UNIVERSITY COLLEGE LONDON

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Carotid Artery Atherosclerosis and Cognitive Decline: An Ultrasound-Based Studies of Southall and Brent Revisited (SABRE) and the National Survey of Health and Development (1946 Birth Cohort)

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for the degree of Doctor of Philosophy

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Declaration

I, Rayan Anbar confirm that the work presented in my thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

This thesis explores the relationship between carotid artery atherosclerosis and cognitive function across different ethnic groups and age cohorts, using a combination of systematic reviews, meta-analyses, and cohort studies.

Introduction Carotid artery atherosclerosis is a significant risk factor for cognitive decline, yet the extent and nature of this relationship remain unclear. This research aims to elucidate these connections, considering diverse ethnicities and age groups.

Hypothesis The hypothesis is that carotid artery atherosclerosis is associated with cognitive decline and that these associations vary across ethnic groups and age cohorts.

Methodology A systematic Review and Meta-Analysis was conducted using electronic databases to identify studies linking carotid atherosclerosis with cognitive function assessed by the Mini-Mental State Examination (MMSE). Data extraction and statistical analyses were performed to assess the strength of these associations.

The SABRE study involved participants from the Southall and Brent Revisited study, examining carotid atherosclerosis using ultrasound and assessing cognitive function and brain health through standardized tests. Blood and urine samples were analysed for cardiovascular risk factors. Generalized linear models were used to evaluate associations.

Data from the MRC National Survey of Health and Development (NSHD) was used to assess carotid intima-media thickness and plaque via ultrasound in relation to

cognitive function at multiple life stages. Regression models analysed the relationships, adjusting for confounders.

Results The systematic Review and Meta-Analysis found inconsistent evidence regarding the association between carotid artery atherosclerosis and cognitive function, highlighting the need for more longitudinal studies.

The SABRE Study revealed significant ethnic differences in carotid plaque prevalence, with African-Caribbean individuals showing lower rates than Europeans and South Asians. Initial associations between carotid plaque and cognitive performance weakened after adjusting for confounders, though neuroimaging indicated increased white matter lesion volume with carotid plaque.

NSHD Cohort: Longitudinal data did not show strong associations between carotid atherosclerosis and cognitive decline, suggesting the influence of other factors over time.

Conclusion The thesis underscores the complex relationship between carotid artery atherosclerosis and cognitive function. While some associations were observed, they were generally weak and confounded by other factors. The findings emphasize the need for ongoing research, incorporating comprehensive assessments and considering social and psychological factors, to develop targeted interventions and public health policies for managing cardiovascular and cognitive diseases. A multidisciplinary approach is essential to address the challenges of cognitive decline in aging populations.

Impact Statement

This thesis investigates the relationship between carotid artery atherosclerosis and cognitive function using ultrasound technology, revealing insights that have implications for academic research and practical applications.

Academic Contributions

This research contributes to the understanding of the interactions between cardiovascular health and cognitive function. By examining diverse ethnic groups and age cohorts, the findings provide a detailed perspective on how carotid atherosclerosis impacts cognitive performance, informing future research directions in vascular contributions to cognitive decline.

Practical Implications

The findings can influence public health strategies and clinical practices. The observed associations between carotid atherosclerosis and cognitive function can help healthcare providers identify individuals at higher risk for cognitive impairment due to vascular factors.

Preventive and Treatment Strategies

The research supports several strategies for preventing and managing cognitive decline:

Enhanced Screening: Regular ultrasound screening for carotid atherosclerosis in high-risk populations can aid in early identification of individuals at risk of cognitive decline.

Targeted Therapies: The findings emphasize the importance of managing cardiovascular health to preserve cognitive function, guiding the development of therapies that address both cardiovascular and cognitive health.

In conclusion, while the association between vascular pathologies and neurodegenerative disorders like Alzheimer's disease remains weak, this research emphasizes the broader impact of vascular health on cognitive function. The findings advocate for a multidisciplinary approach in both research and practical interventions to enhance cognitive health outcomes.

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Table of Contents

•

List of tables

NO TABLE OF FIGURES ENTRIES FOUND.

List of figures

FIGURE 5. 1 FLOW DIAGRAM FOR NATIONAL SURVEY OF HEALTH AND DEVELOPMENT DATA USED IN THIS STUDY. 154

FIGURE 5. 2 A) COMPARISON OF ACEIII (VISUOSPATIAL SUBSET) AT AGE 68-70 BY PRESENCE OF PLAQUE AT AGE 60-64. PEOPLE WITHOUT PLAQUES (BLUE) AND WITH (ORANGE). 164

List of publications

- Publication 1 Anbar R, Sultan SR, Al Saikhan L, et al. Is carotid artery atherosclerosis associated with poor cognitive function assessed using the Mini-Mental State Examination? A systematic review and meta-analysis BMJ Open 2022; 12: e055131. ....**Error! Bookmark not defined.**
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GLOSSARY OF ABBREVIATIONS

Abbreviation	Full Form
2D	Two-dimensional
3D	Three-dimensional
ABI	ankle-brachial index
CAD	Coronary artery disease
CA	Carotid Artery
CVD	Cardiovascular disease
ECA	External carotid arteries
ECG	Electrocardiogram
HDL	High-density lipoprotein
ICA	Internal carotid arteries
MMSE	Mini-mental state examination
MOCA	Montreal cognitive assessment
LDL	Low-density lipoprotein
PAD	Peripheral artery disease
WHO	World health organization

Chapter 1: Background

Cardiovascular disease

Cardiovascular disease (CVD) is a term used to describe a collection of disorders affecting the heart and blood vessels. The many subtypes of cardiovascular disease are addressed in more detail below. Cardiovascular disease (CVD) is a serious public health concern that causes considerable morbidity and death globally.(WHO, 2021) CVD includes coronary artery disease, stroke, heart failure, peripheral artery disease, carotid artery disease (which will be covered in more detail in a different section) and venous thromboembolic disease.(Nabel, 2003) It is increasingly recognised that CVD also contributes to cognitive decline and dementia beyond vascular dementia.(Paciaroni and Bogousslavsky, 2013)

In 2017 CVD was responsible for an estimated 17.9 million deaths worldwide (32% of all fatalities globally), making it the one of the leading causes of death (Li et al., 2021b). Furthermore, CVD is a leading cause of disability and has a considerable influence on quality of life. The burden of CVD is not evenly distributed across populations, and is influenced by a range of factors, including age, gender, ethnicity, socioeconomic status, and geography. CVD is more common in older individuals, with risk increasing significantly after the age of 45 for men and 55 for women. Men are generally at higher risk of CVD than women, although this difference narrows after the menopause. CVD is a substantial public health burden that demands immediate attention from healthcare providers, politicians, and individuals. Effective CVD prevention and management techniques, such as lifestyle modifications and early identification and

treatment, can help minimize the burden of CVD on people and society while also improving global health and well-being (Deaton et al., 2011).

There are also significant differences in CVD burden by ethnicity, with certain ethnic groups at higher risk of CVD than others.(Williams et al., 2010) For example, South Asian and African-Caribbean individuals in the UK have been found to have a higher risk of some CVD conditions than the general population.(Tillin et al., 2013c) Socioeconomic factors also play a role in CVD burden, with individuals from lower socioeconomic backgrounds at higher risk of CVD.(Schultz et al., 2018, Rosengren et al., 2019) This may be due to a range of factors, including differences in lifestyle behaviours,(Tousoulis et al., 2020) access to healthcare, racism,(Javed et al., 2022b) and differential exposure to environmental factors.(Münzel et al., 2021)

Geography is also associated with CVD burden, with higher rates of CVD in some countries, in general, this corresponds with national income status but other factors may also contribute.(Levenson et al., 2002)

Risk factors for CVD include both modifiable and non-modifiable risk factors (Dahlof, 2010, Leritz et al., 2011, Yusuf et al., 2020) as discussed in more detail below. CVD prevention and treatment requires focusing on modifiable risk factors through lifestyle modifications and medication. Lifestyle changes such as eating healthier foods, frequent physical activity, and giving up smoking can all help lower the risk of CVD. Statins, antihypertensives, and antiplatelet medications may also be utilised to control CVD, but as other studies suggests, a population approach to prevention should be the main focus of policy, as it can have a greater impact on reducing the overall incidence of disease, and should be supported by a strategy involving identifying risk

factors and implementing effective interventions to address them in high risk individuals(Rose, 2001).

Atherosclerosis

Atherosclerosis is a chronic inflammatory condition that contributes significantly to morbidity and death globally and has widespread detrimental effects on cardiovascular health.(Stoll and Bendszus, 2006, Keaney Jr, 2000). Atherosclerotic lesions begin to develop in childhood, if not before, and are influenced by risk factors such as hypertension, diabetes and hyperlipidaemia.(Hong, 2010) Their development represents a dynamic process where the earliest manifestations, fatty streaks, evolve into raised fibrosis plaques which are the forerunners of stable and unstable or vulnerable plaques,(Milei et al., 2008) Plaques can undergo erosion(Luo et al., 2021), or rupture(Bentzon et al., 2014)

During the process of atherogenesis, low-density lipoprotein (LDL) cholesterol, in particular, builds up in the artery's intimal layer, which causes fatty streaks to develop.(Garcia and Khang-Loon, 1996) This accumulation is widely believed to occur due to endothelial dysfunction, possibly related to flow patterns at bifurcations where atherogenesis commonly occurs.(Gimbrone and García-Cardeña, 2016) These fatty streaks have the potential to turn into fibrous plaques, which are more serious lesions that may be recognised by a thickening of collagen and smooth muscle cells in the intima. Stenosis, or vascular narrowing, can occur as a result of plaques that advance and intrude into the artery's lumen. While stenosis, which restricts blood flow, continues to be a key source of tissue ischaemia, plaque rupture is presently thought to be the primary mechanism responsible for much acute CVD, such as myocardial infarction or stroke.

Risk factors contribute to the development and progression of atherosclerotic thrombosis by a variety of mechanisms - by enhancing the inflammatory/immune response, decreasing endothelial function, boosting oxidative stress, increasing the biomechanical pressures on plaques, or encouraging thrombosis.(Ross, 1993, Ross, 1986, Falk, 2006, Munro and Cotran, 1988, Schwartz et al., 1991)

RISK FACTORS FOR ATHEROSCLEROSIS

CVD is a complex, multifactorial disease, and its aetiology and pathogenesis are influenced by many risk factors, some (such as age, sex, genetic endowment, family history of CVD and ethnicity) are non-modifiable and have been alluded to above, others are (potentially) modifiable. Traditional modifiable risk factors for CVD include hypertension, hyperlipidaemia, diabetes mellitus, smoking, obesity, unhealthy diet, and physical inactivity. In recent years, non-traditional or novel risk factors have also been identified, including inflammatory markers, psychosocial factors, air pollution, and sleep apnoea. Controlling or managing modifiable CVD risk factors can help to reduce the risk of developing CVD and related complications such as stroke, heart attack, and peripheral artery disease.

Modifiable Risk Factors Associated with Cardiovascular Disease (CVD)

While certain risk factors are outside the realm of an individual's control, a significant number of them can be altered through modifications in one's lifestyle.

Tobacco smoking, widely recognized as a modifiable risk factor, has been found to substantially elevate the likelihood of developing cardiovascular disease

(CVD).(Erhardt, 2009) Smoking has been found to contribute to the development of atherosclerosis, diminish the delivery of oxygen to the heart, and facilitate the formation of blood clots. Ceasing smoking has the potential to significantly decrease the risk of cardiovascular disease (CVD).(on Smoking et al., 2010, Bazzano et al., 2003)

Hypertension, also known as high blood pressure, constitutes a significant modifiable risk factor for cardiovascular disease (CVD).(Fuchs and Whelton, 2020) An increased blood pressure level is a risk factor for the development of cardiovascular complications, including stroke and coronary artery disease. Research has demonstrated that the utilization of suitable therapeutic interventions is associated with a decrease in the probability of stroke occurrence and a mitigation of the risk of developing heart disease.(Assmann et al., 1999) Hypertension can also be managed through the implementation of lifestyle modifications, which include weight reduction, regular physical activity, and diet. In general these lifestyle modifications are used alongside appropriate pharmacological interventions.(Gupta and Guptha, 2010).

Diabetes mellitus, a medical condition characterized by elevated levels of glucose in the bloodstream,(Alam et al., 2014) is also known to be a contributing factor to the risk of cardiovascular disease (CVD).(Nesto, 2004) Maintenance of ideal blood glucose levels usually entails medication, including sometimes insulin therapy as deemed necessary, in conjunction with lifestyle modifications. Individuals can contribute to maintaining stable blood sugar levels by adopting a balanced diet that is abundant in whole grains, fruits, vegetables, lean proteins, and healthy fats. Regular physical activity is an essential component that enhances insulin sensitivity and overall well-being.(Balakumar et al., 2016)

Dyslipidaemia is a medical condition characterized by abnormal blood lipid levels, specifically an increase in low-density lipoprotein (LDL) cholesterol, colloquially referred to as "bad" cholesterol, and a decrease in high-density lipoprotein (HDL) cholesterol, colloquially referred to as "good" cholesterol.(Gilbert, 2004)

Atherogenic dyslipidaemia is distinguished by alterations in the concentrations of cholesterol and other lipids in the blood, which have been linked to an increased vulnerability to cardiovascular disease (CVD). It is a pathological state frequently associated with obesity and type 2 diabetes mellitus. The relationship between the levels of low-density lipoprotein cholesterol (LDL-C) and the occurrence of cardiovascular disease (CVD) is well established and HDL-C has been discussed above.(Musunuru, 2010) In addition to cholesterol, triglycerides in VLDL have been found to play a role in the promotion of inflammation and atherogenesis (Lorenzatti and Toth, 2020). Lipids and lipoproteins play pivotal roles in the development of atherosclerosis and are key targets for therapeutic interventions.(Linton et al., 2019)

Recently, there has also been an increasing acknowledgment of non-conventional risk factors that may exert an influence on the onset of cardiovascular disease (CVD), alongside the widely recognized traditional risk factors and inherent genetic vulnerabilities. Non-conventional factors can encompass for example, sleep apnoea, which is characterized by the repetitive occurrence of either partial or complete blockage of the upper respiratory tract while an individual is asleep led to (hypoxia).(Lattimore et al., 2003, Monahan and Redline, 2011) and the inflammatory impact of air pollution, specifically fine particulate matter, on the cardiovascular system.(Basith et al., 2022) Many of these novel underlying factors are associated with worldwide phenomena such as urbanization, demographic shifts towards older populations, and socioeconomic

transformations. Moreover, various factors such as socioeconomic disadvantage, psychological distress, are also known to contribute to CVD. The influence of socioeconomic status (SES) on cardiovascular health may be mediated through various indirect pathways,(Albert et al., 2006) including, but not limited to, lifestyle choices, stress levels, environmental exposures, limited access to healthcare services, and overall state of well-being.(Clark et al., 2009) Also education, which is often considered as an indicator of SES, is widely recognized as a social determinant that influences the likelihood of developing cardiovascular disease (CVD).(Havranek et al., 2015).

In conclusion, it is evident that both non-modifiable and modifiable risk factors play a significant role in the initiation and advancement of cardiovascular disease. In order to assess an individual's overall risk of cardiovascular disease (CVD) and implement appropriate preventive measures, it is crucial to have a thorough understanding of these factors. Understanding disease progression, implementing effective strategies, and raising awareness at all levels are imperative in addressing this dual burden. The promotion of awareness and education through public health campaigns on a global scale has the potential to facilitate the adoption of healthier lifestyles and enhance disease management.

Subtypes of cardiovascular disease

Most, but not all cases of CVD are due to atherosclerotic disease. Most common types of atherosclerotic CVD include:

CORONARY ARTERY DISEASE (CAD)

Coronary artery disease, also termed ischemic heart disease, is a disorder in which the arteries that deliver blood to the heart muscle become narrowed or blocked due to accumulation of atheroma. This can result in decreased blood supply to the heart, resulting in symptoms including chest discomfort (angina pectoris), shortness of breath, and exhaustion. If the atherosclerotic plaque ruptures, occlusion of the artery or downstream embolization can result, leading to myocardial ischaemia, infarction and unexpected cardiac death.(Okrainec et al., 2004)

The formation of atheromatous plaque, a combination of cholesterol, fat, and other substances in the walls of the coronary arteries causes CAD. Atherosclerosis develops over an extended period beginning early in life, and can be accelerated by risk factors such as smoking, high blood pressure, high cholesterol, diabetes, obesity, and a sedentary lifestyle.(Strong et al., 1997) An electrocardiogram (ECG), stress tests, coronary angiography, and imaging tests such as computed tomography (CT), intravascular ultrasonography, or magnetic resonance imaging (MRI) can all be used to diagnose CAD. Treatment for (CAD) varies according to severity and can include lifestyle changes (such as healthy eating, regular physical activity, and smoking cessation), medication (such as statins, blood pressure-lowering drugs, and aspirin), and invasive procedures such as angioplasty or bypass surgery.(Hertzer et al., 1984) Preventing CAD involves managing risk factors, such as maintaining a healthy weight,

exercising regularly, eating a healthy diet (Willett et al., 2006), not smoking (Goldenberg et al., 2003), and managing other health conditions such as high blood pressure and diabetes (Hajar, 2017).

Peripheral artery disease

Poor blood circulation to the legs and feet as a result of peripheral artery disease (PAD) can cause a variety of symptoms and problems. One of the most typical PAD symptoms is claudication, a cramping or agonizing discomfort in the legs. (Criqui and Aboyans, 2015) Usually, resting relieves the discomfort, but it returns as the action is resumed. (Gornik and Beckman, 2005) In severe cases of PAD, pain may occur at rest and interfere with sleep. Other symptoms of PAD include numbness, weakness, or a feeling of coldness in the legs and feet. Diagnosis of PAD involves a physical exam, medical history, and various imaging tests, such as ankle-brachial index (ABI), Doppler ultrasound, and angiography.(Xu et al., 2010, Potier et al., 2011) Treatment of PAD aims to reduce symptoms, prevent complications, and improve quality of life. Lifestyle changes, such as quitting smoking, eating a healthy diet, and regular exercise, can help improve symptoms and prevent further progression of the disease(Hankey et al., 2006). Early diagnosis and treatment of PAD are important to prevent complications and improve quality of life(Olin and Sealove, 2010).

