# Investigating the Link Between Cardiovascular Diseases and Neurodegenerative Disorders

By
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A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy

Brac University

November 2022

## Declaration

It is hereby declared that

1. The project submitted is my own original work while completing a degree at Brac University.

2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all main sources of help.

**Student's Full Name & Signature:**

**Manashi Dey**

**17346002**

# Approval

The project titled "Investigating the Link Between Cardiovascular diseases and Neurodegenerative disorders" submitted by Manashi Dey (17346002) of Summer, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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## Ethics Statement

This study does not involve any kind of animal and human subject.

# Abstract

Neurodegenerative (ND) disturbances (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and spinal cord injury) are a notable public health concern across the world, and they are growing more widespread as the average age of the population progresses. On the other side, there are an examined 17.9 million fatalities a year from cardiovascular disease (CVD) globally, which accounts for practically one-third of all deaths. This examination aims to construct probable the correlation between cardiovascular diseases and Neurodegenerative disorders. Extensive literature review using secondary research methods such as research articles, news articles, academic published papers. A leading availing factor is that the diagnostic criteria for ND commonly prevent patients who have any significant cardiovascular disease (CVD). On the other hand, cardiovascular disease (CVD) may cause analytical impairment and dementia, also other neurodegenerative disorders. A link prevails between ND and CVD, without a doubt, not only because they share common risk points but also because they have similar molecular processes of onset. Understanding the etiology and mechanisms of one of these diseases may pave the way for building up novel therapeutic strategies that apply to both ND and CVD if they are determined.



**Keywords:** Neurodegenerative disorder, Alzheimer’s disease, Parkinson's disease, Huntington’s disease, Electrocardiogram, etc

# Dedication

*Dedicated to my parents.*

## Acknowledgement

First and foremost, I would like to express my deepest gratitude towards Almighty God for giving me the blessing, the strength, the patience and chance to complete my project work properly.

I am really fortunate that I had the kind and supportive supervision of Faruque Azam (Lecturer, School of Pharmacy of Brac University). His constant encouragement and careful monitoring motivated me to do my work properly. He was very helpful to me whenever I faced any problem in my work and helped me to resolve any kind of inaccuracy in my work. Moreover, I would like to express my special thanks to Professor Dr. Eva Rahman Kabir, Dean of School of Pharmacy of Brac University who gave me the opportunity to conduct my project work.

In the end, I acknowledge my sincere gratitude to my parents, friends and seniors for their devotion, support and faith in my ability throughout the whole journey.

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# List of Acronyms

| | |
|---|---|
| ALS | Amyotrophic lateral sclerosis |
| ANS | Autonomic nervous system |
| APA | American Psychological Association's |
| CTE | Chronic traumatic encephalopathy |
| CHD | Coronary heart disease |
| CES-D | Center for Epidemiological Studies Depression |
| CHD | Coronary heart disease |
| DM | Diabetes mellitus |
| ECG | Electrocardiogram |
| GHDs | Global Burden of Diseases |
| HPA | Hypothalamic-pituitary-adrenal |
| FTLD-TDP | Frontotemporal lobar degeneration associated with TDP-43 pathology |
| IHD | Ischemic heart disease |
| IMT | Intimal-medial thickening |
| KIHD | Kuopio Ischemic Heart Disease |
| NHNES | National Health and Nutrition Examination Survey |
| Presenilin-1 | PSEN-1 |
| Presenilin-2 | PSEN-2 |
| VILIP-1 | Visinin-like protein-1 |
| SAD | Sporadic Alzheimer's disease |
| WHIOS | Women's Health Initiative Observational Study |
| AD | Alzheimer Disease |
| CVD | Cardiovascular disease |

# Chapter 1

## 1.1 Introduction

The most prevalent clinical manifestations of neurodegenerative disorders are extrapyramidal and pyramidal movement problems and cognitive or behavioral impairments. More often than not, individuals have a combination of clinical symptoms rather than a single condition (Gibb WR & AJ Lees, 1988). Currently, neuropathological examination at autopsy is the diagnostic gold standard. Neurodegenerative conditions experience many significant processes accompanied with progressive neuronal dysfunction and death, carrying proteotoxic stress, deformities in the ubiquitin–proteasomal and autophagy/lysosomal systems, oxidative stress, and prioritized cell death, and neuroinflammation (Sparks DL, 1994). Moreover, protein deformities that mark neurodegenerative diseases might be present before any impersonal symptoms appear. Many of the underlying mechanisms that are linked with increasing neuronal dysfunction and death are shared by both conditions, such as proteotoxic stress and its attending deformities in oxidative stress, programmed cell death, ubiquitin–proteasomal, autophagy/lysosomal systems, and neuroinflammation (Gijselinck I. et al., 2016), are common to neurodegenerative diseases. As a result, it is important to underline that the protein anomalies that identify neurodegenerative disorders may be present before clinical manifestations, and many neurodegenerative disease processes can be observed in a single person (William W Seeley, 2016). If a genetic mutation is shown to be the condition's cause, diagnostic biomarkers are not yet accessible. A primary focus is identifying particular in vivo biomarkers, such as those found in biofluids and molecular images. For many neurodegenerative diseases, postmortem examinations of brains from individuals with varying degrees of clinical or pathological severity have shown that the evolution of the disease may be characterized in terms of phases. Dementia with Lewy bodies (DLB) (McKee AC et al.,

2013), ALS, FTLD-TDP (Brettschneider J et al., 2014), and CTE all have staging systems in place to help doctors determine the progression of these illnesses/CTE. New ideas concerning neurodegenerative illnesses' selective susceptibility have emerged as a result of the studies included in this book and evidence of functional connection from in vivo imaging (Thal DR et al., 2002).

There are an expected 17.9 million casualties a year from cardiovascular disease (CVD) globally, accounting for nearly one-third of all deaths (Canter R.G., 2016). Nearly 85% of fatalities are caused by stroke and heart failure. CVDs, which include heart disease, atherosclerosis, and cerebrovascular disease, represent a heterogeneous group of disorders. Pathological changes are typically permanent and cannot be reversed, despite the development of several medicines in recent decades. Thus, as with Alzheimer's, the best course of action is to pursue preventative measures to reduce risk factors and encourage a healthy lifestyle. Tobacco and alcohol use, lack of exercise, being overweight seem, and poor eating habits are the most significant risk factors (Weller J., 2018).

## 1.2 Goal of the research

This study aims to assemble probable the connection between cardiovascular diseases and Neurodegenerative disorders.

