lackland, D., …

American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. (2018). Heart disease and stroke statistics-2018 update: A report from the american heart association. *Circulation*, *137*(12), e67–e492. https://doi.org/10.1161/CIR.0000000000000558

Biasucci, L. M., Vitelli, A., Liuzzo, G., Altamura, S., Caligiuri, G., Monaco, C., Rebuzzi, A. G., Ciliberto, G., & Maseri, A. (1996). Elevated levels of interleukin-6 in unstable angina. *Circulation*, *94*(5), 874–877. https://doi.org/10.1161/01.cir.94.5.874

Bitton, A., & Gaziano, T. A. (2010). The Framingham Heart Study's impact on global risk assessment. *Progress in Cardiovascular Diseases*, *53*(1), 68–78. https://doi.org/10.1016/j.pcad.2010.04.001

Boyette, L. C., & Manna, B. (2022). Physiology, myocardial oxygen demand. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK499897/

Cao, X., Zhang, J., Ma, C., Li, X., Kuo, C.-L., Levine M., Hu, G., Allore, H., Chen, X., Wu, X., & Liu, Z. (2021). *Life course traumas, phenotypic aging, and cardiovascular disease: Retrospective analysis of 104,939 UKB participant.* https://doi.org/10.1101/2021.11.24.21266842

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, *24*(4), 385–396. https://doi.org/10.2307/2136404

Coughlin, S. S. (2011). Post-traumatic stress disorder and cardiovascular disease. The Open Cardiovascular Medicine Journal, 5, 164–170. https://doi.org/10.2174/1874192401105010164

D'Agostino, R. B., Pencina, M. J., Massaro, J. M., & Coady, S. (2013). Cardiovascular disease risk assessment: Insights from framingham. *Global Heart*, *8*(1), 11–23. https://doi.org/10.1016/j.gheart.2013.01.001

D'Agostino, R. B., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care. *Circulation*, *117*(6), 743–753. https://doi.org/10.1161/CIRCULATIONAHA.107.699579

Deckers, K., Schievink, S. H. J., Rodriquez, M. M. F., Oostenbrugge, R. J. van, Boxtel, M. P. J. van, Verhey, F. R. J., & Köhler, S. (2017). Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. *PLOS ONE*, *12*(9), e0184244. https://doi.org/10.1371/journal.pone.0184244

Dregan, A., Stewart, R., Gulliford, M. (2013). Cardiovascular risk factors and cognitive decline in adults aged 50 and over: a population-based cohort study, *Age and Ageing*, 42(3), 338-345, https://doi.org/10.1093/ageing/afs166

Eisen, A., Bhatt, D. L., Steg, P. G., Eagle, K. A., Goto, S., Guo, J., Smith, S. C., Ohman, E. M., Scirica, B. M., & null, null. (n.d.). Angina and future cardiovascular events in stable patients with coronary artery disease: Insights from the reduction of atherothrombosis for continued health (Reach) registry. *Journal of the American Heart Association*, *5*(10), e004080. https://doi.org/10.1161/JAHA.116.004080

Emdin, C. A., Odutayo, A., Wong, C. X., Tran, J., Hsiao, A. J., & Hunn, B. H. (2016). Meta-Analysis of Anxiety as a Risk Factor for Cardiovascular Disease. *The American journal of cardiology*, *118*(4), 511–519. https://doi.org/10.1016/j.amjcard.2016.05.041

Fontes, J. A., Rose, N. R., & Čiháková, D. (2015). The varying faces of IL-6: From cardiac protection to cardiac failure. *Cytokine*, *74*(1), 62–68. https://doi.org/10.1016/j.cyto.2014.12.024

Gallo, L. C., Roesch, S. C., Fortmann, A. L., Carnethon, M. R., Penedo, F. J., Perreira, K., Birnbaum-Weitzman, O., Wassertheil-Smoller, S., Castañeda, S. F., Talavera, G. A., Sotres-Alvarez, D., Daviglus, M. L., Schneiderman, N., & Isasi, C. R. (2014). Associations of chronic stress burden, perceived stress, and traumatic stress with cardiovascular disease prevalence and risk factors in the Hispanic Community Health Study/Study of Latinos Sociocultural Ancillary Study. *Psychosomatic Medicine*, *76*(6), 468–475. https://doi.org/10.1097/PSY.0000000000000069

Ganguli, M., Fu, B., Snitz, B. E., Unverzagt, F. W., Loewenstein, D. A., Hughes, T. F., & Chang, C. C. (2014). Vascular risk factors and cognitive decline in a population sample. *Alzheimer disease and associated disorders*, *28*(1), 9–15. https://doi.org/10.1097/WAD.0000000000000004