Cerebrovascular disease and stroke

A range of disorders collectively known as "cerebrovascular disease" affect the brain circulation.(Pantoni, 2010) The term covers a variety of conditions including: cerebral aneurysms, arteriovenous malformations, haemorrhagic stroke, ischemic stroke, small vessel disease and cerebral venous thrombosis. (Chandra et al., 2017, Yaqub et al., 1991)

Arterial stenosis or occlusion is a common factor that leads to ischemic cerebrovascular disease and carotid stenosis is a major risk factor for ischemic stroke.(Woo et al., 2017) Typically, atherosclerosis with or without thrombosis can restrict blood flow to a region of the brain and may result in infarction - an ischemic stroke. In most regions of the world, this is the most frequent form of stroke, accounting for around 85% of all instances of stroke in UK.(NHS, 13 September 2022) Smoking, hypertension, diabetes, excessive cholesterol, atrial fibrillation, and other heart conditions are risk factors for ischemic stroke.(Tsao et al., 2023, Lackland et al., 2014, Feske, 2021)

Haemorrhagic stroke is less frequent and occurs when a blood vessel in the brain ruptures, causing bleeding and damage to brain tissue.(Williams et al., 2023, Sacco et al., 2013) Intracerebral haemorrhage and subarachnoid haemorrhage are the two primary forms of haemorrhagic stroke.(Unnithan and Mehta, 2020).

Atherosclerotic cardiovascular disease (ASCVD) manifests in various forms, including CAD, carotid artery disease, and PAD, each contributing to the overall burden of cardiovascular morbidity and mortality. The COMPASS study, a large-scale investigation, highlighted the interconnected nature of these conditions. The study demonstrated that individuals with one form of ASCVD, such as CAD, are at a higher risk of developing other forms, like carotid artery disease and PAD. This overlap suggests common

underlying mechanisms, including systemic atherosclerosis and shared risk factors such as hypertension, hyperlipidaemia, diabetes, and smoking. The COMPASS study found significant incidences of CAD, carotid disease, and PAD within the cohort, underscoring the importance of comprehensive cardiovascular risk management. Patients with cardiovascular disease, involving multiple vascular territories, exhibited higher rates of adverse cardiovascular events compared to those with single-territory disease. These findings emphasize the need for integrated diagnostic and therapeutic approaches to address the full spectrum of ASCVD manifestations. By recognizing the interrelated nature of these conditions, healthcare providers can better identify high-risk individuals and implement strategies to prevent the progression and complications of systemic atherosclerosis(Anand Sonia et al., 2019, Kaplovitch et al., 2021, Sharma et al., 2019).

A range of disorders collectively known as "cerebrovascular disease" affect the brain's circulation. This term covers conditions including cerebral aneurysms, arteriovenous malformations, haemorrhagic stroke, ischemic stroke, small vessel disease, and cerebral venous thrombosis. Arterial stenosis or occlusion often leads to ischemic cerebrovascular disease, with carotid stenosis being a major risk factor for ischemic stroke. Typically, atherosclerosis with or without thrombosis can restrict blood flow to a brain region, potentially resulting in an ischemic stroke. In the UK, ischemic stroke accounts for around 85% of all stroke cases. Risk factors for ischemic stroke include smoking, hypertension, diabetes, high cholesterol, atrial fibrillation, and other heart conditions.

Cerebrovascular Disease and Mechanisms of Cognitive Impairment

Multiple cerebral vascular conditions can cause cognitive impairment. Cerebrovascular disease is the major cause of vascular dementia, but may also contribute to non-vascular dementias, such as Alzheimer's disease. (Love and Miners, 2016) Vascular dementia develops when the arteries in the brain are damaged, termed small vessel disease (SVD). SVD can adversely affect the brain through several mechanisms including a reduction in brain perfusion, compromised integrity of the blood-brain barrier, or adverse effects on neurovascular coupling. (Knopman, 2007) These processes may result in cognitive deficiencies, including memory loss, trouble understanding and communicating with others, and poor decision making.(Kalaria, 2012)

Imaging for cerebrovascular disease

Ultrasound is a valuable tool for screening individuals at risk for carotid artery disease, or with cerebrovascular disease including those with stroke.(Saxena et al., 2019a) Transcranial Doppler ultrasound can also detect the presence of microemboli, which are small fragments of plaque or thrombus that break off and can travel to the brain, leading to ischemic strokes.(Fernandes et al., 2016) Carotid ultrasound can help identify those at risk for stroke, guide treatment decisions, and monitor the effectiveness of interventions.(Sarkar et al., 2007)

In addition to ultrasound, magnetic resonance angiography (MRA), CT angiography (CTA) (Lin and Liebeskind, 2016), and positron emission tomography (PET)(Heiss, 2014) imaging are other diagnostic tests that can be used to assess cerebral haemodynamics and cerebrovascular disease.

Carotid artery disease

This PhD mainly focuses on carotid artery disease (CA), consequently this section discusses it in more detail.

The carotid arteries are found on either side of the neck and carry blood to the brain. Typically carotid artery disease is the result of atherosclerosis, so risk factors for CA overlap with those for atherosclerosis generally, and include age, sex, smoking, high blood pressure, high cholesterol, diabetes, obesity, and a family history of the disease.(Song et al., 2020a)

Asymptomatic carotid artery plaque is frequently found incidentally, during routine screening or imaging procedures. Despite usually being asymptomatic, carotid artery plaque is linked to a higher risk of stroke and other cardiovascular events. CA disease is a progressive condition and the risk of stroke rises as the amount of plaque accumulates.(Flaherty et al., 2012) Therefore, a critical component of prevention is recognising and treating asymptomatic carotid artery plaque.(Carr et al., 1996)

The diagnosis of CA typically involves a physical exam, medical history, and various imaging tests, such as ultrasound, angiography, and magnetic resonance imaging (MRI). These tests can help determine the extent of the plaque build-up and assess the risk of stroke.

Anatomy of head and neck arteries

The head, neck, face and brain receive blood supply from the right and left carotid arteries. The right common carotid artery (RCCA) arises from the brachiocephalic (also known as the innominate) artery which is a branch of the aorta. The left common carotid artery (LCCA) arises directly from the aorta. Both carotid arteries branch into

internal carotid arteries (ICA) and external carotid arteries (ECA) as the right and left common carotid arteries ascend through the neck. The ECA delivers blood to the face, neck, and scalp, while the ICA supplies blood to the brain.(Sethi et al., 2019) The carotid artery anatomy exhibits several clinically significant variations. The common carotid artery can originate from different locations. Typically, the left common carotid artery arises from the aortic arch, while the right originates from the brachiocephalic trunk; however, variations in their origins can occur. The common carotid artery usually bifurcates into the internal and external carotid arteries at the level of the fourth cervical vertebra (C4), but this can vary between C3 and C5. Some individuals may exhibit tortuosity, kinking, or coiling of the carotid arteries, which can be benign or associated with pathology such as atherosclerosis.

Variations in the branches of the internal and external carotid arteries can occur, such as the superior thyroid artery arising from the internal carotid artery. In rare cases, parts of the carotid artery system may be underdeveloped (hypoplasia) or absent (agenesis), often compensated by collateral circulation. Duplication of the carotid artery, where two parallel arteries run in place of a single one, is a rare anatomical variant. Additionally, fenestration involves a single artery splitting into two distinct luminal channels that later rejoin, which can be observed in the internal carotid artery.

These variations affect the position of the bifurcation, the number of branches, the vessel's width, and its length, which may have significant clinical ramifications. These include a higher chance of developing carotid artery disease, difficulty in carrying out surgery, and challenges in imaging studies. Recognizing these variations is crucial for surgeons and radiologists to avoid complications during diagnostic and therapeutic procedures. Some examples of these variations are shown in (FIGURE 1.

1),(Cappabianca et al., 2016, Tan et al., 2010, Farina et al., 2019, Cobzeanu et al., 2023)

In addition to the carotid arteries, the vertebral arteries supply the posterior part of the brain. The vertebral arteries combine to create the basilar artery, which supplies the brainstem and cerebellum (Figure1.3). **Error! Reference source not found.**(Gofur and Singh, 2021) Another key component of the brain circulation is a circle of linked arteries, called the circle of Willis. The main blood vessels that supply the circle of Willis are the internal carotid arteries and the basilar artery. Blood is supplied to the anterior part of the circle of Willis (the anterior cerebral artery (ACA) and the middle cerebral artery (MCA)) by the internal carotid arteries, and the posterior part is supplied by the basilar artery.(Liu et al., 2016a) The circle of Willis helps ensure enough blood supply to all areas of the brain and acts as a backup mechanism for blood flow to the brain in the event that any of the feeding arteries become blocked or stenosed(Figure1.4).(Hendrikse et al., 2005) A blockage in the carotid artery can cause a considerable reduction in brain perfusion if the collateral circulation in the brain is insufficient.(Lal et al., 2011)

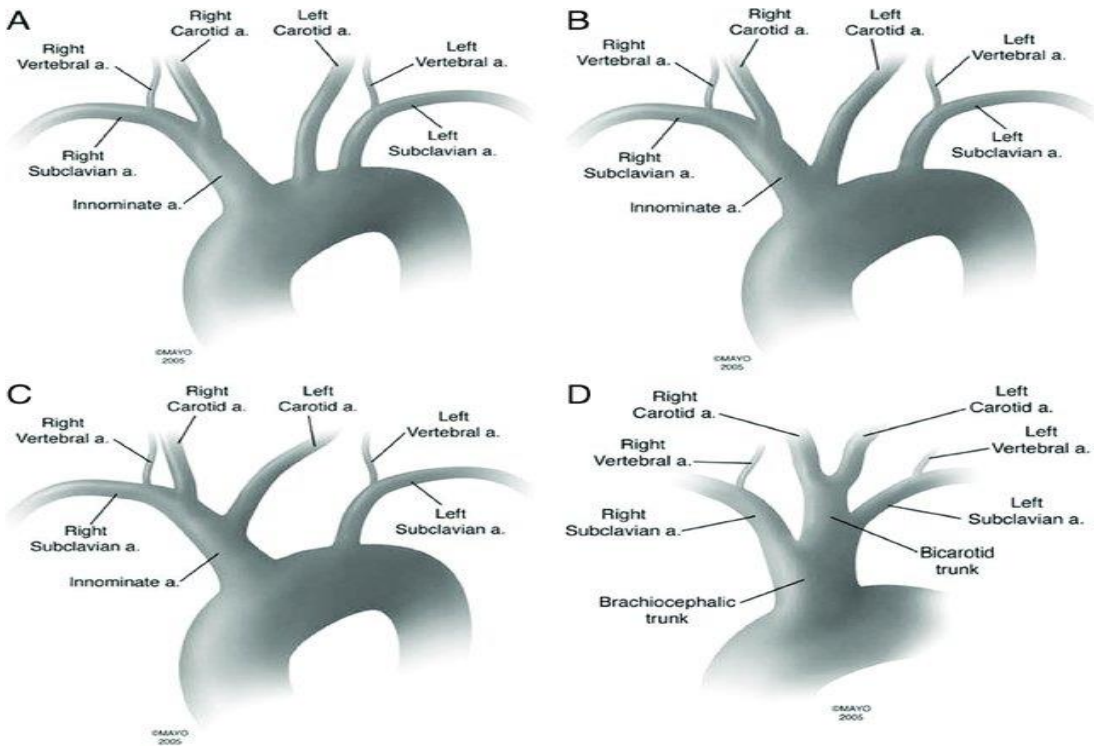

FIGURE 1. 1 Some examples of anatomical variants of the origin and the branches of the carotid arteries adapted from (Shuaib et al., 2014)

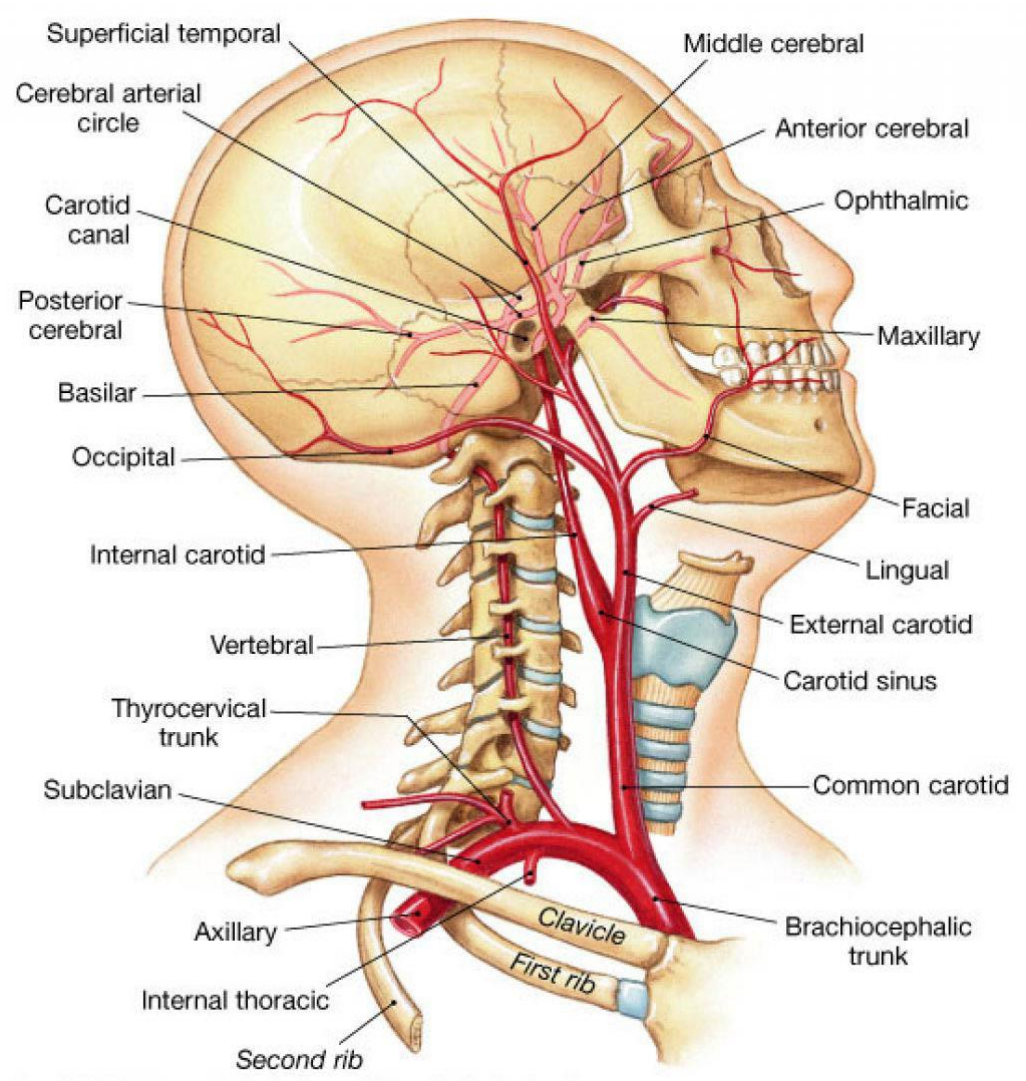

FIGURE 1. 2 **Anatomy of the blood vessels of the head and neck. Adapted from https://anatomy-medicine.com/cardiovascular-system/124-blood-vessels-of-the-head-and-neck.html**

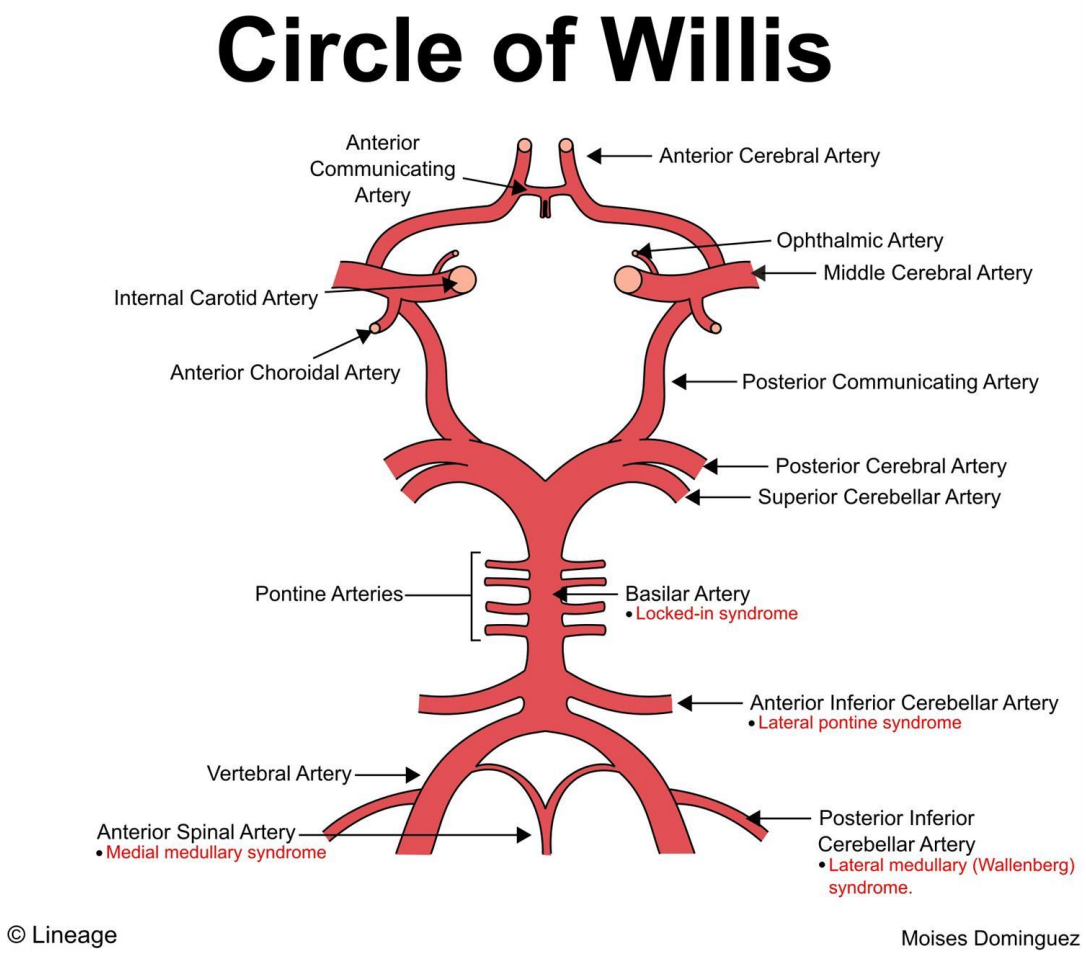

FIGURE 1. 3 **Anatomy of the Circle of Willis. Adapted from https://step1.med-bullets.com/neurology/113022/circle-of-willis**

Imaging carotid disease using ultrasound.