## 1.3 Objectives

The following are the review's goals:

- To gather factors about cardiovascular diseases and Neurodegenerative disorders.
- Gathering data on the relationships among “Alzheimer’s disease”, “Parkinson's disease” “Huntington’s disease” and cardiovascular diseases.
- Find out the most effects of dementia on CVDs

# Chapter 2

# Literature Review

## 2.1 Cardiovascular Diseases

Many people think of cardiovascular disease (CVD) in terms of disorders that cause restricted or blocked blood arteries, which may lead to ischemic heart disease or stroke. In this way, blood cannot reach the heart or the brain. Because of the buildup of fat securities on the inner bars of blood vessels, the clump (clot) occurs, obstructing blood flow (Bonow RO et al., 2002). One of the most common causes of a stroke is an embolism or bleeding from a brain blood artery. Heart disease kills an estimated 18 million people globally each year. Despite having a lower load of risk factors, major cardiovascular events are more common in low-income nations than in higher-income ones (Cooper T et al., 1981).

Strokes and MI both add to the global toll of cardiovascular disease (CVD). Between 1990 and 2010, the worldwide toll of IHD was raised by 29 million adjusted life years (29%) (McGee D et al., 1996). Between 1990 and 2010, the number of persons who had an incident stroke, fatalities, and years of incapacity lost due to the stroke all grew dramatically. Studies in this thesis have included these particular CVDs (acute myocardial infarction, unstable angina, and stroke) because of their high mortality rates (Mokdad AH et al., 2001).

## 2.2 Acute myocardial infarction & Unstable angina

Sudden myocardial infarction is characterized by myocardial necrosis and mortality when an unstable burst plaque ruptures. Symptoms including chest discomfort or heaviness, ECG, biochemical assessments, and nosy and noninvasive illustration are used to diagnose and evaluate it clinically (Kaplan GA & J E Keil., 1993). At rest or with modest exercise, myocardial ischemia is defined as myocardial ischemia in the deficiency of death of heart strength. Ischemic heart disease is primarily responsible for the overall rise in total mortality

from cardiovascular illnesses, with a 19.0 percent increase in deaths from 7.96 million in 2006 to 9.48 million in 2016.

### 2.2.1 Stroke

Abruptly focused damage to brain parenchyma caused by vascular thrombosis manifests as neurological impairment. Stroke is the contributing cause of impairment and death worldwide, covering cerebral infarction (from arterial thrombosis), intracerebral hemorrhage, and subarachnoid hemorrhage (100). In terms of mortality, stroke comes in at number two. According to the World Health Organization (WHO), 11.8 percent of the world's deaths occur from reasons other than heart disease.

Assessment of CVD Self-reports may be used to assess the cardiovascular disease. Symptoms of chest discomfort, an ECG, and troponin I blood test are all clinical diagnostic benchmarks for ischemic heart disease (Cho HW & Chaeshin Chu., 2016). Acute myocardial infarction and ischemic heart disease may also be diagnosed with specialist diagnostic tests such as myocardial perfusion imaging, coronary angiography, and echocardiography (both at rest and during activity) (Fox KA et al., 2004). An abrupt loss of function in any body region is a clinical diagnostic criterion for stroke evaluation. Stroke diagnosis is enhanced by CT and MRI of the brain (Stilletman AE et al., 2011).

CVD risk assessment may also be done using patient records from health care institutions. The Swedish National Patient Register (NPR) was utilized in this research to evaluate cardiovascular disease (CVD). From 1964 until 1987, there was full nationwide coverage of the NPR (Ludvigsson JF et al., 2011). Only a small percentage of discharges from mental or somatic hospitals are not recorded in the database (Brooke HL et al., 2017). The National Board of Health and Welfare confirmed that between 85 and 95 percent of diagnoses are correct,

which is a significant number. NPR can correctly diagnose 90,3 percent of myocardial infarctions that it sees. All doctors must provide the NPR with patient data (excluding primary care). Hospital discharges are connected to an individual's unique identifier number. NPR's primary diagnosis rate is 0.8 percent for bodily care, 2.4 percent for senior care, 3.1 percent for mental treatment, and 0.5 percent for general surgery. (126). Since 1952, the cause of death registration in Sweden has been accessible online (Johansson LA et al., 2009). An estimated 77% of causes of death marked in the origin of death registry match the predicted cause of death from case summaries.

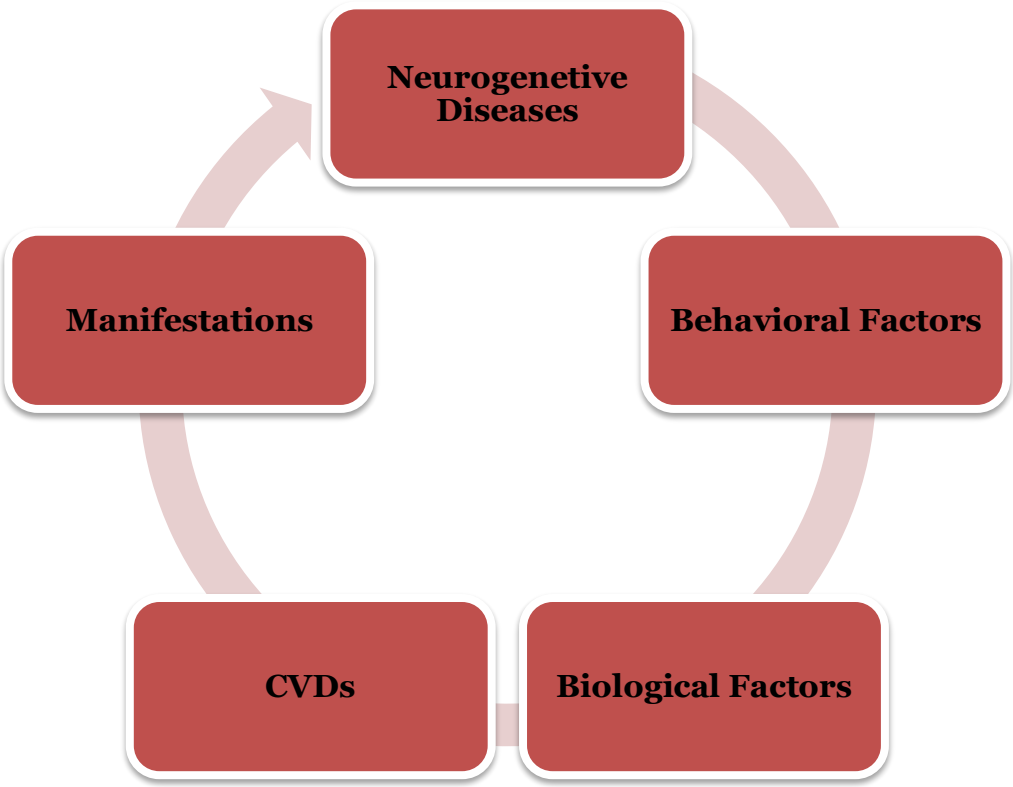


*Figure 1: Relationship between neurodegenerative disorders and cardiovascular disorders (Adopted from:Johansson LA et al., 2009)*