Hajar R. (2017). Risk Factors for Coronary Artery Disease: Historical Perspectives. *Heart views : the official journal of the Gulf Heart Association*, *18*(3), 109–114. https://doi.org/10.4103/HEARTVIEWS.HEARTVIEWS_106_17

Hartanto, A., Yong, J. C., Toh, W. X., Lee, S. T. H., Tng, G. Y. Q., & Tov, W. (2020). Cognitive, social, emotional, and subjective health benefits of computer use in adults: A 9-year longitudinal study from the Midlife in the United States (Midus). *Computers in Human Behavior*, *104*, 106179. https://doi.org/10.1016/j.chb.2019.106179

Hermiz, C., & Sedhai, Y. R. (2022a). Angina. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK557672/

Hughes, M. L., Agrigoroaei, S., Jeon, M., Bruzzese, M., & Lachman, M. E. (2018). Change in Cognitive Performance From Midlife Into Old Age: Findings from the Midlife in the United States (MIDUS) Study. *Journal of the International Neuropsychological Society : JINS*, *24*(8), 805–820. https://doi.org/10.1017/S1355617718000425

Karlamangla, A. S., Miller-Martinez, D., Lachman, M. E., Tun, P. A., Koretz, B. K., & Seeman, T. E. (2014). Biological correlates of adult cognition: Midlife in the United States (Midus). *Neurobiology of Aging*, *35*(2), 387–394. https://doi.org/10.1016/j.neurobiolaging.2013.07.028

Katsarou, A. L., Triposkiadis, F., & Panagiotakos, D. (2013). Perceived stress and vascular disease: Where are we now? *Angiology*, *64*(7), 529–534. https://doi.org/10.1177/0003319712458963

Kiecolt-Glaser, J. K., Preacher, K. J., MacCallum, R. C., Atkinson, C., Malarkey, W. B., & Glaser, R. (2003). Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(15), 9090–9095. https://doi.org/10.1073/pnas.1531903100

Kumar, S. (2017). Cardiovascular disease and its determinants: Public health issue. *J. Clin. Med. Ther*, *2*(1).

Lachman, M. E., Agrigoroaei, S., Tun, P. A., & Weaver, S. L. (2014). Monitoring cognitive functioning: Psychometric properties of the brief test of adult cognition by telephone(Btact). *Assessment*, *21*(4), 404–417. https://doi.org/10.1177/1073191113508807

Lee, A. Y. (2011). Vascular dementia. *Chonnam Medical Journal, 47*(2), 66–71. https://doi.org/10.4068/cmj.2011.47.2.66

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. https://doi.org/10.1037/neu0000324

Ohlin, B., Nilsson, P. M., Nilsson, J.-A., & Berglund, G. (2004). Chronic psychosocial stress predicts long-term cardiovascular morbidity and mortality in middle-aged men. *European Heart Journal*, *25*(10), 867–873. https://doi.org/10.1016/j.ehj.2004.03.003

Patterson, C. C., Smith, A. E., Yarnell, J. W. G., Rumley, A., Ben-Shlomo, Y., & Lowe, G. D. O. (2010). The associations of interleukin-6 (IL-6) and downstream inflammatory markers with risk of cardiovascular disease: The Caerphilly Study. *Atherosclerosis*, *209*(2), 551–557. https://doi.org/10.1016/j.atherosclerosis.2009.09.030

Passos, I. C., Vasconcelos-Moreno, M. P., Costa, L. G., Kunz, M., Brietzke, E., Quevedo, J., Salum, G., Magalhães, P. V., Kapczinski, F., & Kauer-Sant'Anna, M. (2015). Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. *The lancet. Psychiatry*, *2*(11), 1002–1012. https://doi.org/10.1016/S2215-0366(15)00309-0

Renjen, P. N., Gauba, C., & Chaudhari, D. (n.d.). Cognitive impairment after stroke. Cureus, 7(9), e335. https://doi.org/10.7759/cureus.335

Rose, G. A. (1962). The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bulletin of the World Health Organization*, *27*, 645–658.

Ruan, Y., Guo, Y., Zheng, Y., Huang, Z., Sun, S., Kowal, P., Shi, Y., & Wu, F. (2018). Cardiovascular disease (Cvd) and associated risk factors among older adults in six low-and middle-income countries: Results from SAGE Wave 1. *BMC Public Health*, *18*(1), 778. https://doi.org/10.1186/s12889-018-5653-9

Santosa, A., Rosengren, A., Ramasundarahettige, C., Rangarajan, S., Chifamba, J., Lear, S. A., Poirier, P., Yeates, K. E., Yusuf, R., Orlandini, A., Weida, L., Sidong, L., Yibing, Z., Mohan, V., Kaur, M., Zatonska, K., Ismail, N., Lopez-Jaramillo, P., Iqbal, R., … Yusuf, S. (2021). Psychosocial risk factors and cardiovascular disease and death in a population-based cohort from 21 low-, middle-, and high-income countries. *JAMA Network Open*, *4*(12), e2138920. https://doi.org/10.1001/jamanetworkopen.2021.38920