Current guidelines do not recommend the routine use of carotid ultrasonography (USS) for risk stratification due to several key factors. First, there is considerable heterogeneity in the methods used for carotid ultrasonography, including differences in equipment, operator expertise, and protocols. This variability can lead to inconsistent and unreliable results. Second, there is a lack of robust outcome data supporting its routine use. While carotid intima-media thickness (CIMT) and plaque detection can

predict cardiovascular events, the evidence is mixed and often inconsistent due to differences in measurement techniques and definitions. Furthermore, routine carotid ultrasonography may not provide significant additional information beyond traditional risk factors and other non-invasive tests like the Framingham Risk Score. The cost and resource utilization for routine screening are also high, making it a less cost-effective option given the uncertain incremental benefit. Additionally, the accuracy of carotid ultrasonography is highly dependent on the operator's skill, further complicating standardization and interpretation of results. As a result, current guidelines from organizations like the American Heart Association and the U.S. Preventive Services Task Force do not support routine carotid ultrasonography for cardiovascular risk stratification in asymptomatic individuals, recommending its use primarily for those with specific clinical indications(Arnett et al., 2019, Cobzeanu et al., 2023, Krawisz et al., 2021).

2D vascular ultrasonography is a useful technique for assessing the characteristics of blood artery walls, plaque volume and early atherosclerosis, as it is simple to perform, and non-invasive.(de Korte et al., 2011) However, 2D ultrasonography has drawbacks; it can provide a limited number of imaging angles, and the operator's skill can affect the quality of the image and data acquired. When data is only taken from a particular area of the plaque and extrapolated to reflect the overall structure, this may affect how well the plaque is identified.(Calogero et al., 2018) There is considerable disagreement about whether routine carotid ultrasonography testing is advisable for the detection of asymptomatic carotid artery atherosclerosis. (Giannoukas et al., 2016) Nevertheless, carotid ultrasonography-based visual evaluation or dynamic alterations may offer an important clinical context and assist in the identification of plaques, acting as a sign of a high risk of myocardial infarction, stroke and mortality. (Li et al., 2021a)

Carotid Artery Intima-Media Thickness (CIMT)

Measurement of carotid intima-media thickness (CIMT) is a commonly used technique for assessing cardiovascular risk and early atherosclerosis.(Pignoli et al., 1986) Due to its size, superficial location, convenience of access, and limited mobility, the common carotid artery (CCA) is commonly used, although measurements of intima media thickness can also be made in the bulb or internal carotid artery.(Stein et al., 2008a) CIMT is assessed using B-mode ultrasonography.(Stein et al., 2008a, Urbina et al., 2009, Cismaru et al., 2021) However, the medical community is uncertain whether to measure CIMT routinely in high risk patients.(Vlachopoulos et al., 2015, Greenland et al., 2010) CIMT is defined as the distance between the leading edges of the first bright line (lumen-intima interface) and the second bright line (media-adventitia interface) on the far wall of the carotid artery (FIGURE 1. 4). (Perwaiz Khan et al., 2013, Sol et al., 2001)

CIMT can be measured at the near wall and/or the far wall of the CCA, with respect to the ultrasound probe.(Bots et al., 1997a) Measurements from the far wall show better reproducibility (Wikstrand, 2007, Peters et al., 2012) and most guidelines (e.g. (Stein et al., 2008c)) advocate making measurements using the far wall; however there is some evidence that using a combination of far and near wall is advantageous.(Seekircher et al., 2023) The ongoing discussion surrounding the choice between near-wall and far-wall CIMT measurement arises from the inherent balance between precision and practicality.(Peters and Bots, 2013)

Accurately measuring CIMT in the curved carotid bulb and the deep internal carotid artery (ICA) poses greater challenges due to the requirement for transducer angulation and limited visualization,(Montauban van Swijndregt et al., 1999) particularly in older

or obese people. (Bots et al., 1997a) reported that there was a positive correlation observed between elevated body mass index (BMI) and an increased likelihood of incomplete carotid intima-media thickness (CIMT) measurements in the bulb and ICA. This is attributed to the difficulties encountered in capturing clear images in individuals with higher BMI values and fatter necks.

Elevated CIMT is linked to CVD and acts as an independent predictor of stroke and CHD.(Nambi et al., 2010) Even low-risk individuals may benefit from screening for subclinical atherosclerosis, especially if they have a family history of early CVD.(Cobble and Bale, 2010, Steinl and Kaufmann, 2015) but current guidelines do not recommend its routine use for cardiovascular risk stratification as it was considered offer no benefit in risk assessment for a first ASCVD event based on little evidence for reclassification, discrimination, calibration, and cost-effectiveness, and concerns about standardization and measurement issues.(Goff et al., 2014)

The extent of carotid atherosclerosis assessed using CIMT is directly related to the number of cardiovascular risk factors a patient possesses.(Ren et al., 2015) Many studies have shown that an elevated CIMT value was linked to an elevated risk of CVD, stroke, and coronary heart disease(Kokubo et al., 2018, van den Oord et al., 2013, Carpenter et al., 2016). The estimated normal range for IMT value increase with age (0.71 mm for people between the ages of 20 and 40; 0.74 mm for those between the ages of 40 and 60; and 0.82 mm for people beyond 60).(Saxena et al., 2017) A meta-analysis of 9341 participants concluded that in individuals with absence of plaque in their carotid arteries, higher carotid intima-media thickness (CIMT) was linked to subsequent development of carotid plaque.(Tschiderer et al., 2020) The relationship between CIMT and Alzheimer's disease (AD), vascular dementia

(VaD)(Hofman et al., 1997) and cognitive function decline(Rao, 2001) is considered in detail as part of a systematic review in a later chapter.

In conclusion, the results of various meta-analyses, including one by (Willeit et al., 2020).have highlighted that CIMT reliably predicts risk of cardiovascular disease (CVD) and that the degree to which interventions slow down the progression of CIMT correlated with the reduction in CVD risk. This underscores the importance of CIMT as a measure to evaluate the effectiveness of interventions in reducing the risk of CVD. Inconsistencies in some research findings have been attributed to differences in measuring segments, varying IMT criteria, and presence of carotid plaque adjacent to the site of CIMT measurement. The inconsistencies in some research findings on CIMT (Carotid Intima-Media Thickness) can be attributed to differences in measurement techniques, varying IMT criteria, and the presence of carotid plaque adjacent to the site of CIMT measurement. Different studies often employ various segments of the carotid artery for measurement, and there is no universal standard for the specific segment to be measured. This variability can lead to differences in reported IMT values and impact the comparability of results across studies. For example, some studies measure CIMT in the common carotid artery (CCA) 1-2 cm proximal to the bifurcation, while others might include measurements in the carotid bulb or the internal carotid artery (ICA). The inclusion or exclusion of these segments can result in different IMT values because the arterial wall characteristics and the likelihood of plaque presence can vary significantly between these regions. Moreover, the presence of carotid plaque near the CIMT measurement site can influence the thickness measurements and potentially confound the results. Plaques can create artifacts and make it challenging to obtain accurate and consistent measurements. Standardizing measurement procedures and clearly defining criteria for CIMT and plaque presence are essential

steps toward improving the reliability and utility of CIMT as a marker for cardiovascular disease risk.

However, more investigation is required to define more standardised measurement procedures and identify the best applications for carotid IMT in various patient demographics and therapeutic contexts.

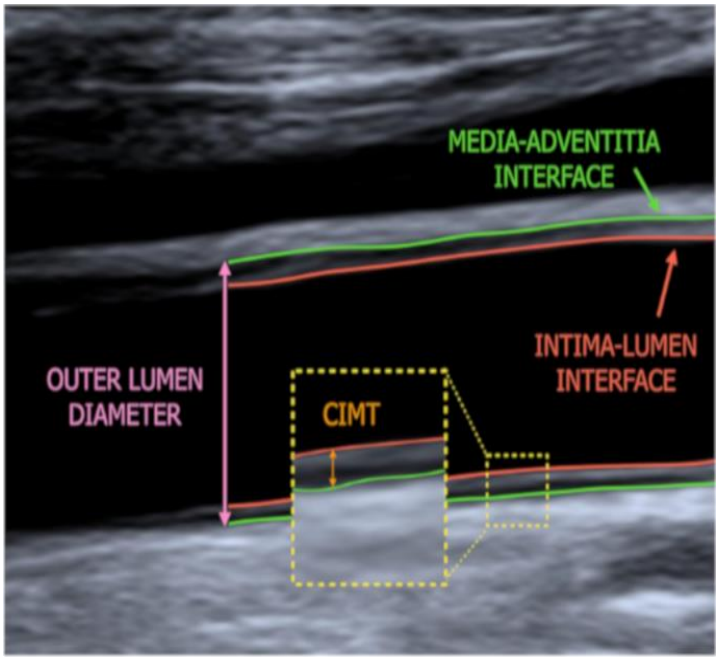

FIGURE 1. 4 ultrasound image of the carotid artery with tracing lines at the intima-lumen interface (red line) and the media-adventitia interface (green line). The pink coloured line represents the outer lumen diameter adapted from(Fernández-Alvarez et al., 2022)

Carotid artery plaques and stenosis

The definition of carotid plaques on ultrasound varies slightly across different worldwide consensus recommendations. According to the Mannheim consensus, plaques are focal structures encroaching into the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT value, or a focal structure with a thickness higher than 1.5

mm.(Touboul et al., 2012a) Plaques are defined by the American Society of Echocardiography as a focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or as a focal region with CIMT greater than 1.5 mm that protrudes into the lumen, and that is distinct from the adjacent boundary (Figure 1.6)(Stein et al., 2008a) The impact of these subtle differences in definition appears not to have been evaluated.

Most plaques do not give rise to a haemodynamically significant degree of stenosis (corresponding to approximately 50-60% diameter or 70-80% area stenosis (Deweese et al., 1970, Tindall et al., 1962, Alexandrov, 2007)), but when they do, this is an important clinical consideration since a surgical carotid endarterectomy treatment can considerably lower the risk of further strokes in individuals who have had strokes or transient ischemic episodes (TIAs).(Flaherty et al., 2012) Carotid endarterectomy reduces the degree of stenosis and helps to restore blood flow, improving the overall prognosis and minimising the risk of stroke in the future.(Rothwell et al., 2003) It is thought that part of the benefit of endarterectomy may also involve a reduction of elevated wall shear stress (WSS) on the plaque surface. High WSS is associated with comparatively large pressure gradients across a narrow stenosis, which may be a contributing factor in plaque instability and WSS increases as stenosis severity increases. Moreover, inadequate cerebral collateralization may result in greater pressure decreases across a related stenosis, raising WSS levels above the level required for plaque rupture.(Li et al., 2008) Elevated heart rate or blood pressure, vasospasm, and internal bleeding are other potential causes of plaque rupture; nevertheless, it is difficult to determine the particular cause of carotid plaque rupture in a given individual.(Golledge et al., 2000, Muller et al., 1989, Penha et al., 1988).

Multiple studies have linked carotid artery stenosis to cognitive impairment, including memory loss. It is suspected that decreased blood flow to the brain caused by a severe carotid artery stenosis can result in brain hypoperfusion, transient ischemic episodes, white-matter damage, or ischemic stroke.(van Oijen et al., 2007, Rao, 2001, Auperin et al., 1996a).

The link between carotid artery stenosis and cognitive impairment highlights the significance of cerebral perfusion in maintaining cognitive function. Reduced cerebral perfusion, due to high-grade stenosis or occlusion of the internal carotid arteries, can lead to chronic ischemia and cognitive impairment even in the absence of overt ischemic lesions(Buratti et al., 2014, Johnston et al., 2004).The brain is endowed with vasoregulatory mechanisms that ensure adequate blood supply to meet its high energy demands. Neural activity, using most of the brain's energy, dynamically regulates cerebral blood flow (CBF) through a coordinated action of neurons, astrocytes, and vascular cells. Various molecular signals including ions, nitric oxide (NO), adenosine, neurotransmitters, and neuropeptides mediate these changes. Endothelial cells, which line cerebral blood vessels, regulate vascular tone by releasing vasoactive factors in response to chemical signals or mechanical forces like shear stress. These mechanisms ensure that the brain receives sufficient blood flow to support the metabolic needs of its active cellular constituents (Ando and Yamamoto, 2009, Johnston et al., 2004). Small vessel disease is a major contributor to vascular cognitive impairment (VCI), particularly affecting the hemispheric white matter. Microvascular alterations lead to various neuropathological lesions such as white matter lesions (leukoaraiosis) and lacunes. These changes are strongly associated with cardiovascular risk factors like hypertension, diabetes, hyperlipidaemia, and smoking. Pathological changes in small vessels include atherosclerosis, arteriolosclerosis, and lipohyalinosis, leading to

white matter damage characterized by vacuolation, demyelination, and axonal loss (Gorelick et al., 2011a, Jellinger, 2013).Collectively, these factors underscore the complex interplay between vascular health and cognitive function. Addressing these multifaceted vascular issues is crucial for developing strategies to prevent and manage cognitive impairment associated with vascular diseases.

Blood flow and perfusion can also be decreased by thrombus development, which may be promoted by narrowing of the arterial lumen, plaque erosion or irregularities in the plaque. Thrombi can also give rise to emboli leading to brain infarction and embolic strokes. The link between hypoperfusion and embolization includes reduced perfusion, which restricts blood flow and nutrition delivery, and decreased blood flow, which makes it challenging to remove emboli.(Caplan and Hennerici, 1998)

Inflammation and elevated levels of inflammatory markers are linked to carotid artery stenosis vulnerability and have the potential to be biomarkers for carotid stenosis risk (Auperin et al., 1996a). The advantages of surgery for some subgroups of patients with symptomatic internal carotid artery (ICA) stenosis were shown by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST).(Group, 1998, Barnett et al., 1998) These parameters (NASCET) and (ECST)are used to characterise the degree of carotid stenosis, with NASCET standards essentially equating to ECST criteria for 75% stenosis. The NASCET and ECST studies had a big impact on clinical practice and still influence how carotid artery disease is managed today (Figure1.7). However, recent work in the UK emphasised the need of uniform reporting in carotid ultrasonography examinations. Various grading standards are currently in use, which causes reporting to be inconsistent.(Oates et al., 2009).

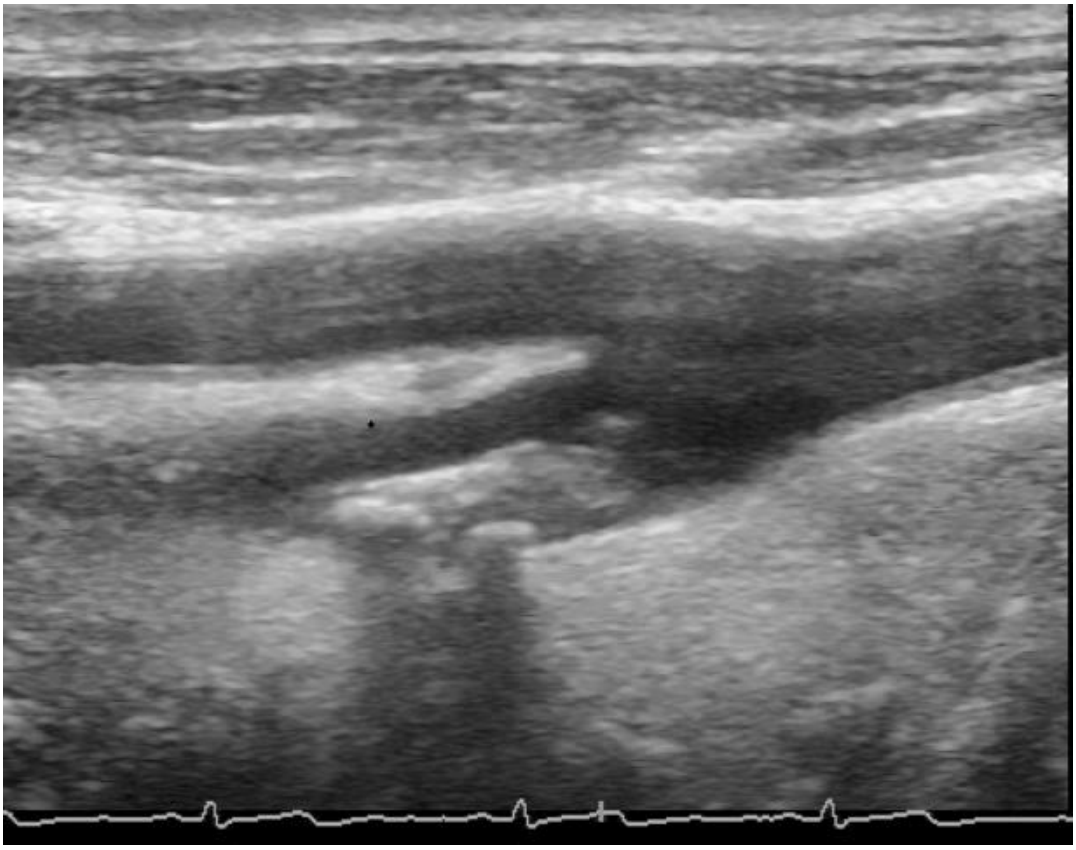

FIGURE 1. 5 ultrasound image showing the presence of plaque with acoustic shadowing.