### 2.2.2 CVD and AD common risk factors

The diagnosis of dementia is still possible even if CVD alone may cause cognitive impairment and the development of dementia (Román G.C. et al., 1993). There is however, proved to

support the theory that CVD may have a part in the development of Alzheimer's disease. Neuropathological investigations show that people with Alzheimer's disease have many more ischemic microvascular lesions in their brains (Skrobot O.A. et al., 2017). Neuropathologically has proven AD cases were 11 times more common in women with autopsy-confirmed cerebral infarctions (Krishnamurthi R.V. et al., 2015). Many epidemiological researches have discovered a link between CVD and neurodegenerative or dementia-related conditions (White L., 2002). Small vessel disease is still to be described in terms of how it influences the clinical course of Alzheimer's and CVDs. Both AD and CVD share several risk factors, although it isn't clear if they are directly or indirectly linked (Snowdon D.A. et al., 1997).

### 2.2.3 Hypertension

As one of the most remarkable risk factors for AD, persistent hypertension has been linked to pharmacological therapy and lifestyle modifications (Qiu C. et al., 2005). Atherosclerotic plaques grow in the cerebral arteries due to hypertension, and hyperlipidemia develops as a result of this (Cipollini V. et al., 2019). Antihypertensive medications may reduce the chance of dementia in the elderly (Iadecola C. & Robin L Davisson, 2008). Dementia incidence was cut in half in a double-blind, randomized, placebo-controlled trial in patients with active hypertension (Skoog I. et al., 2006). These medications, notwithstanding this discovery, have not been shown to improve cognition in people with AD (Verghese J. et al., 2003). It is yet unclear why anti-hypertension medication reduces the risk of dementia in this group and whether this is due to a drug-specific impact or a general upshot of lowering blood pressure (Forette F. et al., 1998). The only thing that can be said with certainty is that controlling blood pressure in intermediate age may prevent the onset of AD.

## 2.3 Cerebrovascular Syndrome

VNCDs, like AD, share similar symptoms and risk factors with VNCDs, including high blood pressure, diabetes mellitus (T2DM), smoking, and others. DSM-5 recommendations from the SyndromePsychiatric Association (APA) state that a probable vascular ND permits either parenchymal scar associated to cardiovascular disease (CVD), physical relation to one or more documented cerebrovascular circumstances, or clinical and genetic evidence (Association, 2013). Major or moderate VNCD patients' clinical pictures may cover various infarctions, white matter lesions, basal ganglia lesions, thalamic lesions, and a steady deterioration in cognition. However, the authors of DSM-5 point out that both VNCD and AD might have mixed etiologies and that it is not always easy to disentangle the two. Mild or moderate neurocognitive dysfunction should be diagnosed in these circumstances, according to the APA.

## 2.4 Dyslipidemia and Hypercholesterolemia

High blood cholesterol levels may cause Alzheimer's disease (AD). High blood cholesterol statuses have been attached to an advanced risk of CVDs. A higher amount of Aβ depositions was discovered in rats given a diet rich in cholesterol. Human investigations have revealed that HDL cholesterol levels are high and low HDL cholesterol levels. Metabolism may also be altered by the disposal and cholesterol grades in brain cells, only a few more factors. Hence, it is not surprising that statins, which decrease blood cholesterol, may also protect against Alzheimer's disease (Bogers R.P. et al., 2007).

Recent research has described that the homeostasis of lipids in the brain, encompassing cholesterol (Koutsouraki E. et al., 2014) and sphingolipids (such as gangliosides), are critical to the cell membrane composition and the creation of lipid rafts related with the production and toxicity of Aβ (Reitz C. et al., 2010). These findings have re-ignited interest in understanding the varied job of lipids, including neuroinflammation, neuroplasticity, amyloidogenesis, and

mitochondrial synaptic function (Vandana Rai, 2017). As a consequence, it's still not clear why AD sufferers have abnormalities in their lipid homeostasis (El Gaamouch F. et al., 2016)..

## 2.5 Hyperhomocysteinemia

Stroke, cardiovascular disease, and AD have been linked to elevated plasma homocysteine levels (Hatzifilippou E. et al., 2008). Alternative vascular risk factors, dietary status, or the MTHFR genotype are unrelated to this risk factor. Homocysteine levels in the blood are linked to the likelihood of developing AD in a meta-analysis of 34 published research. As a result of this meta-analysis, we have gained new observations into the genesis and prevention of AD. That homocysteine may influence AD through increasing -amyloid brain deposition or indirectly via cerebrovascular illness (Hu Q. et al., 2016).

### 2.5.1 GENETICS OF AD

SAD is well recognized as a complex condition with several underlying causes. However, the evolution of SAD is not yet completely described. Scientists from all across the globe have been working to figure out the enigma (Castellano J.M. et al., 2011). There are a lot of genetic and genomic investigations going on right now. Furthermore, numerous investigations have shown the linkage between APOE allele type and amyloid plaques formation (Reiman E.M. et al., 2020). It has been discovered that individuals with the APOE2/APOE2+ allele type had decreased likelihood of developing SAD and a greater load of the disease-causing plaque. The probability increases sequentially from 2/3, 3/.3, and.2/.4 to.3/.4 and.4/.4 (Parcon P.A. et al., 2018). According to several research findings, the severity of tau-pathology is made worse in people with APOE4. Analyses in silico and in vitro have shown that APOE4 binds persistently to CLEAR motifs and competes with transcription element TFEB (Romito-DiGiacomo R.R. et al., 2007). However, APOE2 and APOE3 were not shown to do this. When this interaction

occurs, pro-autophagic genes, such as SQSTM1/P62, MAPLC3B, and LAMP2, may be downregulated, increasing cellular susceptibility in SAD (Yin Y.W., 2012). However, in a different study, researchers found that the pro-autophagic gene transcripts were particularly abundant in the neurons and astrocytes of SAD patients. Because neurons vary in sensitivity based on the layer of their disposition, these results imply that neurons in the deeper sheets are more invulnerable to amyloid toxicity.