Shortridge, E. F., Marsden, P. V., Ayanian, J. Z., & Cleary, P. D. (2009). Gender differences in the relationships of cardiovascular symptoms and somatosensory amplification to mortality. *Research in Human Development*, *6*(4), 219–234. https://doi.org/10.1080/15427600903281236

Song, J., Lee, W. T., Park, K. A., & Lee, J. E. (2014). Association between risk factors for vascular dementia and adiponectin. *BioMed Research International*, *2014*, 261672. https://doi.org/10.1155/2014/261672

Song, R., Xu, H., Dintica, C. S., Pan, K.-Y., Qi, X., Buchman, A. S., Bennett, D. A., & Xu, W. (2020). Associations between cardiovascular risk, structural brain changes, and cognitive decline. *Journal of the American College of Cardiology*, *75*(20), 2525–2534. https://doi.org/10.1016/j.jacc.2020.03.053

Spitzer, C., Barnow, S., Völzke, H., John, U., Freyberger, H. J., & Grabe, H. J. (2009). Trauma, posttraumatic stress disorder, and physical illness: Findings from the general population. *Psychosomatic Medicine*, *71*(9), 1012–1017. https://doi.org/10.1097/PSY.0b013e3181bc76b5

Stampfer, M. J. (2006). Cardiovascular disease and Alzheimer's disease: Common links. *Journal of Internal Medicine*, *260*(3), 211–223. https://doi.org/10.1111/j.1365-2796.2006.01687.x

Thom, T., Haase, N., Rosamond, W., Howard, V. J., Rumsfeld, J., Manolio, T., Zheng, Z.-J., Flegal, K., O'Donnell, C., Kittner, S., Lloyd-Jones, D., Goff, D. C., Hong, Y., Adams, R., Friday, G., Furie, K., Gorelick, P., Kissela, B., Marler, J., … American Heart Association Statistics Committee and Stroke Statistics Subcommittee. (2006). Heart disease and stroke statistics--2006 update: A report from the american heart association statistics committee and stroke statistics subcommittee. *Circulation*, *113*(6), e85-151. https://doi.org/10.1161/CIRCULATIONAHA.105.171600

Timmis, A. D., Feder, G., & Hemingway, H. (2007b). Prognosis of stable anginapectoris: Why we need larger population studies with higher endpoint resolution. *Heart*, *93*(7), 786–791. https://doi.org/10.1136/hrt.2006.103119

Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Alonso, A., Beaton, A. Z., Bittencourt, M. S., Boehme, A. K., Buxton, A. E., Carson, A. P., Commodore-Mensah, Y., Elkind, M. S. V., Evenson, K. R., Eze-Nliam, C., Ferguson, J. F., Generoso, G., Ho, J. E., Kalani, R., Khan, S. S., Kissela, B. M., … null, null. (2022). Heart disease and stroke statistics—2022 update: A report from the american heart association. *Circulation*, *145*(8), e153–e639. https://doi.org/10.1161/CIR.0000000000001052

Tursich, M., Neufeld, R. W. J., Frewen, P. A., Harricharan, S., Kibler, J. L., Rhind, S. G., & Lanius, R. A. (2014). Association of trauma exposure with proinflammatory activity: A transdiagnostic meta-analysis. *Translational Psychiatry*, *4*, e413. https://doi.org/10.1038/tp.2014.56

Venkat, P., Chopp, M., & Chen, J. (2015). Models and mechanisms of vascular dementia. *Experimental Neurology*, *272*, 97–108. https://doi.org/10.1016/j.expneurol.2015.05.006

Weinstein, G., Preis, S. R., Beiser, A. S., Au, R., Kelly-Hayes, M., Kase, C. S., Wolf, P. A., & Seshadri, S. (2014). Cognitive performance after stroke – the framingham heart study. *International Journal of Stroke : Official Journal of the International Stroke Society*, *9*(0 0), 48–54. https://doi.org/10.1111/ijs.12275

Xie, W., Zheng, F., Yan, L., & Zhong, B. (2019). Cognitive decline before and after incident coronary events. *Journal of the American College of Cardiology*, *73*(24), 3041–3050. https://doi.org/10.1016/j.jacc.2019.04.019

Zhang, B., Li, X.-L., Zhao, C.-R., Pan, C.-L., & Zhang, Z. (2018). Interleukin-6 as a predictor of the risk of cardiovascular disease: A meta-analysis of prospective epidemiological studies. *Immunological Investigations*, *47*(7), 689–699. https://doi.org/10.1080/08820139.2018.1480034