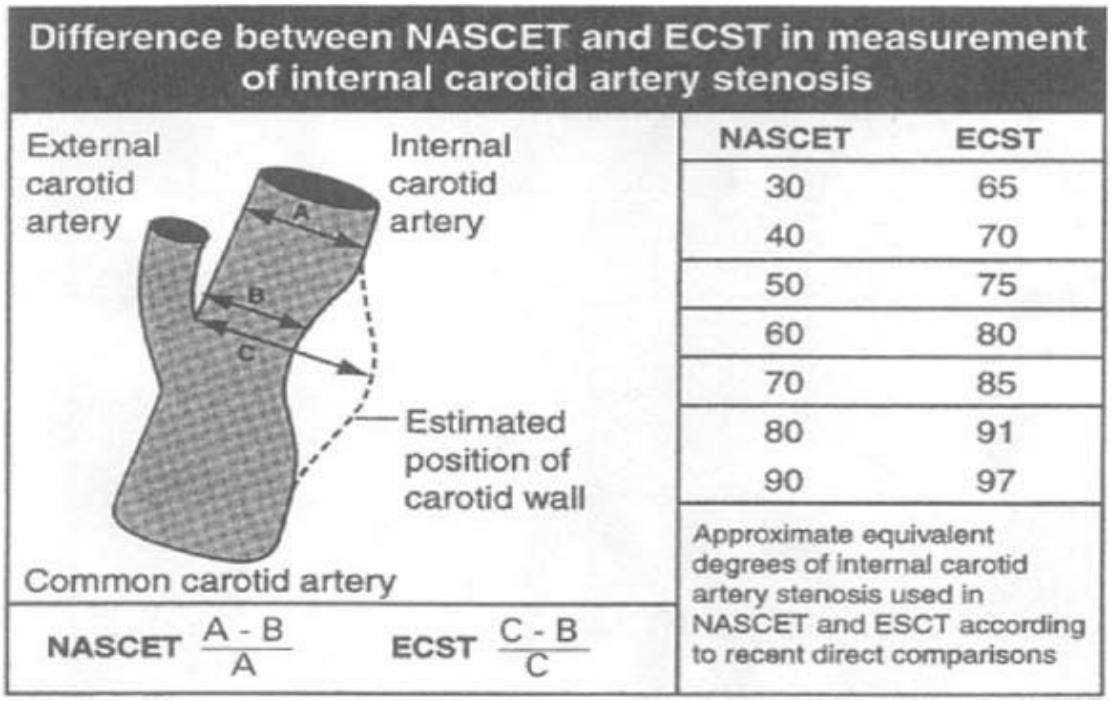

FIGURE 1. 6 ECST and NASCET methods for measuring stenosis. Adapted from (Donnan et al., 1998)

Morphological characteristics of atherosclerotic plaque using ultrasound

For the purpose of determining vulnerability, morphological features of the carotid plaque can be evaluated. Typically, the histo-morphological characteristics of vulnerable plaques include a large lipid core, a thin fibrous cap, and increased neovascularity.(Alsheikh-Ali et al., 2010) These characteristics increase the possibility of problems, including rupture and thrombosis and add to the plaque's instability.(Jashari et al., 2013)

Commonly utilised ultrasound criteria to assess plaque composition and vulnerability include echogenicity, greyscale heterogeneity, and surface morphology, including smoothness or ulceration.(Nezu and Hosomi, 2020) The term "echogenicity" refers to how effectively a tissue transmits or reflects ultrasound waves in comparison to nearby

tissues. A structure can be categorised as hyperechoic white (echo-rich), hypoechoic (grey) or anechoic dark (echolucent) (Figure1.8&1.9).(Ihnatsenka and Boezaart, 2010) The darker appearance of echolucent plaques on ultrasonography is associated with a greater level of lipid and haemorrhage.(El-Barghouty et al., 1996) In contrast, the brighter-appearing hyperechoic plaques have more calcification and fibrous tissue which can also cause acoustic shadowing in the image making the examination more difficult.

The presence of lipids, necrotic components, and neovascularization inside the core of the atherosclerotic plaque has an impact on its echogenicity. Additionally, the echogenicity of the plaque may be affected by the presence of mineralized or fibrous components. A thin or ruptured fibrous cap is also associated with haemorrhage and a larger percentage of lipid-rich or necrotic core (Figure1.10). (Hellings et al., 2010, Ota et al., 2009) However, ultrasonography is not very effective in differentiating between plaque types. (Bock and Lusby, 1992, Grønholdt, 1999)

Measures of plaque composition are related to other vascular diseases: according to (Zureik et al., 2003) carotid plaques that appear hyperechoic on ultrasonography are linked to aortic stiffness and the presence of haemorrhage inside the plaque can aid in the prediction of a woman's development of cardiovascular disease.(Toorn et al., 2022).

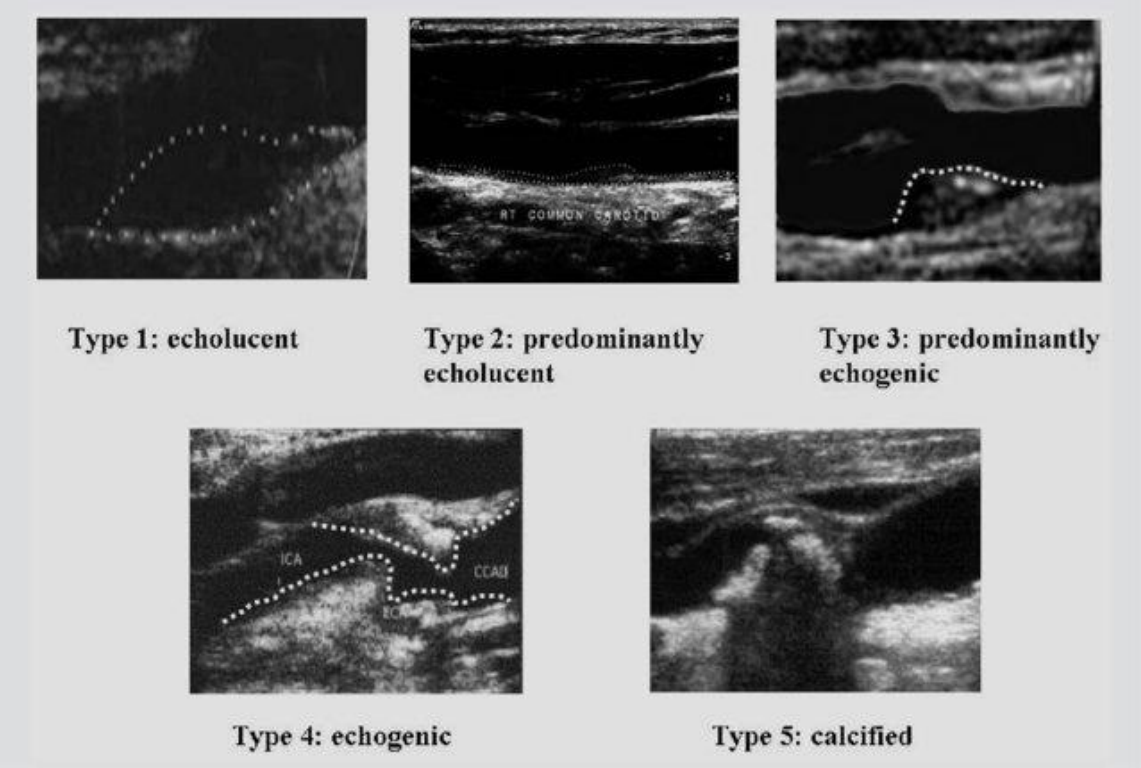

FIGURE 1. 7 Carotid plaque classified according to their echogenicity and appearance in ultrasound images. Adapted from (Sirico et al., 2009).

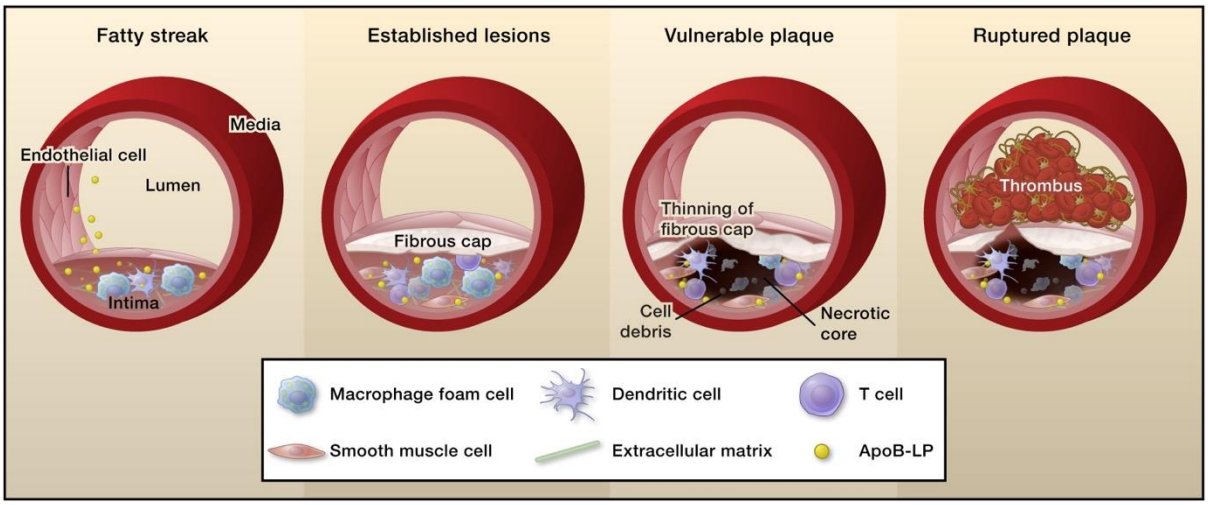

FIGURE 1. 8 Progression of an Atherosclerotic Lesion Adapted from https://sprintmedical.in/blog/cardiovascular-disease

In summary, ultrasonography has become a useful tool in the management of carotid atherosclerotic disease due to its non-invasiveness, and affordability. Although

alternative imaging techniques like contrast-enhanced magnetic resonance angiography and CT angiography have valuable applications, ultrasonography is still widely used for both initial and subsequent imaging of the carotid bifurcation.(Saxena et al., 2019b) Ultrasonography will probably continue to play a significant role in stroke prevention plans and the general treatment of patients with carotid atherosclerosis as the therapy of carotid disease develops.(Keller et al., 1976, von Reutern et al., 2012, Kristensen et al., 2018)

Later life cognition and the impact of carotid atherosclerosis

Cardiovascular disease (CVD) is believed to be an important risk factor for cognitive impairment and dementia,(Beeri et al., 2009) especially in older individuals.(Stanek et al., 2011) This topic is dealt with in more detail in Chapter 2 but a brief outline is presented here.

Proactively preventing atherosclerosis in those who are at risk may be able to slow the progression of cognitive decline.(Lin et al., 2020) CIMT, as a measure of atherosclerosis, has been shown to be inversely correlated with cognitive performance.(Wendell et al., 2009a, Komulainen et al., 2007a, Gardener et al., 2017).

The impact of atherosclerosis on cognitive function is believed to involve a range of mechanisms. Atherosclerosis is thought to exert a direct impact on cognition through reduced cerebral perfusion or ischaemia as discussed above.(de la Torre, 2016) Associations between atherosclerosis and cognitive decline can also be attributed to shared risk factors; such as hypertension, dyslipidaemia, and diabetes (Leszek et al., 2021). It has been proposed that a considerable proportion, perhaps as much as 40%,

of instances of dementia may be averted through a strategic focus on modifiable risk factors, with a primary emphasis on those related to cardiovascular health.(Nordestgaard et al., 2022)

Assessment of cognitive function and brain health

Cognitive function refers to internal mental processes which help people to think, make decisions and solve problems.(Roy, 2013)

The assessment of cognitive function involves a diverse array of tools and methodologies that are employed to appraise an individual's cognitive capacities. Cognitive screening tests such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) provide assessments of overall cognitive functioning, rendering them well-suited for preliminary or population-level evaluations.(Pinto et al., 2019)

Neuropsychological assessments, exemplified by the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955) and the Trail Making Test (TMT)(Llinàs-Reglà et al., 2017), offer extensive appraisals of distinct cognitive domains, thereby facilitating the process of diagnosing and formulating treatment strategies.

Advanced brain imaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), offer valuable insights into the intricate structure and dynamic function of the brain. By harnessing the power of these cutting-edge technologies, researchers and clinicians are able to delve deeper into the complexities of cognitive processes and gain a more comprehensive understanding of the underlying mechanisms that govern them.(Xue et al., 2010) Moreover, these sophisticated imaging modalities play a pivotal role in the early detection and diagnosis of various

brain abnormalities, facilitating timely interventions and improved patient outcomes. Further details regarding these methods are included in the introduction to relevant chapters.

Thesis Hypothesis:

The present study aims to investigate the association between carotid artery atherosclerosis and cognitive decline in two diverse cohorts: the Southall and Brent Revisited (SABRE) study and the National Survey of Health and Development (1946 Birth Cohort). We hypothesize that individuals with a higher burden of carotid artery atherosclerosis will exhibit poorer cognition (or a more pronounced cognitive decline over time) and poorer imaging markers of brain health, and this association will be independent of various demographic, lifestyle, and cardiovascular risk factors.

Thesis Aims:

1. Assess the prevalence and severity of carotid artery atherosclerosis in the SABRE and 1946 Birth Cohort populations through ultrasound-based imaging techniques.

2. Examine the cognitive function of participants in both cohorts and quantify the associations between measures of carotid artery atherosclerosis and cognitive function. Examine the association between imaging markers of brain health and carotid artery atherosclerosis in SABRE.

3. Explore the role of factors such as age, gender, socioeconomic status, and cardiovascular risk factors that may confound the relationship between carotid artery atherosclerosis and cognition.

Through this research, I aim to enhance our understanding of the relationship between carotid artery atherosclerosis and cognitive decline, potentially providing insights for targeted interventions and public health initiatives aimed at mitigating cognitive decline in aging populations.

Chapter 2: Is carotid artery atherosclerosis associated with poor cognitive function assessed using the Mini-Mental State Examination? A systematic review and meta-analysis

ABSTRACT

Objectives: To determine associations between carotid atherosclerosis assessed by ultrasound and the mini-mental state examination (MMSE), a measure of global cognitive function.

Design: Systematic review and meta-analysis.

Methods: MEDLINE and EMBASE databases were searched up to 01/05/2020 to identify studies that assessed associations between asymptomatic carotid atherosclerosis and the MMSE. Studies reporting strength of associations between carotid plaque or intima-media thickness (CIMT) and dichotomised MMSE were meta-analysed. Publication bias of included studies was assessed.

Results: A total of 31 of 378 reviewed articles met the inclusion criteria; together they included 27,738 participants (age 35 to 95 years). Fifteen studies reported some evidence of a positive association between measures of atherosclerosis and poorer cognitive performance in either cross-sectional or longitudinal studies. The remaining 16 studies found no evidence of an association. Seven cross-sectional studies provided data suitable for meta-analysis. Meta-analysis of three studies that assessed carotid plaque (n= 3,549) found a positive association between the presence of plaque and impaired MMSE but with a wide 95% confidence interval (CI) that was compatible with no association (pooled estimate for the odds ratio (OR) (CI) 2.72 (0.85, 4.59)). An association between CIMT and impaired MMSE was reported in six studies (n=4,443) with a pooled estimate for the OR being 1.13 (1.04, 1.22), providing weak evidence to support a positive association. Heterogeneity across studies was moderate to small (carotid plaque with MMSE, I^2=40.9%; CIMT with MMSE, I^2=4.9%). There was

evidence of publication bias for carotid plaque studies (p=0.02), but not CIMT studies (p=0.2).

Conclusions: There was some, limited cross-sectional evidence indicating an association between CIMT and poorer global cognitive function assessed with MMSE. Estimates of the association between plaques and poor cognition were too imprecise to draw firm conclusions and evidence from studies of longitudinal associations between carotid atherosclerosis and MMSE is limited.

INTRODUCTION

Improvements in life expectancy have led to a dramatic increase in the worldwide burden of age-related diseases, notably atherosclerotic cardiovascular disease, and cognitive decline and dementia.(Naghavi et al., 2017)

Atherosclerosis affects most large arteries, including the common carotid artery (CCA) and its major branch the internal carotid artery.(Sobieszczyk and Beckman, 2006) Carotid artery atherosclerosis is common (Song et al., 2020b) and may be an important cause of cerebral ischaemia and cognitive impairment. While assessment of carotid disease can be performed using a range of imaging methods, (e.g. magnetic resonance imaging (MRI), computed tomography (CT), angiography, and ultrasound,(Davis et al., 2001)) ultrasound is the most commonly used,(Breteler et al., 1994, Stein et al., 2008a, O'Leary and Bots, 2010, Touboul et al., 2012b) as it is inexpensive, non-invasive and widely available.

A decline in cognitive function is common with advancing age,(Chaytor and Schmitter-Edgecombe, 2003) and severe cognitive impairment and dementia are increasingly

frequent as the proportion of older people in the population increases. Cognitive function refers to internal mental processes which help people to think, make decisions and solve problems,(Roy, 2013) and cognitive function decline can affect patients' health, daily routine, learning new things, speech and writing abilities, and to live independently. Mild Cognitive Impairment (MCI), dementia and Alzheimer's are the most common types of cognitive dysfunction.(Knopman and Petersen, 2014) A comprehensive assessment of neuropsychological cognitive performance at the domain level is time consuming and most studies use brief cognitive screening tools.(Faber, 2009) The most widely-used tool for cognitive testing is the MMSE.(Tsoi et al., 2015, Mitchell, 2009, Patnode et al., 2020) The MMSE contains 11 tasks and covers 7 domains: visuospatial skills, language, concentration, working memory, memory recall, and orientation and is scored out of a maximum 30 points.(Meyers and Wefel, 2003) The commonest cut-points to detect dementia with the MMSE are ≤23 or ≤24, although higher and lower cut-points have been used in some studies.(Mitchell, 2009, Patnode et al., 2020) While it is relatively easy to use, the MMSE has a number of limitations, including non-linearity, a floor effect in advanced dementia, a ceiling effect in very mild disease, and bias in people with little formal education or in non-English speaking groups.(Tsoi et al., 2015, Mitchell, 2009, Patnode et al., 2020)

Several studies have used a combination of carotid ultrasound and MMSE to look for associations between carotid atherosclerosis and cognitive performance, either cross-sectionally or longitudinally; however, these studies have yielded conflicting results. For example, the Rotterdam Study (van Oijen et al., 2007) reported that common carotid artery intima-media thickness (CIMT) was associated with increased risk of Alzheimer's disease, but not vascular dementia, whereas carotid plaques were not associated with either Alzheimer's disease or vascular dementia. In contrast, the

Framingham Offspring Cohort study (Romero et al., 2009c) reported that CIMT was not associated with any measure of cognition, although there was evidence of an association between CIMT and impaired verbal memory and nonverbal memory, and that carotid stenosis ≥50% was associated with impaired executive function, but not verbal and non-verbal memory.