### 2.5.2 Cardiovascular Risk Elements and PD

The heart-brain relationship is indisputable and complex. Alzheimer's disease and CVD risk elements have been at the limelight of dementia analysis. The etiology of AD and dementia may be associated to diabetes mellitus (DM), hypertension (HTN), obesity, and hypercholesterolemia, which have been linked in well-designed longitudinal studies (Vicario A. et al., 2010). Research on Parkinson's disease and heart disease has been more popular in recent years; however, most studies have focused on PD patients with CV complications or cardiac autonomic dysfunction (e.g., orthostatic hypotension). Contrary to popular belief, oxidative stress and chronic inflammation have been hypothesized to participate an act in Parkinson's disease (Tolppanen AM. Et al., 2012) and CHDs (e.g., diabetes, high blood pressure, and obesity). This association between conventional CV risk factors and Parkinson's disease is difficult to decipher since the evidence is frequently contradictory, ambiguous, or

erroneous (Lang AE & Alberto J Espay, 2018).

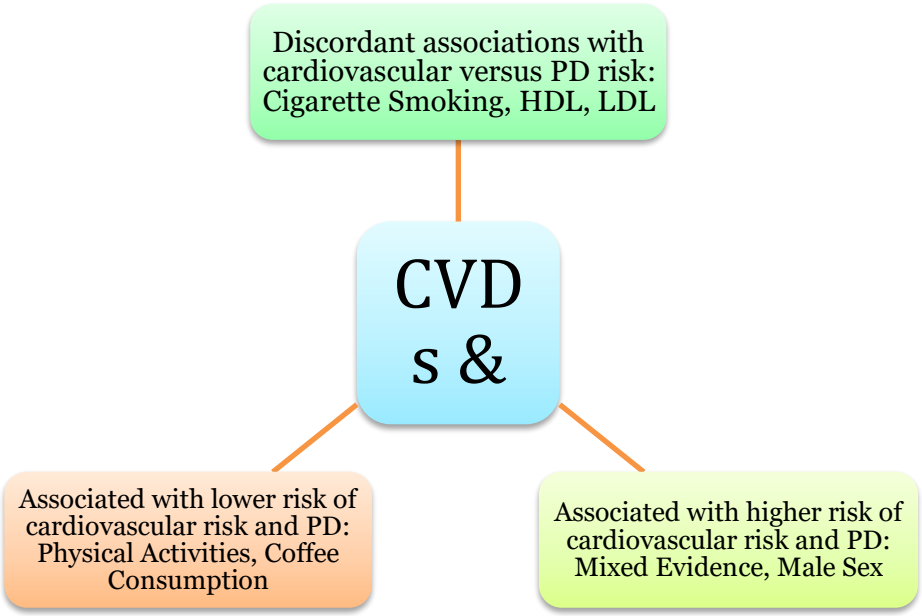


*Figure 2: Associations between cardiovascular risk factors and Parkinson's disease (Adopted from:Lang AE & Alberto J Espay, 2018).*

### 2.6 Factors that have concordant associations with cardiovascular risk and PD

Cardiovascular illnesses and strokes are less likely to occur in those who engage in even moderate amounts of physical activity (Lavie CJ, 2015). One of the most rational epidemiological results, established by many longitudinal and well-designed case-control inspections, is an inverse connection between leisure-time physical exercise and PD. Caution is, of course, warranted (Thacker EL. Et al., 2008). First and foremost, moderate to vigorous activity has the greatest effect on risk reduction. There is also a lack of consistency in the data on the link between early-life physical exercise and Parkinson's disease risk (Xu Q et al., 2010). Reverse causation cannot be ruled out because of the protracted prodromal stage of PD development. In addition, it is possible that greater neuroplasticity and brain-derived neurotrophic factors as well as a decrease in neuroinflammation, participate a role in the

association between exercise and a decreased risk of Parkinson's disease.Drinking 3–5 cups of coffee a day has been connected to a decreased risk of a variety of cardiovascular events (Schwarzschild MA et al., 2003). As a complex blend of components, coffee may describe the probable U-shaped correlations between coffee intake and CVDs risk, which are varied and occasionally hostile. A nonspecific adenosine A2A receptor antagonist has been proposed as the mechanism by which coffee intake protects against Parkinson's disease (Ding M et al., 2014).

### 2.6.1 Components that have discordant associations with cardiovascular versus PD risk

Smoking is a considerable risk circumstance for a comprehensive range of chronic illnesses, including CVDs, according to research by the Global Burden of Diseases (GBD). It is challenging to comprehend the guiding causes of the inverse link between smoking and Parkinson's disease (Ritz B et al., 2014). Smokers are roughly half as likely as nonsmokers to acquire Parkinson's disease. A greater death rate among smokers (the competing risk theory) cannot account for the association, but this does not suggest causation. PD's prodromal period is so protracted and unclear that competing ideas like reverse causation and personality confounding are difficult to rule out. The public health consequences of this causal inference challenge are enormous. Smoking may lessen the chance of developing Parkinson's disease or postpone its beginning, as some studies have revealed. As a result, the declining trend in smoking may raise the burden of PD on our growing population (Rossi A et al., 2018).

Relationships with serum cholesterol are also contradictory. Epidemiological studies have shown that greater grades of total or LDL cholesterol are related to a deteriorated risk of Parkinson's disease (PD) and a slower rate of disease development (Huang X A. P. et al., 2011), even though these levels are harmful to cardiovascular health. There is a good deal of improvement for this, including support from several future cohorts (Huang X C. H. et al.,

2006). If future research reveals that statin usage in PD patients or those at risk for PD has a causative effect, this has substantial clinical implications (Huang X A. A. et al., 2015).

### 2.6.2 Connection between cardiovascular disease and spinal cord injury

The third-leading cause of death in spinal cord injury patients is hypertension and ischemic heart disease, according to the National Spinal Cord Injury Statistical Center's most recent data (SCI) (Matos-Souza JR, 2010). The elevated levels of inflammatory and vascular biomarkers indicate an elevated risk of cardiovascular disease (Claydon VE & Andrei V Krassioukov et al., 2008). The degree and severity of insult to descending autonomic (sympathetic) circuits correlate with abnormal cardiovascular regulation. SCI status was a poor predictor of cardiovascular morbidity and death in a comprehensive evaluation of research published in English between 1990 and 2007 in the United States (Wilt TJ. et al., 2008). The few studies that looked at a connection between cardiovascular disease (CVD) and spinal cord injury (SCI) had small sample sizes, lacked sufficient control groups or adjustments for important variables, and reported results varied substantially (Cragg JJ et al., 2013)

### 2.6.3 Negative emotions, psychological stress to CVDs

CVD and its related risk factors have been linked to a broad range of psychological and social characteristics and characteristics. According to clinical anecdotes and historical data, cardiovascular illness has long been linked to emotional and psychological qualities. (a) negative emotional states such as depression or depressive symptoms; (b) chronic psychosocial stressors including occupational or work-related stress; (c) social elements that include social support and conflict. It's no surprise that these topics have taken up so much space in the literature.

## 2.7 Negative Emotional States associated with CVDs

The field of cardiovascular disease (CVD) and CVD-related health outcomes has evolved enormously in the last 15–20 years of research on the role of negative emotional states. Depression, aggression, and anxiety have all been studied extensively. Below, we'll take a closer look at each of these topics.

### 2.7.1 Depression and Depressive symptoms

Studies have shown a link between a history of depression and an elevated risk of cardiovascular disease (CVD) morbidity and death. As early as the 1930s, it was discovered that depressed mental inpatients were more likely to die from coronary artery disease than their nonpsychiatric counterparts. Recent investigations of people with mental health conditions also indicated that people with unipolar or bipolar depression had increased risks of cardiovascular disease mortality (B. Malzberg. 1937). Individuals who have had a MI are more likely to be depressed, and their prognosis for cardiovascular disease (CVD) is negatively affected by depression (Tsuang MT. et al., 1980). There are also higher risks of sudden cardiovascular mortality among dusky patients. These discoveries have been validated in empirical research with cardiac patients (Frasure-Smith N et al., 1995).

The evidence for the cardiovascular repercussions of depression or depressive symptoms comes from male and female volunteers ranging in age from early adulthood to old life. For more than 2800 originally healthy men and women from the NHEFS (Ferketich AK et al., 2000), the depressing effect was related to a 50%-60% increased risk of fatal and nonfatal IHD after adjustment for conventional coronary risk variables after 12 years of follow-up (NHEFS). Numerous community and demographic studies conducted in the following years produced similar findings (Weeke A. et al., 1987).

Those with a history of dysphoria had a 2.7-fold greater risk of self-reported MI in a sample of 1551 people taken from the general community and who were otherwise healthy. As evaluated by the CES-D Scale (Anda R. et al., 1993), the CES-D Scale predicted more than 70 percent additional risk of incident CHD and 2.34-fold worse CHD mortality in males in the first NHNES. Using data from the WHIOS, which tracked nearly 94,000 women aged 50–79 years for about four years (Ferketich AK. Et al., 2000), researchers recently discovered that current depressive symptoms, as measured by a short form of the CES-D, was associated with a significant 1.5-fold higher risk of death, even after adjusting for education, income, and traditional coronary risk factors. Symptoms of depression have been related to an increased risk of stroke and hypertension (Everson SA. Et al., 1996).

According to research, hopelessness is a sign of sadness that has been shown to hurt health. One item on despair from their scale of sad affect predicted a more than twofold incidence of fatal and nonfatal IHD and was a better predictor than the full measure (Mendes de Leon CF. et al., 1998). It was shown in the San Antonio Heart Study that high levels of despair predicted both all-cause and cardiovascular disease mortality in Mexican Americans and Caucasians (Jackson-Triche ME, 2000). After adjusting for demographics, cardiovascular risk factors, and overall depressive symptoms, a population sample of middle-aged Finnish men from the KIHD study predicted a two-fold increase in CVD mortality, MI, and all-cause mortality over a six-year follow-up period. KIHD researchers found that hopelessness increased the evolution of carotid artery intimal-medial thickening (IMT) and tripled the risk of incident hypertension over four years (Everson SA K. G., 1997).

According to some research, there is no link between depression and an increased risk of cardiovascular disease (CVD) morbidity or death (Roberts RE et al., 1990). In addition, studies have differed in their ability to adjust for possible confounding variables, such as current health state and behavioral risk factors (Ulbrich PM et al., 1989. ). A range of evaluation measures

used in various demographics has consistently shown a positive correlation between depression or depressive symptoms, as detailed above, in several studies using a solid methodology (Yan LL. Et al., 2003).

However, since most published research did not involve racial or ethnic minorities, little is known about how depressive symptoms affect CVD in these groups (Davidson K, 2000). There is evidence that depressed symptoms increase CVD risk among African Americans, notably hypertension and stroke. After five years of follow-up, high scores on the CES-D were related to a 2.8-fold greater risk of hypertension in African Americans but not in Caucasians. More recent CARDIA data with 15 years of follow-up indicated no racial differences in psychosocial risk factors for hypertension (Kessler RC, 1994). Over 7–22 years of follow-up, two NHEFS studies indicated that negative affect (anxiety and depressive symptoms) predicted twice the risk of incident hypertension and 1.73 times the risk of stroke. Contrary to past data, African Americans report greater levels of depressive symptoms than Caucasians, but no difference in the incidence of major depressive disorder. Given the increased prevalence of CVD among African Americans and other minorities, further research is required on the influence of depressive symptoms and other psychosocial features (Jonas BS & J F Lando., 2000).

### 2.7.2 Anger and Hostility

Researchers have long studied the link between rage and cardiovascular disease. Early psychoanalytic and psychodynamic literature revealed angry or hostile outbursts in individuals with cardiovascular disease or hypertension. Together with the requirement to define and measure “coronary-prone behavior,” these findings prompted research on the Type A behavior pattern in the 1950s and 1960s (Friedman M & R H Rosenman., 1971). Rosenman & Friedman defined the Type A personality as being driven, time-pressed, ambitious, competitive, extremely quick-tempered, and wound up. Together with the requirement to define and measure “coronary-prone behavior,” these findings prompted research on the Type A behavior

pattern in the 1950s and 1960s. The Western Collaborative Group Study, including almost 3100 middle-aged men, identified Type A as a risk factor for CHD (Rosenman RH et al., 1975). Within 8.5 years, Type A men were twice as likely as Type B men to have CHD—A level of risk compared to any known coronary risk factor. To understand psychosocial aspects and CVD risk, we needed further research on the Type A behavior pattern. Type A was the first psychosocial component to be identified as a cardiac risk factor by the medical profession (JA., 1945).