The aim of this study therefore was to systematically review evidence of an association between carotid atherosclerosis assessed by ultrasound and global cognitive function assessed using the MMSE, also to perform a meta-analysis of quantitative measures of association between carotid atherosclerosis and global cognitive function.

METHODS

This study was conducted in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement,(Moher et al., 2009) and was registered in the international prospective register of systematic reviews (PROSPERO) (registration number CRD42021240077). Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Search strategy

The search was conducted systematically (up to 01/05/2020) by two authors (Rayan Anbar and Salahaden Sultan) independently using two online databases: MEDLINE and EMBASE Classic + EMBASE. A combination of synonyms and related words and text word searching was used to extract all relevant articles. A combination of indexed (MesH) terms and keyword searches in titles and abstracts was used: (1) cognition,

cognitive function, dementia, Alzheimer disease; (2) atherosclerosis, intima media thickness, plaque; (3) carotid arteries; (4) All searches were limited to (English language and humans). Specific inclusion criteria were set to target more direct vascular pathologies, ensuring a more homogeneous data set. The results from databases were exported to an Endnote library, and any duplicate results were identified and removed before screening the records. Non-relevant articles were excluded by screening titles and abstracts by three authors working independently. The remaining publications were assessed by screening the full texts for eligibility and were retrieved and double screened. Discrepancies were reviewed and resolved through consensus.

Inclusion criteria

Relevant studies were required to include the following: (1) Adults (defined as ≥18 years) (2) Carotid intima media thickness and/or carotid artery plaque measured using ultrasound (the decision to include stenosis greater than 50% was based on its clinical relevance and the need to capture a comprehensive range of cases, including those that may not yet meet the >70% threshold but still present significant clinical symptoms and risks.) and (3) Mini-mental state examination (MMSE) as a global cognitive function test.

Exclusion criteria

The exclusion criteria were as follows: (1) Adults following stroke (if results in stroke patients were reported separately these were excluded, or if the study only included participants with stroke the entire study was excluded); (2) Patients who had undergone carotid surgical or invasive intervention (e.g. a stent); (3) Studies performed in animals; (4) Studies that used medical imaging modalities other than ultrasound to assess the presence of plaque and to measure carotid atherosclerosis; (5) Review articles, conference abstracts, case reports, letters to the editor, or commentary articles.

Data extraction

To ensure the integrity and reliability of the data extraction process, we involved two external researchers. This decision was made for several reasons. Firstly, to ensure objectivity and reduce potential bias in data collection: The use of two external researchers helps to minimize the risk of subjective bias that might arise from a single researcher's perspective. This approach ensures that the data collection process remains impartial and objective. Moreover, verify the accuracy and reliability of the extracted data through independent verification: Independent verification by two researchers enhances the accuracy and reliability of the data. Each researcher can cross-check the data extracted by the other, identifying and rectifying any discrepancies, which leads to more precise and trustworthy results. Also enhance the credibility and robustness of the study findings by incorporating multiple perspectives: Including multiple researchers in the data extraction process introduces diverse viewpoints and expertise, which contributes to a more comprehensive and nuanced understanding of the data. This practice strengthens the overall credibility and robustness of the study

findings. Data extraction from the included studies was performed by three researchers (Rayan Anbar, Lamia Al Saikhan and Salahaden Sultan) independently using standardized forms; any discrepancies were resolved by consensus. The extracted data from the eligible studies consisted of study characteristics such as author, year of publication, sample size, characteristics of participants (age, and gender), study region, MMSE cognitive function test score, and CIMT measurements The detailed data extracted and analysed are presented in (Tables 2.1, 2.2, and 2.3, which can be found in the appendix). Means and standard deviations and sample sizes of study results for CIMT and MMSE were extracted from the included papers. If means and standard deviations were not provided, median and range or other measures of central tendency and dispersion were extracted. Maximum CIMT was extracted if the mean value was not reported in the studies. If necessary, odds ratios for CIMT were converted to be per 1mm CIMT to provide a comparable metric of effect size across studies. If the percentage of people with plaques was reported but the total number of participants was not reported, the total number was calculated from the percentage. For studies in which stroke sufferers were included in the sample size, the total number of subjects were re-calculated by removing subjects with stroke and data modified accordingly. If different numbers of subjects underwent CIMT and MMSE assessments, the lower number was recorded and used for analysis. If the total number of females was provided, this was extracted and the percentage of females in the overall sample size was calculated. For longitudinal studies the data was collected at baseline or nearest value to the baseline if baseline was not available. If there were data from the article that was deficient, the authors were contacted by email and asked to provide additional information. The Data extraction was performed by two researchers (Rayan Anbar, and Salahaden Sultan) independently using standardized forms (an example

is shown in appendix 2) and any discrepancies were resolved by consensus (Lamia Al Saikhan & Alun Hughes).

Statistical analysis and meta-analysis

To summarise data from various studies, a meta-analysis was planned using odds ratios (OR) with 95% confidence intervals (CI) as the estimates of the strength of association between carotid atherosclerosis and MMSE. This was chosen as OR was the most used measure of association in cross-sectional studies, which were in turn the commonest mode of study. MMSE was categorised into normal or impaired based on a cut-point of 24, which was the commonest threshold used in the papers identified. If other statistical measures of dispersion were reported (e.g. standard error of the mean, standard deviation), these were converted into 95% CI. To facilitate comparisons with results from cross-sectional studies which typically used OR to summarise findings, hazard ratios or risk ratios from longitudinal studies were converted to OR using the equation described by Grant (Grant, 2014). Meta-analysis was performed using Stata/SE Statistical Software version 16.1 (StataCorp., College Station, TX). Q-test and I^2 statistics were used to assessed heterogeneity between studies. We used the Egger's test and funnel plots to look for the possibility of publication bias.

Quality Assessment

The quality of included studies was scored using a modified seven-point criteria were derived from Newcastle-Ottawa scale.(Wells et al., 2000) Scores covered the 1) representativeness of the target sample, 2) non-response satisfactorily dealt with, 3) use of a validated measurement tool, 4) relevant confounders measured, 5) appropriate assessment of outcome, 6) appropriate statistical analysis clearly described and 7) reporting missing data if present. Each criterion was assigned one point if met. The quality assessment was performed by two researchers (Rayan Anbar, and Salahaden Sultan) independently using standardized forms (an example is shown in appendix 3) and any discrepancies were resolved by consensus.

RESULTS

The PRISMA flowchart showing the study selection process is shown in (Figure 2.1). We identified 378 potential studies from the electronic databases after exclusion of duplicates. Title and abstract screening resulted in 48 records that were reviewed for eligibility in full text. Of those studies, 17 were excluded with reasons. The reasons were: no CIMT measurement (n = 4), or no MMSE data (n = 9) or use of a modified version of MMSE (n = 3), review articles, conference abstract, letters to the editor or case reports (n = 1).

Characteristics of studies included in the systematic review

The total number of participants in the 31 included studies was 26,178, with an age range from 35 to 95 years. Twenty of the studies were cross-sectional ; eight were longitudinal .The remaining 3 studies included a mixture of cross-sectional and longitudinal data.The geographical distribution of the studies was diverse: with 5 from Italy, 5 from Japan, 5 from USA, 3 from France, 2 from Brazil, 2 from China, 3 from UK, and 1 from each of Egypt, Netherlands, Norway, Serbia. And The details pertaining to CIMT (the exposure variable) all the table are in the appindex.

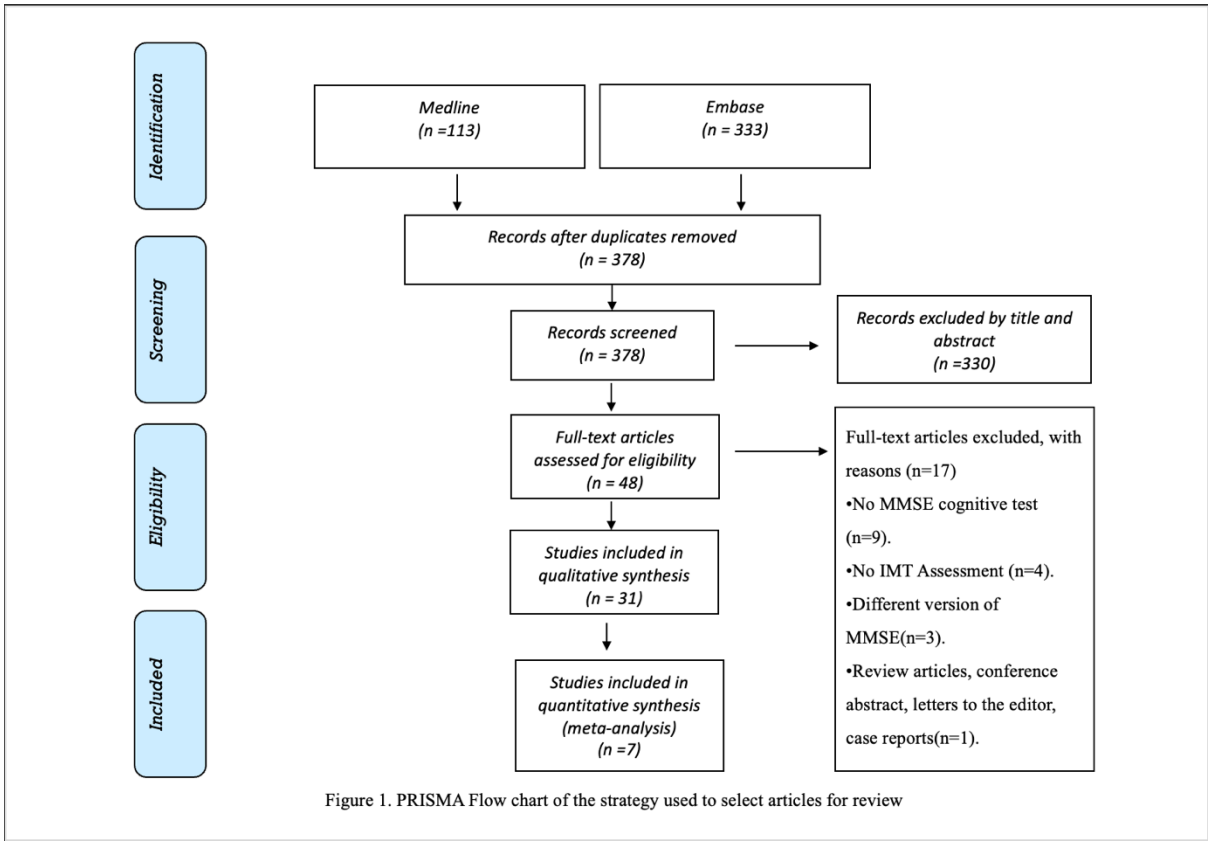

Figure 1. PRISMA Flow chart of the strategy used to select articles for review

Figure 2. 1 **PRISMA flow chart of the strategy used to select articles for review. IMT, intima-media thickness; MMSE, Mini-Mental State Examination; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.**

Sweden, and Uganda. One study failed to mention the geographical location. Only one study (Auperin et al., 1996b) failed to report the patients' health conditions and risk factors, such as diabetes mellitus, hypertension, and chronic kidney disease. Two studies included only male participants,(Muller et al., 2007, Watanabe et al., 2004) and one study included only female participants,(Komulainen et al., 2007b) the remaining studies included both male and female participants.These studies cover a wide age range, spanning from 35 to 95 years. Age is often considered one of the most potent risk factors for cardiovascular disease. The risk of developing CVD grows significantly as one gets older. This association is due to a multitude of physiological changes that occur with age, including arterial stiffness, endothelial dysfunction, and an increased risk of atherosclerosis. These age-related alterations contribute to the accelerated progression of cardiovascular illnesses such as hypertension, coronary artery disease, and stroke(Rodgers et al., 2019).details of the key exposure measures are shown in Table 2.4.

29 studies reported the mean of carotid intima media thickness measurement (Table 1).(Auperin et al., 1996b, Watanabe et al., 2004, Haley et al., 2007, Komulainen et al., 2007b, Muller et al., 2007, Singh-Manoux et al., 2008a, Carlsson et al., 2009, El-Kattan et al., 2009, Kearney-Schwartz et al., 2009b, Silvestrini et al., 2009, Zhong et al., 2011b, Dias et al., 2012, Stefanova et al., 2012, Viticchi et al., 2012, Zhong et al., 2012a, Rogne et al., 2013, Xiang et al., 2013, Buratti et al., 2014, Nagai et al., 2014, Yano et al., 2014, Carcaillon et al., 2015, Liu et al., 2016b, Wendell et al., 2016, Alhusaini et al., 2018, Falsetti et al., 2018, Matsumoto et al., 2018, Muela et al., 2018, Rouch et al., 2018, Mworozi et al., 2019b) 14 studies did not mention the presence of carotid plaques.(Matsumoto et al., 2018, Muela et al., 2018, Falsetti et al., 2018, Liu et al., 2016b, Wendell et al., 2016, Nagai et al., 2014, Yano et al., 2014, Rogne et al.,

2013, Dias et al., 2012, Carlsson et al., 2009, Singh-Manoux et al., 2008a, Haley et al., 2007, Komulainen et al., 2007b, Muller et al., 2007) Seven studies did not provide MMSE scores.(Zhong et al., 2012a, Rogne et al., 2013, Carcaillon et al., 2015, Kawasaki et al., 2016a, Wendell et al., 2016, Matsumoto et al., 2018, Mworozi et al., 2019b)

Associations between atherosclerosis measures and MMSE score

Cross-sectional associations with plaques and/or CIMT

Presence of carotid plaques was associated with poorer cognitive function in 3 studies. (Zhong et al., 2011b, Kawasaki et al., 2016a, Mworozi et al., 2019b) Auperin et al. (Auperin et al., 1996b) reported an association between higher prevalence of carotid plaque and lower MMSE in men, but not in women. One study (Singh-Manoux et al., 2008a) concluded that the association between CIMT and cognitive function was observed only in a low SES group. Another study (Stefanova et al., 2012) found a significant correlation between higher CIMT and plaques with poor MMSE score in people with evidence of vascular cognitive decline, but not in a group of people with Alzheimer's disease. Watanabe et al. (Watanabe et al., 2004) reported that vascular dementia patients were more likely to have low MMSE score with thicker CIMT and frequent presences of carotid plaques.

Ten cross-sectional studies (Haley et al., 2007, Carlsson et al., 2009, Wendell et al., 2009b, Dias et al., 2012, Viticchi et al., 2012, Xiang et al., 2013, Nagai et al., 2014, Liu et al., 2016b, Muela et al., 2018, El-Kattan et al., 2009) reported that CIMT was not associated with changes in MMSE, although some of these studies reported evidence of associations with a selected aspect of cognitive performance.

Longitudinal associations

Zhong et al. reported an association between higher CIMT and a reduction in MMSE score after 10 years of follow-up but not after 5-years; a similar association between presence of carotid plaque and change in MMSE was not observed at any follow-up interval.(Zhong et al., 2012a) Rouch et al. (Rouch et al., 2018) found that both CIMT and carotid plaques were associated with progression to dementia in univariable analyses, but neither predicted progression after multivariable adjustment. Another study found that the plaque index, and CIMT were predictive of an increased risk of conversion of mild cognitive impairment to dementia including after multivariable adjustment using a backwards stepwise method.(Buratti et al., 2015) While Carcaillon et al. (Carcaillon et al., 2015) reported that there was an association between presence of carotid plaque in two sites or more and incidence of dementia, they observed no association between CIMT measured at plaque-free sites with incident dementia. Silvestrini et al. (Silvestrini et al., 2009) found that baseline CIMT and increase in CIMT adjusted for baseline were associated with decline in MMSE. Wendell et al. (Wendell et al., 2016) found no association between baseline CIMT and change in MMSE but observed that higher CIMT was associated with future changes in selected aspects of cognitive performance. One study did not provide quantitative data about possible associations between carotid plaque or CIMT and MMSE,(Falsetti et al., 2018) while 4 other studies found no evidence that CIMT was associated with future global cognitive impairment.(Buratti et al., 2014, Rogne et al., 2013, Komulainen et al., 2007b, Matsumoto et al., 2018)

Quality

One study received quality scores of 6 out of 7;(Viticchi et al., 2012) five received a quality score of 5 out of 7;(Rouch et al., 2018, Kawasaki et al., 2016a, Carcaillon et al., 2015, Buratti et al., 2014, Watanabe et al., 2004) twenty a quality score of 4 out of 7; (Liu et al., 2016b, Wendell et al., 2016, Alhusaini et al., 2018, Falsetti et al., 2018, Buratti et al., 2015, Nagai et al., 2014, Xiang et al., 2013, Rogne et al., 2013, Zhong et al., 2012a, Stefanova et al., 2012, Dias et al., 2012, Zhong et al., 2011b, Silvestrini et al., 2009, Kearney-Schwartz et al., 2009b, El-Kattan et al., 2009, Carlsson et al., 2009, Singh-Manoux et al., 2008a, Muller et al., 2007, Komulainen et al., 2007b, Haley et al., 2007) four a quality score of 3 out of 7;(Mworozi et al., 2019b, Muela et al., 2018, Yano et al., 2014, Auperin et al., 1996b) and one a quality score of 2 out of 7. (Matsumoto et al., 2018) These data are illustrated in (Figure 2.5.) Among the 31 included studies, 24 studies were adequately designed to represent the target sample. 9 publications used validated ultrasound measurement tools, 6 reported blinding assessment of outcome and blinding of outcome measurements, 29 described the statistical analysis satisfactorily.

Publication Bias

Egger`s test showed evidence of bias in studies assessing between carotid plaque and MMSE (p=0.02), but not in CIMT with MMSE (p=0.2) (Figure 2.4 A&B).