### 2.7.3 Psychosocial Stressors and CVDs Risk

Many studies have looked at how psychosocial factors affect cardiovascular disease. It has long been known that stresses such as poverty, inadequate housing, and working circumstances may negatively influence the health of communities (WB., 1935). As with CVD, research into the effect of psychosocial stresses has a lengthy history. In the early days of epidemiology and sociology, stresses like poverty, substandard housing, and hazardous working conditions negatively influenced people's health. As with CVD, research into the effect of psychosocial stresses has a lengthy history as well (H., 1956). Poverty, substandard living circumstances, and unsafe working conditions were all seen in the early days of epidemiology and sociology to negatively influence people's health. As a series of physiological reactions to threats or challenges, the fight or flight response was the first to understand that chronic stress might lead to tissue damage and illness (Kuper H & M Marmot. 2003). Findings from a wide range of domains have contributed to elucidating the physiologic processes through which psychosocial factors may increase the risk of CVDs.

### 2.7.4 Pathophysiological mechanisms

Recent decades of study on psychosocial variables and cardiovascular disease (CVD) morbidity and mortality have led to an increased emphasis on the pathophysiological processes

through which psychosocial factors impact disease genesis and progression. Significant and interconnected physiological processes might explain the discovered relationships. Emotional and social variables may directly impact the pathophysiology of illness (BS McEwen., 1997). Atherosclerosis may be exacerbated by stimulating the hypothalamic-pituitary-adrenal (HPA) axis and ANS, serotonergic dysfunction, the release of proinflammatory cytokines, and the activation of platelets. An integrated model demonstrates some of the co-relationships between these processes and the routes via which psychological variables may contribute to atherosclerosis and associated clinical consequences. Psychosocial variables and cardiovascular disease (CVD) have a complicated and multi-factored interaction that has to be understood. As a result of this review's emphasis on hypothetical and known physiological pathways, environmental, social, and behavioral impacts on this connection have been omitted from the diagrams (Lewis, 2005).

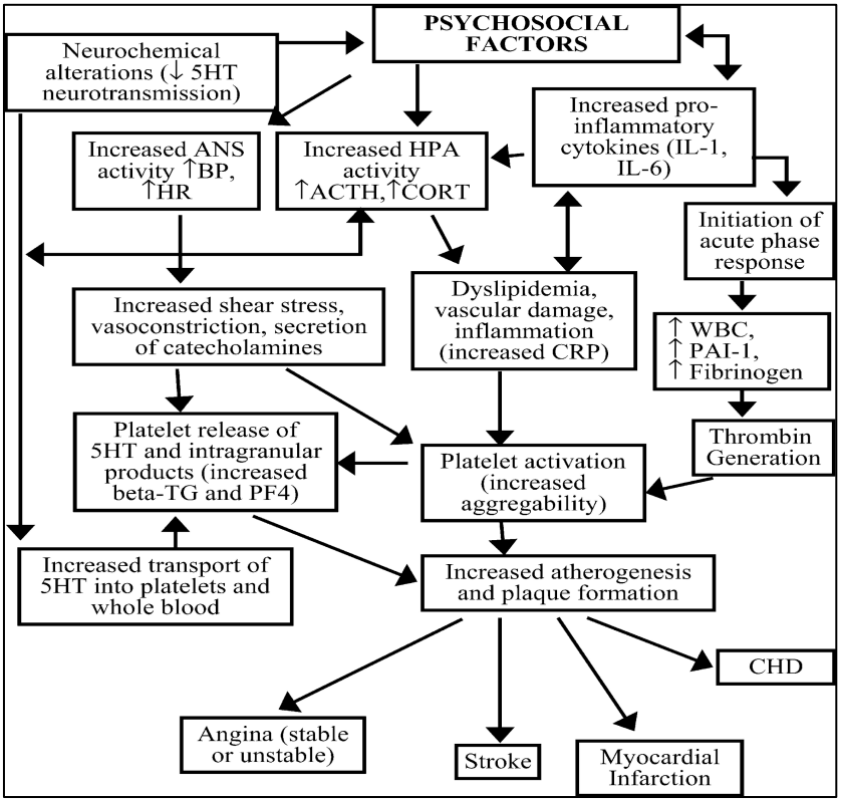


*Figure 3: A proposed integrative model that links psychosocial factors may lead to atherosclerosis and related clinical outcomes (Lewis, 2005).*

# Chapter 3

## Methodology

Research articles, news stories, academic publications, and government websites were used to compile this extensive literature assessment on the relationship between cardiovascular disease (CVD) and neurological disorders (ND). For this research, articles from notable publications, including Nature, Elsevier, and MDPI, were analyzed. A qualitative approach was also applied in this investigation. Studies published in peer-reviewed journals and other studies with published results helped identify the link between cardiovascular disease and neurodegenerative illnesses.

# Chapter 4

# Result

## 4.1 Connection between the Alzheimer’s disease and cardiovascular diseases

Searching internet databases like Google Scholar, Science Direct, and PubMed for relevant publications was the primary method used in this research. For this search, we used the phrases Alzheimer' AGEs, RAGE, and oxidative stress, as well as the time period 2006-2021, as well as RAGE-related pathways in CVD and hypertension, as well as RAGE and RAS system. We also used the terms RAGE in Alzheimer's and AGEs in Alzheimer's. For the sake of completeness, we also looked at relevant papers published after the time period specified above. There were no restrictions on the kind of articles that might be published in this journal. Only original research, reviews of existing literature, comments, or letters to the editor were allowed. There is a lot of overlap between Alzheimer's disease (AD), type 2 diabetes (DI), and cardiovascular disease (CVD) in terms of the shared variables and targets of these diseases. We investigated the probable processes and pathways associated with these illnesses in an effort to identify a link between them. As a whole, these illnesses are shown as interacting with one another.

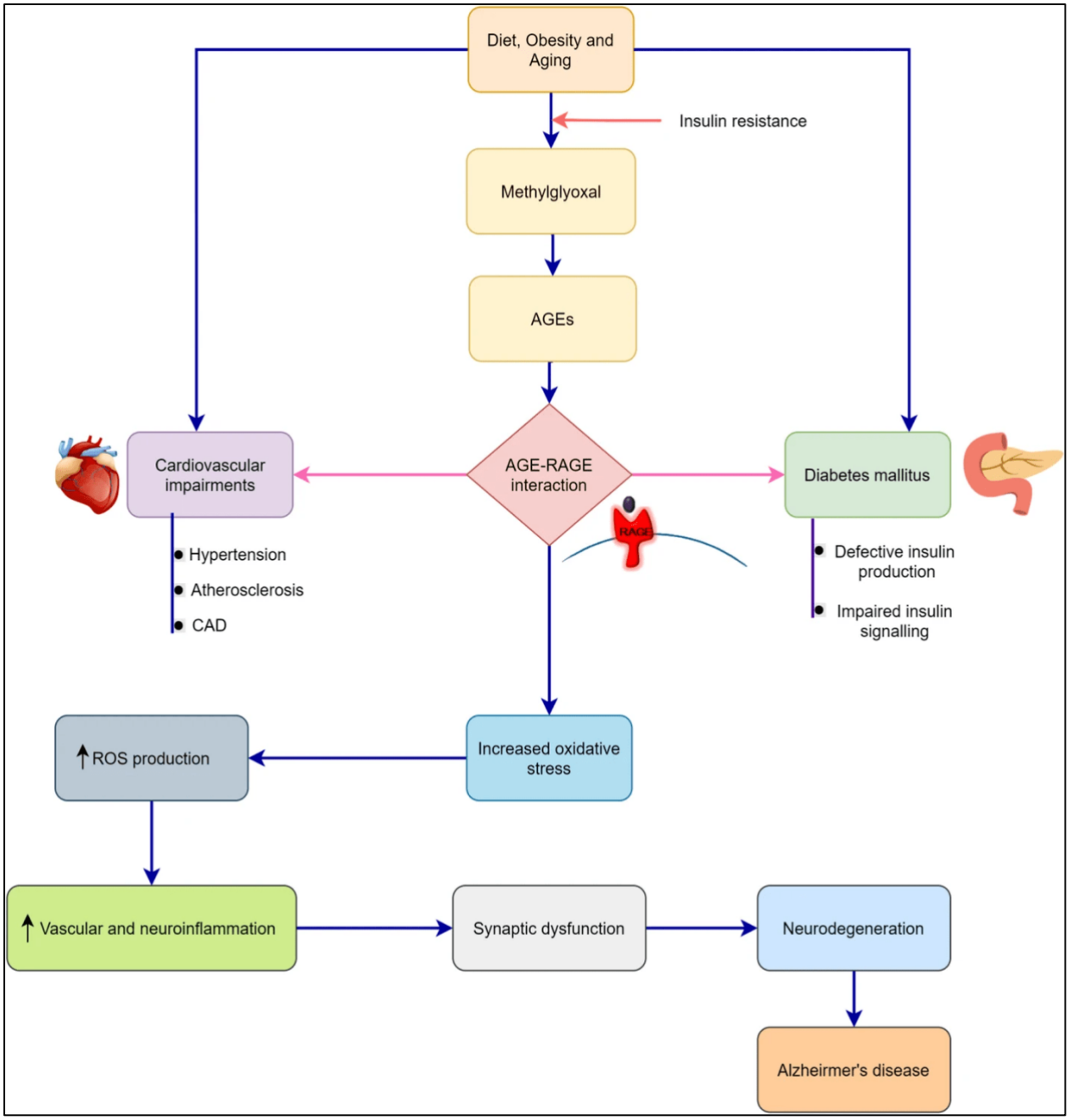


*Figure 4: Overview of the relationships among the Alzheimer's disease and cardiovascular diseases (Adopted from:Ashraf Abugroun, 2020).*

## 4.2 Connection between the Parkinson's disease and cardiovascular diseases

In a research, we sought to evaluate the association between Parkinson's disease (PD) and vascular disease, as well as risk factors, by recruiting participants from a nationally

representative sample. The National Inpatient Sample was queried for all individuals under the age of 65 who were diagnosed with Parkinson's disease during the year 2016. Each patient diagnosed with Parkinson's disease was frequency matched to controls in a 1:4 ratio based on age and gender. The study's outcomes included hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, and stroke. A total of 57,914 Parkinson's disease patients (weighted: 289,570) were included in the study. The majority of patients were of Caucasian descent (80.8 percent ). Females accounted for 42.4% of the population, with an average age of 79 years (Ashraf Abugroun, 2020).

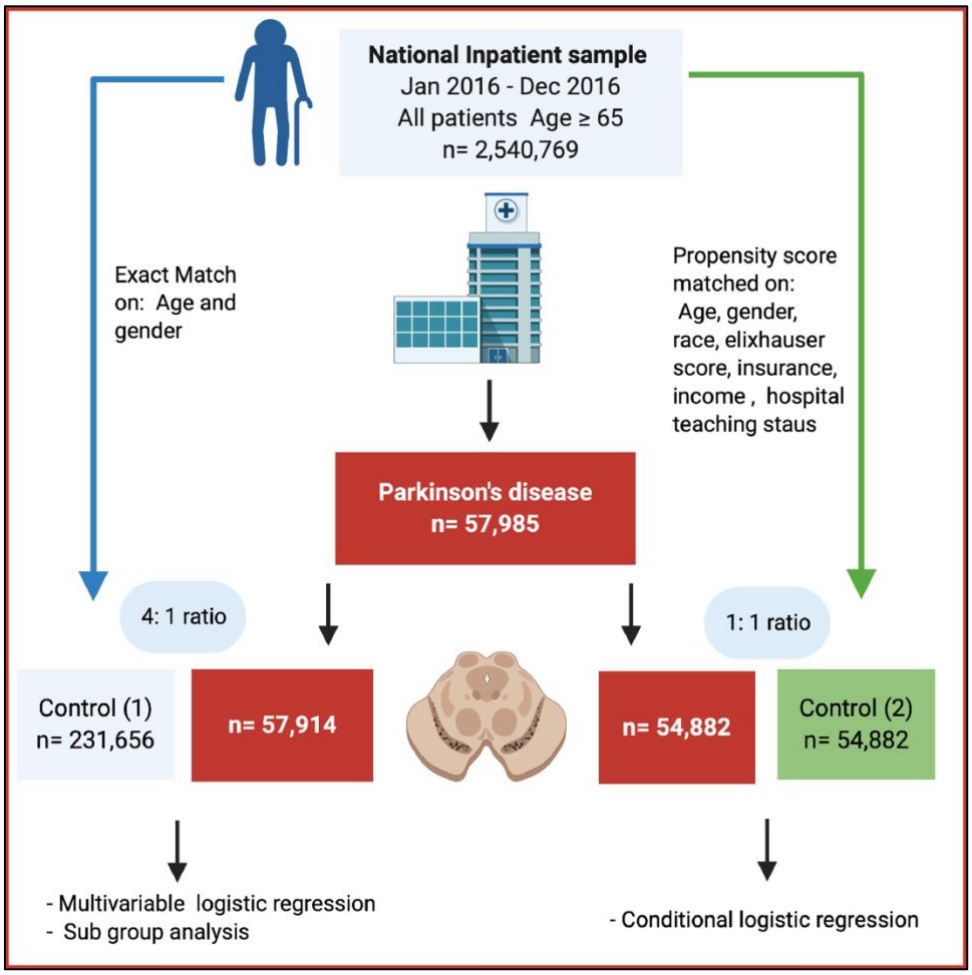


*Figure 5: Graphical Representation of linking between PD & CVD by quantitative research (Ashraf Abugroun, 2020).*