Meta-analysis

Seven of the 31 studies reported data that were suitable for inclusion in a meta-analysis.(Auperin et al., 1996b, Muller et al., 2007, Dias et al., 2012, Zhong et al., 2012a, Xiang et al., 2013, Matsumoto et al., 2018, Mworozi et al., 2019b) All included studies were cross-sectional, and all but one drew from population samples. Of all studies, 3 reported associations between carotid plaque and impaired MMSE,(Auperin et al., 1996b, Xiang et al., 2013, Mworozi et al., 2019a) and 6 that reported the association between CIMT and impaired MMSE.(Auperin et al., 1996b, Muller et al., 2007, Dias et al., 2012, Xiang et al., 2013, Buratti et al., 2015, Matsumoto et al., 2018)There was only one suitable longitudinal study,(Zhong et al., 2012a) so a meta-analysis was not possible for this category of study.

Carotid plaque and MMSE meta-analysis

Meta-analysis showed an association between presence of carotid plaque and impaired MMSE. The overall OR for the association between carotid plaque and impaired MMSE was 2.06 (95% CI: 1.16, 2.96) for presence of plaque, and with Z-score = 4.49, $P < 0.01$ (Figure 2.2).

Association between CIMT and MMSE

Meta-analysis showed an association between CIMT and impaired MMSE. The overall OR for the association between CIMT and impaired MMSE was 1.13 (95% CI: 1.04, 1.22) per 1mm CIMT, with Z-score = 24.7, $P < 0.01$ (Figure 2.3).

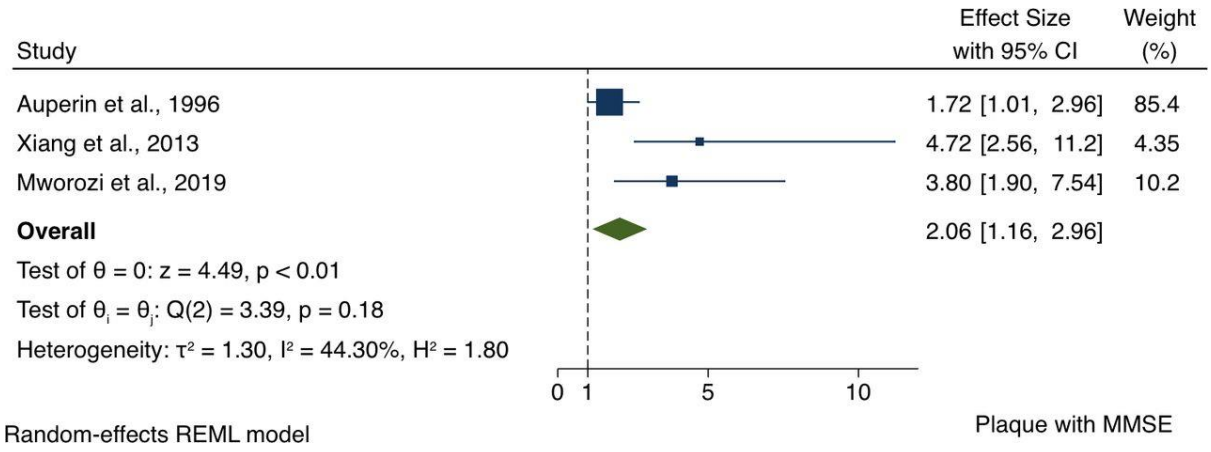

Figure 2. 2 Forest plots of the association between carotid plaques and Mini-Mental State Examination. IMT, intima-media thickness. REML, restricted maximum likelihood

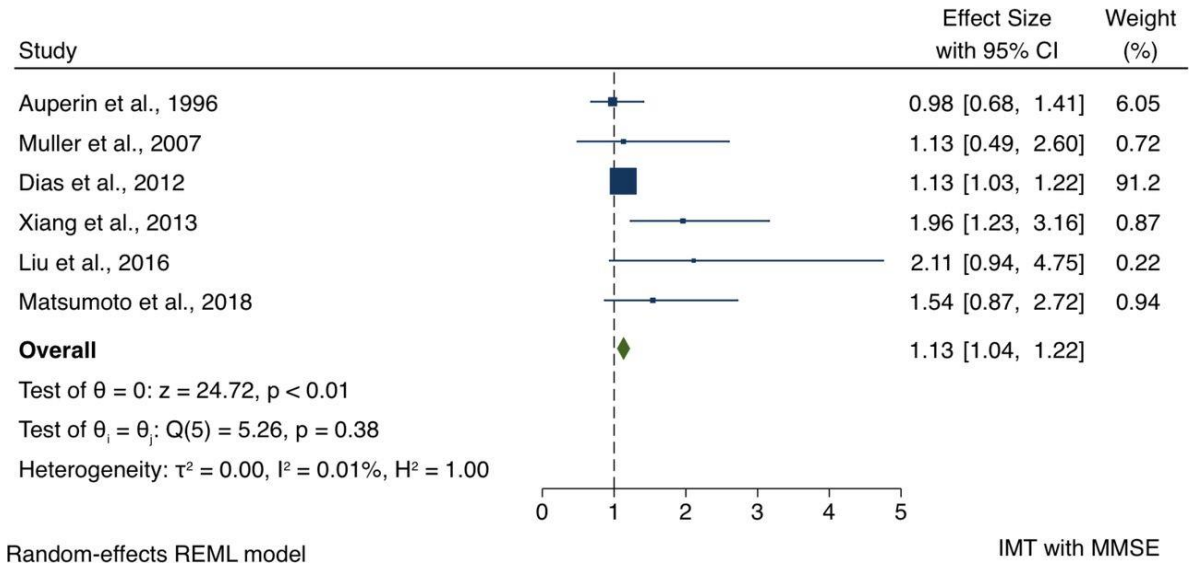

Figure 2. 3 **Forest plots of the association between carotid intima-media thickness (IMT) and Mini-Mental State Examination (MMSE). REML, restricted maximum likelihood.**

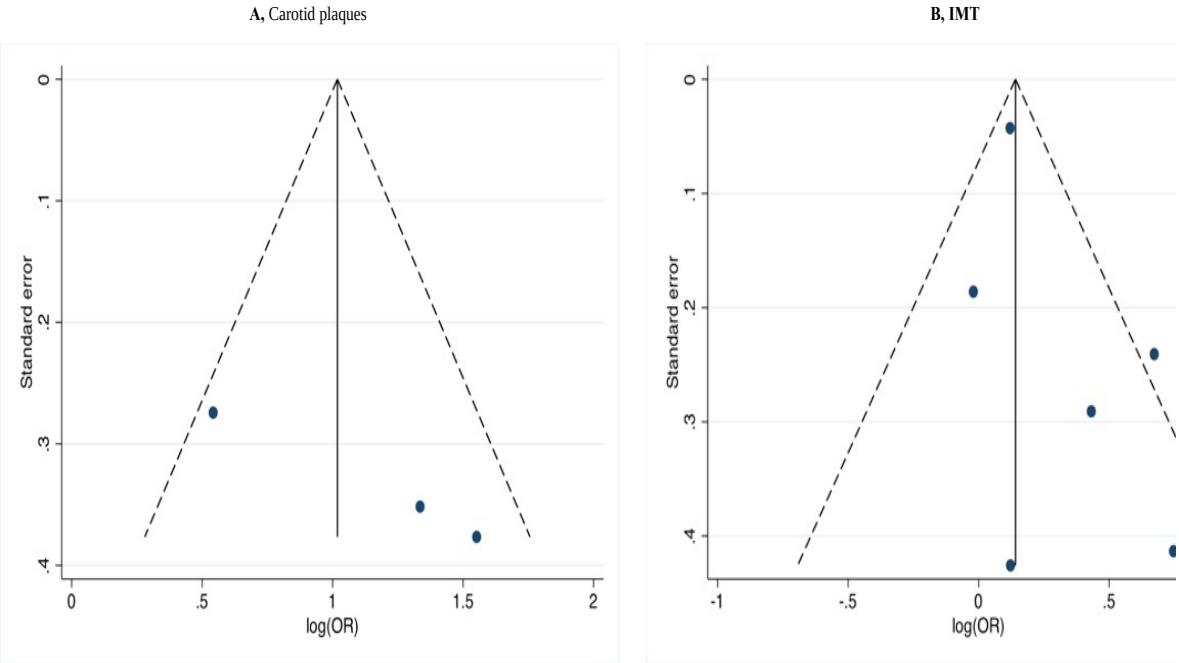

Figure 2. 4 Funnel plots for each outcome evaluating publication bias. (A) Studies assessed the association between carotid plaque and Mini-Mental

State Examination (MMSE) shows evidence of bias (p=0.02). (B) Studies assessed the association between carotid intima-media thickness and MMSE shows no evidence of bias (p=0.2).

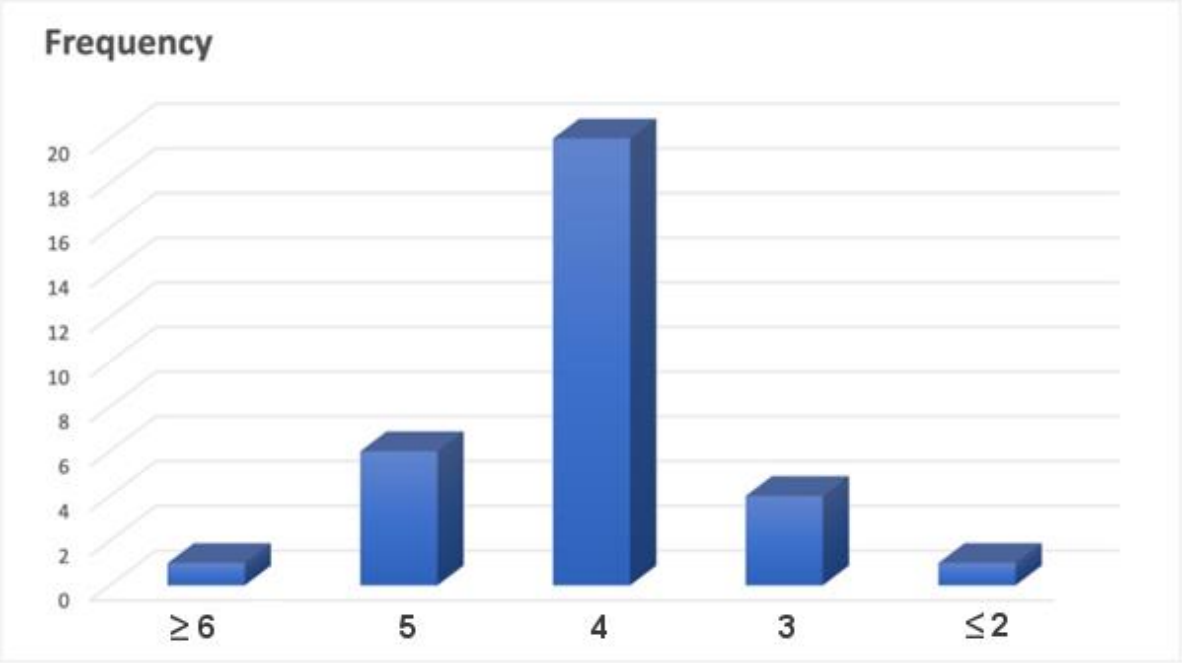

Figure 2. 5 Frequency distribution of quality scores. The distribution of quality scores among the studies was as follows: one study obtained a score of 6 out of 7, five studies received a score of 5 out of 7, twenty studies were assigned a score of 4 out of 7, four studies garnered a score of 3 out of 7, and one study had a score of 2 out of 7.

DISCUSSION

This systematic review examined and quantified the evidence regarding a possible association between measures of atherosclerosis in the carotid arteries by ultrasound and generalised impairment of cognitive function assessed using the MMSE. From the limited studies available, our analysis showed there is inconsistent evidence of a cross-sectional association between carotid artery atherosclerosis and poorer MMSE, with the 15 out of 31 studies finding some evidence of an association. These discrepancies could be due to inadequate sample size leading to a false negative conclusion (type II error), bias due to sample selection, or limitations of the MMSE for the detection of mild cognitive impairment.(Tsoi et al., 2015, Mitchell, 2009, Patnode et al., 2020)

Risk factors for CVD have been frequently reported to be related to poorer cognitive function,(Breteler, Grodstein, 2007, Skoog, 1998, Lai et al., 2020) and many factors could link carotid atherosclerosis with cognition. As discussed in chapter 1, these include thromboembolic consequences of carotid disease, cerebral perfusion abnormalities, or shared risk factors such as small vessel disease, blood pressure, dyslipidaemia, diabetes, genetic predisposition, or other shared risk factors over the life course. A recent study that observed a relationship between CIMT and MMSE, memory and executive function, also found an association between CIMT and a decrease in brain matter volumes and cerebral hypoperfusion.(Zheng et al., 2020)

There is little information regarding factors, such as age, gender, socioeconomic state, and pre-existing CVD, which might modify any relationship between carotid atherosclerosis and cognitive impairment. Effect modification by some factors, e.g. sex, is not implausible, but frequently, studies have been underpowered to look for

differences between subgroups (i.e. a statistical interaction).(Altman and Bland, 2003) Studies rarely state whether such interactions were specified in advance of analysis, so the possibility of chance findings achieving statistical significance through multiple testing cannot be excluded.(Simmons et al., 2011) For example, one study reported that there was a moderate association between presence of plaques and impaired MMSE in men, but no association in women.(Auperin et al., 1996b) In contrast, many studies failed to report evidence of sex differences in the association between carotid atherosclerosis and cognitive impairment,(Van den Berg et al., 2017, Aartsen et al., 2004, Novella and Olivera, 2019) although it was usually not clear whether such an interaction was sought. Limited evidence suggests that SES, which includes income, education, and social supports may modify the association between atherosclerosis and cognitive performance. In the Whitehall study of UK-based civil servants,(Singh-Manoux et al., 2008a) an association between higher CIMT and poorer cognitive function was only observed in individuals classified as low SES. Another study done in USA, (Wendell et al., 2016) reported that the association between CIMT and measures of cognition differed as a function of race and socioeconomic status.

Limitations

This systematic review has several limitations. Restricting the search to only literature published in the English language only may have reduced the number of citations identified. The primary aim of some the studies reviewed was not to assess the association between atherosclerosis in carotid arteries and cognitive function. It is also worth noting that there was significant heterogeneity with regards to atherosclerosis measurements and scanning techniques and, most of studies reviewed did not perform a comprehensive carotid ultrasound scan. The use of B-mode ultrasound to

detect carotid atherosclerosis has well-recognised limitations,(Touboul et al., 2012c, Stein et al., 2008c) as discussed in Chapter 1, and more advanced ultrasound imaging including 3D ultrasound,(Cires-Drouet et al., 2017) or other imaging techniques, such as MRI,(Gupta et al., 2013) or PET(Piri et al., 2020) that better quantify and characterise vulnerable atherosclerosis may have advantages in future, but there is little existing data using these approaches. Similarly, use of the MMSE which has several limitations, as discussed above, provides only a limited insight into the complex process of cognitive decline and use of a wider range of tools would be worthwhile in future analyses.

3 Carotid atherosclerosis in people of European, South Asian and African Caribbean ethnicity in the Southall and Brent Revisited study (SABRE) retrospective study

Abstract

Background Atherosclerotic cardiovascular disease (ASCVD) risk differs by ethnicity. In comparison with Europeans (EA) South Asian (SA) people in UK experience higher risk of coronary heart disease and stroke, while African Caribbean people have a lower risk of coronary heart disease but a higher risk of stroke.

Aim To compare carotid atherosclerosis in EA, SA and AC participants in the Southall and Brent Revisited (SABRE) study and establish if any differences were explained by ASCVD risk factors.

Methods Cardiovascular risk factors were measured, and carotid ultrasound was performed in 985 individuals (438 EA, 325 SA, 228 AC). Carotid plaques, and intima-media thickness (CIMT) were measured. Associations of carotid atherosclerosis with ethnicity were investigated using generalized linear models, with and without adjustment for non-modifiable (age, sex) and modifiable risk factors (education, diabetes, hypertension, total cholesterol, HDL-C, alcohol consumption, current smoking).

Results: Prevalence of any plaque was similar in EA and SA, but lower in AC (17%, 17%, and 6% respectively; $p < 0.001$). In those with plaque, total plaque area, numbers of plaques, plaque class, or greyscale median did not differ by ethnicity; adjustment for risk factors had minimal effects. CIMT was higher in AC than the other ethnic groups after adjustment for age and sex, adjustment for risk factors attenuated this difference.

Conclusions: Prevalence of carotid artery atherosclerotic plaques varies by ethnicity, independent of risk factors. Lower plaque prevalence in in AC is consistent with their lower risk of CHD but not their higher risk of stroke. Higher CIMT in AC may be explained by risk factors. The similarity of plaque burden in SA and EA despite

established differences in ASCVD risk casts some doubt on the utility of carotid ultrasound as a means of assessing risk across these ethnic groups.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality and morbidity worldwide.(Naghavi et al., 2017) There are marked differences in ASCVD risk in different ethnic groups, even within the same country. For example the risk of coronary heart disease (CHD) is ~1.7-fold higher in migrants from the Indian subcontinent than in people of European origin in UK.(Tillin et al., 2013b) In contrast, people of African-Caribbean ethnicity in the UK have markedly elevated risk of stroke, but their risk of CHD is lower in comparison with Europeans or migrants from the Indian subcontinent.(Tillin et al., 2013b) In all ethnic groups, established risk factors (e.g. blood pressure (BP), total cholesterol, high-density lipoprotein cholesterol (HDL-C), diabetes, education, alcohol consumption, and tobacco smoking) predict risk of ASCVD,(Eriksen et al., 2015, Yusuf et al., 2020) although some the prevalence of some risk factors, such as dysglycaemia, smoking and adiposity patterns differ by ethnicity.(Tillin et al., 2013a, Eastwood et al., 2015) Previous work suggests differences in these factors only partially explain ethnic differences in ASCVD risks.(Tillin et al., 2013b)

Detailed phenotyping of subclinical atherosclerosis may provide more insights into ethnic differences in ASCVD risk. Ultrasonography is a reliable and non-invasive technique that is widely used to assess atherosclerosis in the carotid artery.(Murray et al., 2018) In addition to measurement of common carotid artery intima-media thickness (CIMT) and quantification of atherosclerotic plaques,(Touboul et al., 2007, Touboul et

al., 2012c) this method can also provide some information on plaque composition and vulnerability.(Gray-Weale et al., 1988, Biasi et al., 1999, Jashari et al., 2016)

Based on the existing evidence in relation to ethnic difference in ASCVD risk, we therefore hypothesized that, in comparison with Europeans, South Asian people would have a greater burden of carotid atherosclerosis and that African Caribbean people would have similar or lower levels. Based on some previous work using coronary CT angiography showing differences in plaque composition between European and South Asian people in UK,(Villadsen et al., 2017) we also aimed to investigate whether plaque characteristics differed by ethnicity, and explored the potential role of established ASCVD risk factors in any differences observed between ethnic groups. Individuals studied were participants in the third follow-up visit of the South and Brent Revisited (SABRE) study, a multi-ethnic longitudinal cohort that has been followed up for over 30 years.