## 4.3 Connection between the Huntington's disease and cardiovascular diseases

There is a lack of evidence in the literature documenting cardiac malformations in HD patients based on the clinical and physiological abnormalities documented in HD mouse models. According to several epidemiological studies, heart disease is the second leading cause of mortality at a rate of 12.2 percent, 19 percent, and up to 24.4 percent. HD patients are not more likely to suffer from heart failure than the general population, according to another research. HD patients' heart rate variability (HRV) was shown to be decreased, despite the lack of evidence on cardiac abnormalities in HD patients. The modulation of cardiovagal activity has been demonstrated to be inversely related to the severity of clinical HD symptoms as measured by the Unified Huntington's Disease Rating Scales UHDRS. Another study found that the heart rate increased by 10.6% before symptoms appeared. The heart rate of pre-symptomatic and early-symptomatic HD patients was found to be 10% and 7% higher, respectively, in response to an exaggerated reaction to the late phase of the cold pressor test. During a head-up tilt test, another research found that the HRV values of HD patients dropped significantly, suggesting impaired vagal control of heart rate. Syncopes may be at danger because of increased sympathetic activity, according to these studies. According to this, the high-order autonomic centers implicated in HD may be dysfunctional, which might explain why HRV and heart rate changes occur. Furthermore, a number of clinical investigations have shown that congestive heart failure is caused by a dysfunction of the sympathetic nervous system, which has an influence on both morbidity and mortality in patients and has been documented in HD patients. No evidence for cardiac problems in HD mice has yet been found (Daniel Cezary Zielonka, 2014).

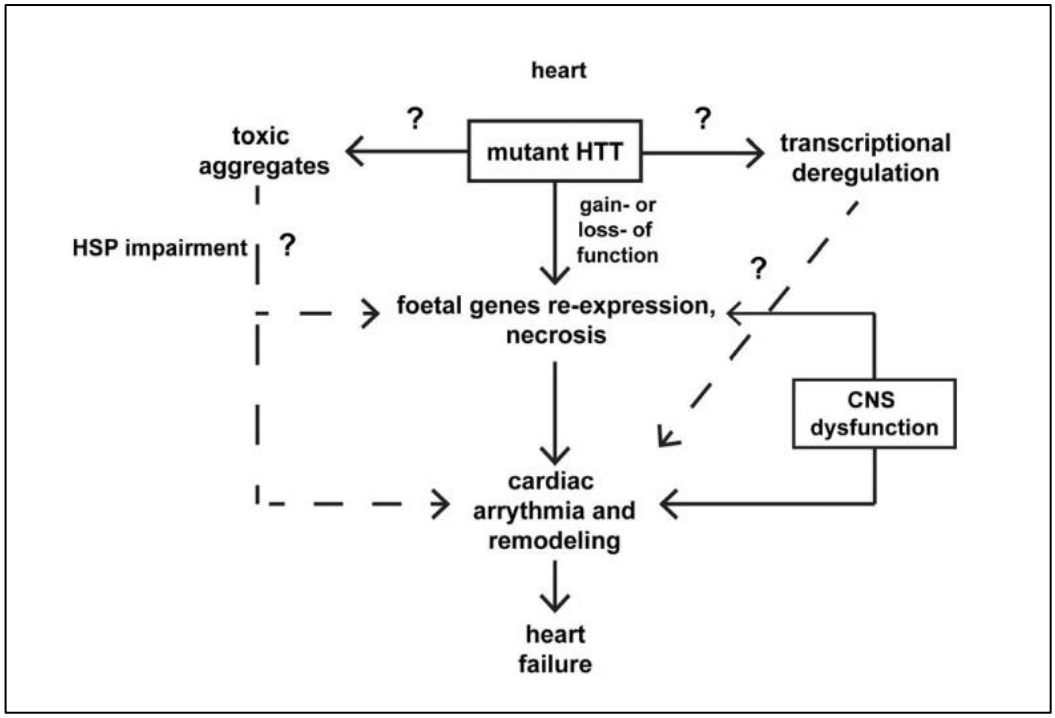


*Figure 6: Graphical Representation of linking between HD & CVD by quantitative research (Daniel Cezary Zielonka, 2014).*

# Chapter 5

# Conclusion

Neurodegenerative (ND) illnesses (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and spinal cord injury) are a major public health concern across the globe, and they are getting more widespread as the average age of the population rises.

Consistent results on the link between cardiovascular risk factors and AD have been demonstrated. The following factors were independently linked to dementia: smoking, diabetes, elevated blood pressure, and hypercholesterolemia. In contrast, one research found that a decrease in serum TC levels may signify preclinical dementia. According to one research, both Alzheimer's disease and vascular dementia had reduced levels of TC. There was no significant link between smoking and dementia in a subsequent examination of the 10/66 cohort trial findings. A higher CVD risk was linked to a higher chance of dementia, according to one long-term research looking at the connection between FGCRS and the condition. In the present investigation, there was an elevated risk of dementia and Alzheimer's disease with FGCRS.

Many of the studies of ND conducted over the past several decades have revealed aspects of the pathophysiology, such as trigger events, to be opaque and elusive. This is consistent with previous findings. According to the APA recommendations, a major availing factor is that the diagnostic criteria for ND typically exclude patients who have any significant cardiovascular disease (CVD). On the other hand, cardiovascular disease (CVD) may cause cognitive impairment and dementia. Nonetheless, there is compelling evidence to support the hypothesis that CVD contributes, at the very least in part, to the advancement of NDs. Several recent studies have revealed an important connection between these two diseases and certain aspects of one's diet, lifestyle, physical activity, homocysteine levels, blood pressure, blood cholesterol levels, and diabetes. A link exists between ND and CVD, without a doubt, not only because

they share common risk factors but also because they have similar molecular mechanisms of onset. Understanding the etiology and mechanisms of one of these diseases may pave the way for developing novel therapeutic strategies that apply to both ND and CVD if they are discovered. Finally, it is concluded that extensive research over several decades has provided us with invaluable information on various processes and the advancement of NDs. The presence of ND is associated with a wide range of risk variables that are either strongly or somewhat correlated. As a result, many critical issues remain unresolved in the pursuit of the discovery and development of effective treatment techniques.

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