Methods

Participants and study design

The Southall and Brent Revisited (SABRE) study is a population-based longitudinal cohort study that began recruiting in 1988 with the aim of investigating the prevalence, incidence, and risk factors for cardiovascular disease (CVD) and diabetes in people of European, South Asian, and African Caribbean ethnicities living in the UK. The study included 4,276 participants aged 40-69 years with 2,235 of European ethnicity, 1,454 of South Asian ethnicity, and 587 of African Caribbean ethnicity. Participants were recruited from primary care practices in the London boroughs of Southall and Brent.

The SABRE study has undergone multiple waves of follow-up, with the most recent visit (visit 3) taking place between 2014 and 2018. This visit included 991 individuals (437 European, 326 South Asian, 228 African Caribbean) who had survived since baseline and remained in the study and Data were collected by other members of the research team of SABRE study. Ethical approval for the study was obtained from Ealing, Hounslow and Spelthorne, Parkside, and University College London Research Ethics Committees, and all participants provided written informed consent. Detailed information about the SABRE study has been published previously.(Tillin et al., 2012a, Jones et al., 2020a). My role in this study was to contribute to the project by undertaking the critical task of data refinement, which involved cleaning and organizing the information gathered by the SABRE investigators. Specifically, I focused on selecting participants with plaques and conducted precise measurements for both plaques and intima-media thickness (IMT) using dedicated software. Subsequently, I carried out comprehensive statistical analyses to derive meaningful insights from the data. Additionally, I wrote the first draft of the manuscript, taking responsibility for the subsequent writing and editing process. This involved synthesizing the research findings, methodologies, and results into a cohesive and well-articulated paper. Through my efforts, I aimed to enhance the overall clarity, coherence, and quality of the document, ensuring that it effectively communicates the significance of our research

Measurement of Carotid Atherosclerosis

This section outlines the methodology used for measuring carotid atherosclerosis in participants. This was performed by two trained sonographers following a standard operating procedure as described previously.(Al Saikhan et al., 2020a)

The participant was positioned supine on the examination couch, with their head and shoulders supported by a pillow. Visualisation of the carotid artery was performed using a Vivid I ultrasound machine equipped with a linear array transducer (12L-RS) with a field of view of 39mm. A three lead ECG was recorded as part of the ultrasound scan to provide an indication of cardiac cycle timings. To optimise visualisation of the carotid artery, the participant's head was rotated ~45° away from the transducer, and the pillow was removed if necessary to allow for slight hyperextension of the neck. The ultrasound gain setting was modified to minimize noise in the lumen and facilitate arterial wall boundary detection. An initial view of the carotid bifurcation was obtained aiming to achieve a tuning fork appearance (Stein et al., 2008b) and, as much as possible, and then the entirety of the carotid artery and its branches were scanned to look for plaque. For measurement of CIMT, the sonographer aimed to ensure that clear intima-media boundaries, especially of the far wall, were visible over a length of ~10mm of the CCA, immediately proximal to the carotid bulb, and that the bifurcation/bulb was also visible on the left-hand side of the screen. A cine-loop of 5 cardiac cycles was recorded at 3 angles (approximately 90˚, 120˚, 150˚ for the right carotid artery and 210˚, 240˚, and 270˚ left carotid artery (LCA)). In addition to the cine loop one single frame image synchronised with the peak of the R-wave (i.e. end-diastole) was also saved for each angle.

If plaque was identified, further images and cine-loops were acquired, including longitudinal and transverse images of the plaque, with additional images using Power Doppler and Colour Doppler to assist in delineating the plaque boundary and the degree of stenosis. The location of the plaque (Right/Left; ICA/ECA/Bulb/CCA) was noted on the electronic care report form saved in a custom written OpenClinica Electronic Data

Capture Platform (written by Daniel Key). Data files in DICOM (cine loops) or jpg format (single frame) were exported to a secure server after each session.

CIMT and carotid lumen diameter were measured from the best visualised image from each of the three angles, over a 10mm segment in the common carotid artery according to the American Society of Echocardiography Carotid Intima-Media Thickness Task Force Consensus Statement(Stein et al., 2008c). Plaque was defined according to the Mannheim consensus,(Touboul et al., 2007, Touboul et al., 2012c) as a focal lesion that encroached into the carotid artery lumen by ≥0.5 mm or ≥50% of the surrounding CIMT value or had a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen boundary. Carotid stenosis >50% was assessed by visual inspection of the B-mode ultrasound scan, using Colour and Power Doppler imaging as needed, and quantified according to NASCET criteria(1991). All quantitative analyses were performed offline using validated software (figure 3.1&3.2) (AMS II),(Wendelhag et al., 1997) that included automated measurement of plaque area, categorization of plaque based on the Gray-Weale score,(Gray-Weale et al., 1988) plaque size and estimation of grey-scale median (GSM).(Bjornsdottir et al., 2018, Ostling et al., 2007) Repeatability and reproducibility of CIMT and plaque characteristics have been reported previously and were good to excellent(Al Saikhan et al., 2020b).

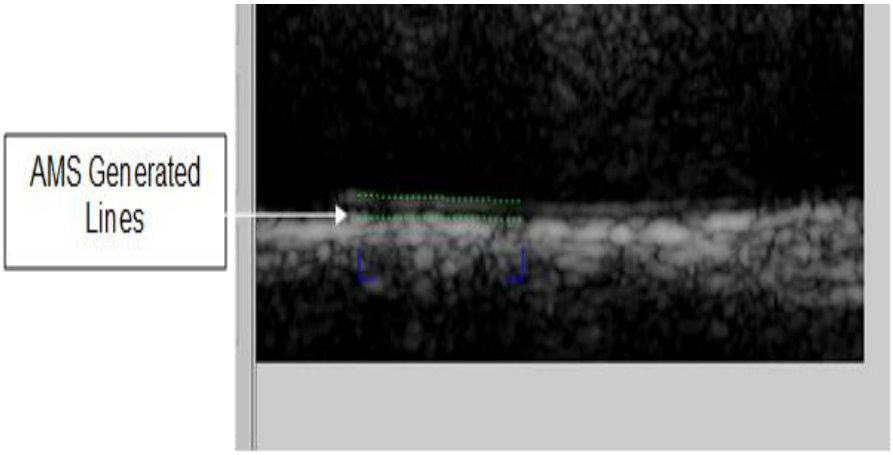

Figure 3. 1 Measurement of carotid intima media thickness in SABRE: The image shows the far wall of the common carotid artery just proximal to the bulb. The distance between the leading edge of the first bright line (the blood–intima interface) of the far wall (identified as the upper green dotted line) and the leading edge of the second bright line (media–adventitia interface – the lower green dotted line) is considered the CIMT. The blue lines define the measurement box which was routinely set to 10mm but could be modified if necessary. The lines were identified automatically by the AMS II software.

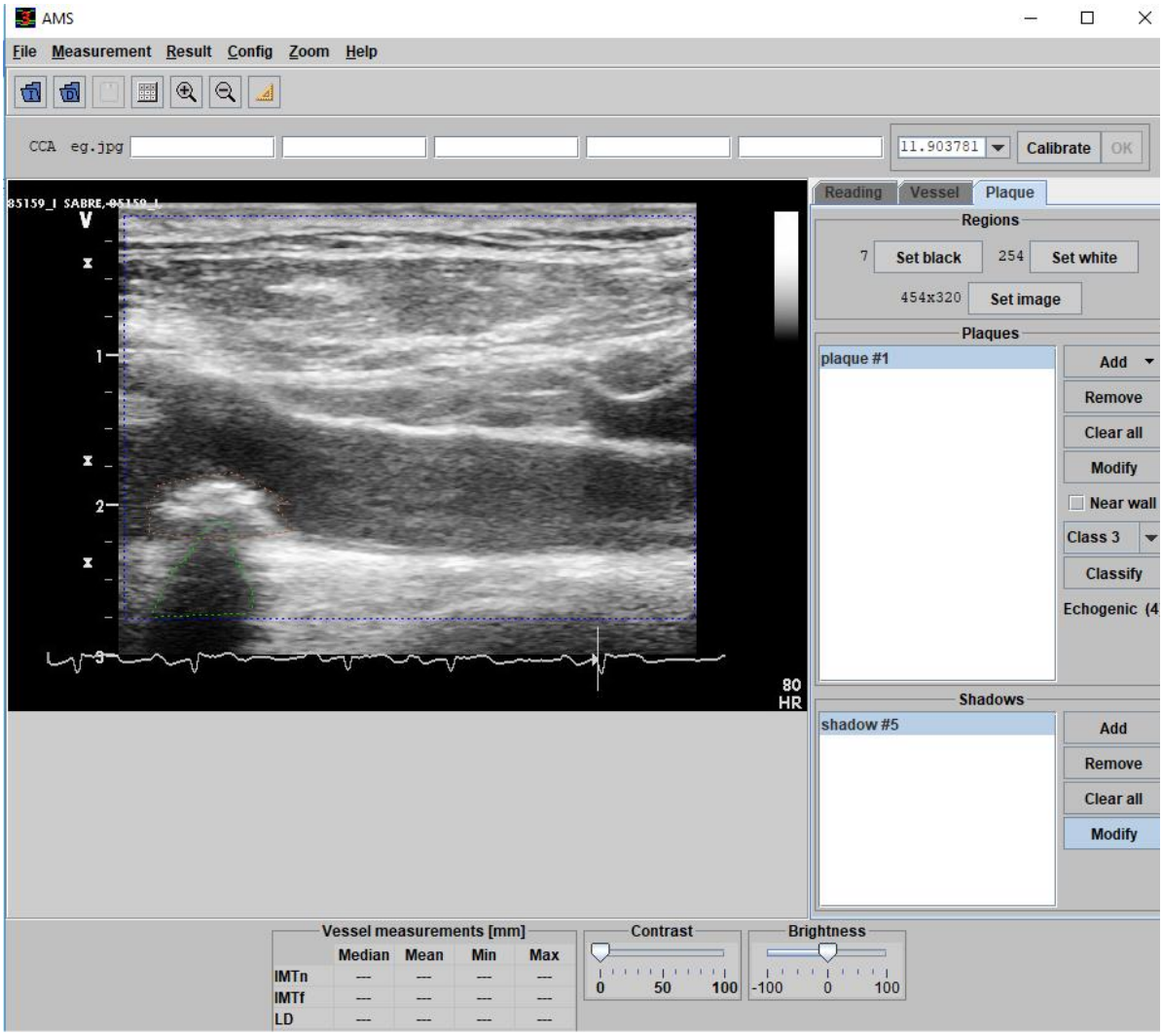

Figure 3. 2 The AMS program's user interface as used for plaque analysis. In the example, plaque is delineated by the (faint) orange dots with the acoustic shadow delineated by green dashes. The field of view for analysis is outlined by blue dashes.

Clinical investigations

Participants were invited to a clinic appointment and were asked to refrain from alcohol, smoking, and caffeine for ≥12 h before attendance, and not to take their medication on the morning of the clinic visit. Information was recorded on age, sex, health behaviours, medical history, and medication.(Jones et al., 2020b) Height and weight were measured using a standardized protocol and body composition was measured using a Tanita BC 418 body composition analyser. Seated brachial BP was measured using an appropriately sized cuff using an automatic Omron 705IT after 5-10 minutes rest according to European Society of Hypertension guidelines.(O'Brien et al., 2005) The average of the second and third recordings was used as the estimate of clinic BP as indication of hypertension. Diabetes mellitus was defined according to the 1999 WHO guidelines(World Health Organization, 1999) or physician diagnosis, or receipt of anti-diabetes medications. Hypertension was defined as physician-diagnosed hypertension, or participant-reported hypertension, or receipt of BP-lowering medication. Smoking was classified into current or not. Alcohol consumption was categorised according to UK guidelines into none, ≤ 14 units per week or > 14 units per week. Blood and urine samples were taken, and whole blood, serum, EDTA plasma and urine stored at −80°C prior to analysis. Glycosylated haemoglobin (HbA1c) was measured on an automated platform (c311, Roche Diagnostics, Burgess Hill UK), serum total cholesterol, HDL-C and triglycerides were measured using enzymatic methods (Roche/Hitachi Cobas c system). Low density lipoprotein cholesterol (LDL-C), All assays used the manufacturers calibration and quality control material.

Statistical analysis

Statistical analyses were performed with Stata v.17.1 (StataCorp, College Station, TX, USA). Continuous data for the sample were summarised as means and standard deviations (SD) or median (interquartile range) for skewed data, categorical data as counts and percentages. Normality was assessed through frequency histograms, QQ plots and Shapiro-Wilk tests. Comparisons between ethnic groups were made using generalized linear modelling (glm). Four models were used: Model 1) unadjusted; Model 2) age and sex; Model 3) Model 2 plus adjusted for established potential mediators (education, diabetes, hypertension, total cholesterol, HDL-C, alcohol consumption, current smoking); Model 4) Model 3 minus total cholesterol and HDL-C plus novel potential mediators (LDL cholesterol, medium HDL, apoB/apoAI ratio, albumin docosahexaenoic acid, histidine, tyrosine, glutamine, urinary albumin creatinine ratio, NT-pro BNP, CRP, TnT). Choice of covariates was based on *a priori* knowledge.(Collins and Altman, 2010, Yusuf et al., 2020) Additional sensitivity analyses were performed where diabetes was replaced by HbA1c, or where systolic blood pressure or BMI (or waist hip ratio) were added to models as potential mediators The possibility of effect modification by sex was looked for in all models by including a sex x ethnicity interaction term, if this was not statistically significant both sexes were pooled for analysis, otherwise it was planned that results for both sexes would be analysed separately.

Dichotomous variables (e.g. presence of plaque or presence of carotid stenosis >50%) were modelled using glm with a binomial family and log link function. Ordered categorical variables with fewer than six categories (median plaque grade (manual and automatic)) were analysed using ordered logistic regression and the proportional-odds

assumption was tested using an approximate likelihood ratio test. If the proportional-odds assumption was not met data were fit with partial proportional odds models using generalized ordinal logistic regression (Stata SJ and community-contributed program gologit2).(Williams, 2006) Numbers of plaques were modelled using negative binomial models as the data were expected to be over-dispersed (i.e., the variance was anticipated to be greater than would be assumed by a Poisson model; this was confirmed using the likelihood ratio test for the overdispersion parameter, alpha = 0). Risk ratios, or marginal probabilities and 95% confidence intervals (CI) were estimated from these models as for common outcomes these measures do not exaggerate relationships when the outcome is frequent and they do not suffer from non-collapsibility unlike odds ratios.(Cummings, 2009) Multiple regression models were used for continuous measures (total area of plaques, lowest GSM of all plaques, CIMT) and marginal means and CI estimated. If regression models showed evidence of heteroskedasticity, robust standard errors were calculated using the Huber-White Sandwich estimator, which assumes that outcomes are IID (independently and identically distributed) but should provide better estimates of variance when the scatter of residuals is not constant (heteroscedastic). Assumptions of linearity were checked by examination of residuals and it was planned that nonlinear models would be constructed using fractional polynomials,(Royston and Altman, 1994) but this proved unnecessary. The primary analysis used listwise deletion (the default for most regression software), which is valid under the assumption that any missingness was independent of outcomes. As a sensitivity analysis, models were fitted using full information maximum likelihood (Stata option mlmv with the sem command) which is valid under the missing at random (MAR) assumption (i.e. probability that a value is missing depends on values of variables that were measured in the study) were also examined for linear models. Inference

was based on a combination of p-values, effect sizes and CI, no adjustment was made for multiple comparisons.

Results

Table 1 shows the characteristics of the sample stratified by ethnicity. Participants were aged between 40 and 69 years and comprised 437 EA (mean age 74 years, 62% male), 326 SA (mean age 73.2 ± 6.3 years, 59.3% male) and 228 AC (mean age 71 years, 35.6% male). On average SA were slightly younger than EA and AC were younger than both EA and SA, and there were more women in the AC sample. AC and SA people were shorter than EA and had higher systolic BP and more diabetes and hypertension. Compared with EA, SA had a higher prevalence of known CHD, more years of education, lower heart rate, lower BMI, and were less likely to be current smokers, and less likely to consume high quantities of alcohol, while AC had a lower prevalence of CHD, higher BMI, higher diastolic BP, more diabetes and hypertension and were less likely to consume high quantities of alcohol.

CIMT was similar by ethnicity in an unadjusted model, but plaques were more frequent in EA and SA than AC (**Table 3.1**); however, there was no difference between EA and SA (**Table 3.1**). Plaques were more common in men than women but there was no evidence that sex modified the ethnic differences in plaque prevalence (**Figure 3.3**). There were no marked differences in distribution of plaques by ethnicity: 57.5% of Europeans had plaques in the left carotid artery, 47.6% in the right carotid artery and 44.1% had plaques bilaterally. 42.5% of South Asians had plaques in the left carotid artery, 44.1% in the right carotid artery and 32.7 % had plaques bilaterally. 10% of African Caribbean's had plaques in left of carotid artery, 8.1% in the right carotid artery and 23.0 % had plaques bilaterally (**Figure 3.4**). In comparison with EA, the risk ratios

for having any plaque in SA after adjustment for non-modifiable, or non-modifiable plus modifiable risk factors were 1.08 (0.79, 1.46); p = 0.65 and 0.98 (0.66, 1.41); p = 0.89 respectively. For AC the comparable risk ratios were 0.48 (0.28, 0.82); p = 0.013 and 0.53 (0.268, 1.047); p = 0.068. The marginal probabilities of having one or more plaques in each ethnic group are shown in (**Table 3.2)** with and without adjustment. The probability of having one or more plaques was similar in EA and SA but was lower by ~50% in AC. Statistical adjustment had little effect on these estimates, although the estimated CI of the fully adjusted model were wider, probably as a result of the reduced sample size of the complete case analysis when non-modifiable plus modifiable risk factors were included (n = 727). Compared with EA, the risk ratio in SA for having a stenosis >50% was 1.56 (0.88, 2.76); p = 0.12 and 1.70 (0.81, 3.52); p = 0.15. For AC the risk ratios were 0.61 (0.23, 1.61); p = 0.32 and 0.65 (0.25, 1.70); p = 0.38. The limited number of stenoses in the sample (n = 50) made these estimates very imprecise and scope for inference was limited.

Table 3. 1 Characteristics of sample by ethnicity

Variables	Ethnicity									ANOVA or Chi^2 p-values
	EA			SA			AC			
	N	Mean/%	(SD)	N	Mean/%	(SD)	N	Mean/%	(SD)	
Age, y	437	74.4	(6.10)	326	73.20*	(6.3)	228	70.5*	(7.91)	<0.001
Male sex	274	49.3%		194	59.3%		85	37.0 %*		<0.001
Systolic blood pressure, mmHg	437	138.67	(18.3)	325	143.63*	(18.62)	228	142.26*	(16.68)	<0.001
Diastolic blood pressure, mmHg	437	78.84	(10.8)	325	78.48	(10.6)	228	81.73*†	(10.25)	<0.001
Heart rate, bpm	437	68.18	(11.33)	325	65.76*	(10.24)	228	68.12†	(11.35)	0.001
Height, cm	437	167.99	(8.7)	326	162.28*	(8.86)	228	164.12*†	(7.79)	<0.001
BMI, kg/m^2	437	28.01	(4.53)	326	26.42*	(3.91)	228	29.94*†	(5.30)	<0.001
HbA1c, mmol/mol	423	38.61	(8.0)	314	43.27*	(9.37)	220	39.98†	(11.04)	<0.001
Years of education	377	11.9	(3.53)	223	13.5*	(3.77)	153	12.01†	(3.69)	<0.001
Diabetes mellitus	53	13%		88	28%*		54	27%*		<0.001

CHD	53	13%		59	19%*		13	6%*†		<0.001
Stroke	8	2%		3	1%		4	2%		0.558
Hyperten-sion	209	49%		210	66 %*		152	69%*		<0.001
Alcohol con-sumption										<0.001
None	107	24%		170	52%		99	43%		
≤ 14 units per week	262	60%		150	46%		129	56%		
> 14 units per week	71	16%		7	3%		2	1%		
Current smoker	16	4%		3	1%*		8	3%†		0.051
Statin use	210	48%		209	64%*		85	37%*†		<0.001
Presence of carotid plaque (s)	74	17%		55	17%		14	6%*†		<0.001
Carotid ste-nosis >50%	22	5%		23	7%		5	2.2%†		0.025

CIMT, mm	407	0. 89	(0.20)	311	0.89	(0.23)	212	0.91	(0.20)	0.73
Total plaque area per individual with plaque, mm^2	74	34.4	(29.2)	55	33.6	(27.5)	14	29.4	(27.6)	0.84
Number of plaques per individual with plaque	74	1.5	(1.1)	55	1.5	(0.8)	14	1.1	(0.86)	0.35
Minimum GSM of all plaques	63	86.9	(35.5)	52	80.1	(28.8)	10	79.8	(12.7)	0.48
Class (manual) of largest plaque	55	2.84	(0.46)	46	2.87	(0.40)	7	2.86	(0.38)	0.93
Class (auto) of largest plaque	63	2.32	(0.53)	52	2.19	(0.40)	10	2.3	(0.48)	0.37

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CIMT, carotid artery intima-media thickness; GSM, greyscale median; HbA1c, glycated haemoglobin; SD standard deviation. p-values were calculated using Chi^2 tests and logistic regression for categorical variable and ANOVA for continuous variables, Wald tests were used for individual comparisons. * $p < 0.05$ compared with Europeans, † $p < 0.05$ compared with South Asians.

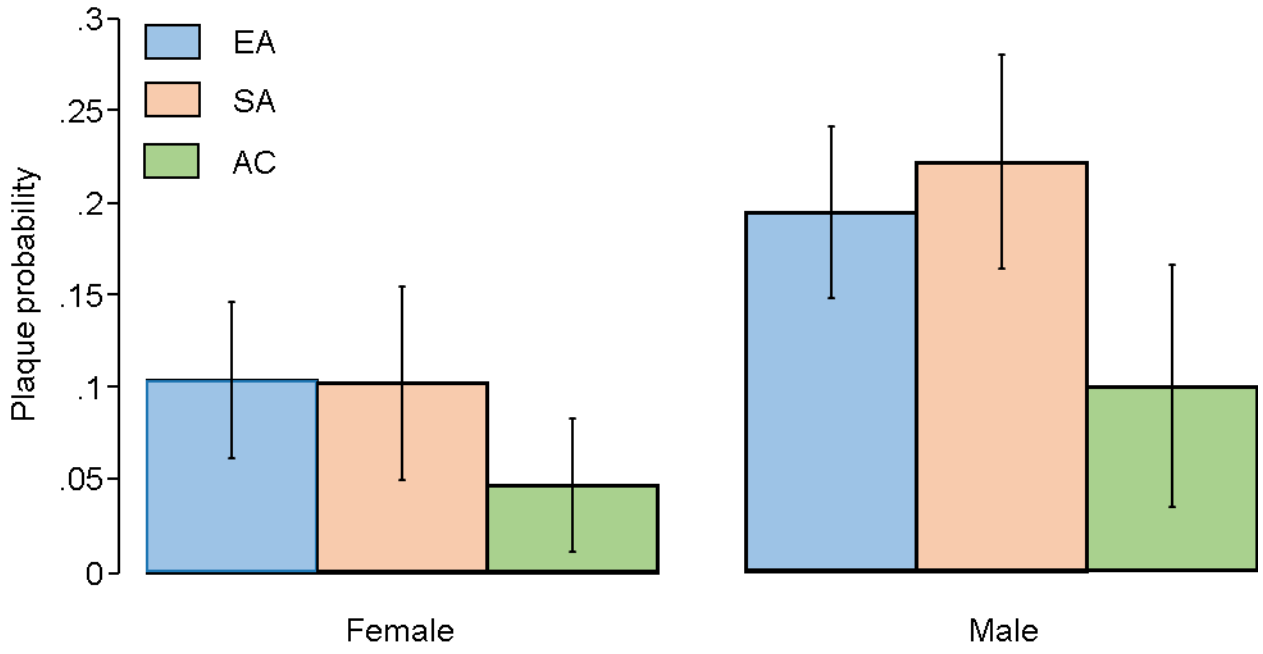

Figure 3. 3 Bar plot showing marginal probabilities with 95% confidence intervals (adjusted for age) of having a plaque by sex and ethnicity. Abbreviations: EA, European; SA, South Asian and AC, African Caribbean.

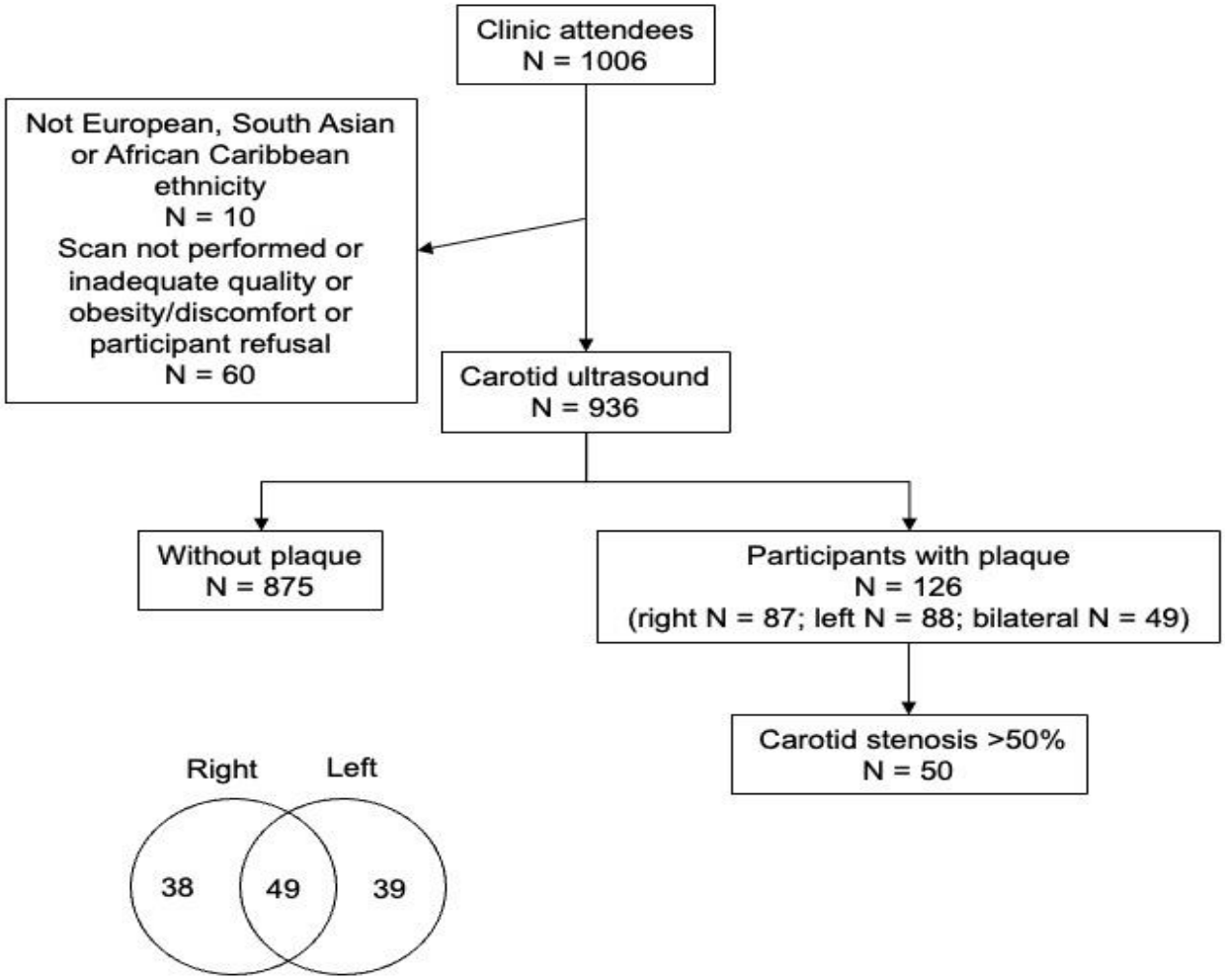

Figure 3. 4 Diagram of participant flow including location of plaques as a Venn diagram.

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Table 3. 2 Marginal probabilities of having any plaques by ethnicity with and without adjustment for risk factors.

Prevalence of plaque by ethnicity			p-value (individual comparisons)			p-value LR test
EA	SA	AC	EA v SA	EA vs AC	SA vs AC	
Unadjusted						
0.16 (0.13, 0.20)	0.16 (0.12, 0.20)	0.06 (0.03, 0.09)	0.992	<0.001	<0.001	<0.001
Model 1						
0.15 (0.12, 0.18)	0.16 (0.12, 0.20)	0.07 (0.03, 0.11)	0.626	0.008	0.004	0.006
Model 2						
0.16 (0.12, 0.19)	0.19 (0.14, 0.24)	0.08 (0.03, 0.13)	0.241	0.068	0.014	0.036

Data are marginal probabilities (95% confidence intervals). Model 1: age, sex adjusted, Model 2: Model 1 + years of education, diabetes, total cholesterol, HDL, alcohol consumption, current smoking, hypertension, statin use. LR: Likelihood-ratio.

After adjustment for age and sex, CIMT was higher in AC than EA or SA but there was no difference in CIMT between EA and SA (**Table 3.3**). Further adjustment for risk factors attenuated differences by ethnicity (**Table 3.4-3.6**).

A comparison of plaque area, maximum plaque height, average number of plaques, minimum greyscale median, and the manual and automatic plaque class is shown in (**Tables 3.3-3.6)**. Total plaque area was similar in EA and SA but considerably lower in AC, adjustment for age and sex, slightly attenuated the difference between EA or SA and AC, but a substantial difference remained, and this was essentially unaltered by further adjustment for potential mediators. Echogenicity as assessed by GSM was similar in EA and SA and lower in AC. Maximum plaque height in those with plaque showed no difference among three different ethnic group; however, the maximum plaque length in AC was longer compared to EA & SA groups, despite AC having the lowest frequency of plaques. There were no differences between ethnic groups for plaque grade either using an automated or manual method. The proportions of carotid stenosis >50% were slightly higher in SA (7%) compared to EA (5%) and AC (2%), although due to the low prevalence of carotid stenosis any differences could have arisen by chance.

Table 3. 3. Ethnic differences in CIMT and plaque characteristics with adjustment for age and sex (Model 1)

Variables	Ethnicity			p-value (individual comparisons)			p-value LR test
	EA	SA	AC	EA v SA	EA vs AC	SA vs AC	
CIMT, mm	0.88 (0.86, 0.90)	0.89 (0.87, 0.92)	0.93 (0.90,0.96)	0.285	0.002	0.033	0.003
Total plaque area per individual with plaque, mm^2	40.6 (33.4, 46.6)	35.2 (27.9, 42.5)	44.5 (27.5, 61.4)	0.343	0.624	0.323	0.473
Number of plaques per individual with plaque	1.76 (1.56, 1.96)	1.64 (1.41, 1.86)	1.62 (1.10, 2.13)	0.416	0.604	0.945	0.667
Minimum GSM of all plaques	87.44 (79.60,95.29)	79.57 (70.89,88.25)	78.58 (58.64,98.52)	0.187	0.414	0.929	0.350
Grey Weale class of largest plaque				0.507	0.820	0.580	0.741
Class 1	0	0	0				
Class 2	0.20 (0.10, 0.30)	0.15 (0.06, 0.25)	0.23 (-0.08, 0.55)				
Class 3	0.78 (0.68, 0.87)	0.82 (0.73, 0.90)	0.75 (0.46, 1.03)				

Class 4	0.02 (-0.01, 0.05)	0.03 (-.01, 0.07)	0.02 (-0.02, 0.06)				
Size class of largest plaque				0.121	0.849	0.296	0.247
Mild	0.01 (-0.01, 0.03)	0.02 (-0.01, 0.05)	0.01 (-0.01, 0.03)				
Moderate	0.66 (0.54, 0.77)	0.77 (0.67, 0.87)	0.63 (0.34, 0.92)				
Severe	0.33 (0.22, 0.45)	0.21 (0.10, 0.31)	0.36 (0.06, 0.67)				
All data are marginal means (95% confidence intervals) or probabilities (95% confidence intervals). Abbreviations as for Table 1 & 2.							

Table 3. 4 Ethnic differences in CIMT and plaque characteristics with adjustment for non-modifiable and modifiable risk factors (Model 2)

Variables	Ethnicity			p-value (individual comparisons)			p-value LR test
	EA	SA	AC	EA v SA	EA vs AC	SA vs AC	
CIMT, mm	0.88 (0.86, 0.90)	0.89 (0.86, 0.92)	0.92 (0.88, 0.95)	0.700	0.091	0.188	0.220
Total plaque area per individual with plaque, mm^2	41.3 (33.9, 48.7)	34.2 (26.6, 43.1)	44.5 (26.5, 62.4)	0.285	0.742	0.332	0.402
Number of plaques per individual with plaque	1.85 (1.63, 2.07)	1.56 (1.32,1.81)	1.57 (1.03, 2.10)	0.111	0.332	0.996	0.196
Minimum GSM of all plaques	87.41 (79.00,95.83)	78.62 (69.23,88.02)	75.80 (55.36,96.23)	0.204	0.306	0.805	0.300
Category of largest plaque				0.335	0.852	0.747	0.616
Class 1	0	0	0				
Class 2	0.23 (0.11, 0.35)	0.15 (0.04, 0.25)	0.20 (-0.13, 0.52)				
Class 3	0.75 (0.64, 0.86)	0.82 (0.72, 0.92)	0.78 (0.49, 1.06)				
Class 4	0.02 (-0.01, 0.05)	0.03 (-0.02, 0.08)	0.02 (-0.03, 0.07)				
Size class of largest plaque				0.498	0.884	0.607	0.748
Mild	0.02 (-0.01, 0.04)	0.02 (-0.01, 0.06)	0.01 (-0.02, 0.05)				
Moderate	0.68 (0.56, 0.79)	0.74 (0.61, 0.87)	0.65 (0.30, 1.00)				
Severe	0.31 (0.19, 0.43)	0.24 (0.10, 0.38)	0.34 (-0.04, 0.71)				

All data are marginal means (95% confidence intervals) or probabilities (95% confidence intervals). Abbreviations as for Table 1 & 2.

Table 3. 5 Marginal means of carotid intima-media and plaque characteristics by ethnicity after adjustment for potential confounders and mediators (Model 3)

Variables	Ethnicity			Difference between ethnic group P-value		
	EA (n = 337)	SA (n = 201)	AC (124)	EA v SA	EA vs AC	SA vs AC
cIMT, mm	0.88 (0.86, 0.91)	0.88 (0.86, 0.91)	0.94 (0.91, 0.97)	0.912	0.005	0.004
Total plaque area, mm^2	5.55 (3.87,7.22)	5.46 (3.54,7.37)	3.79 (1.49,6.08)	0.949	0.243	0.275
Maximum plaque Height, mm	3.72 (3.34,4.09)	3.20 (2.78,3.61)	4.00 (3.10,4.91)	0.090	0.568	0.113
Maximum plaque length, mm	12.05 (10.35,13.74)	12.23 (10.33,14.12)	14.33 (10.21,18.45)	0.898	0.319	0.363
Number of plaques per individual with plaque	1.85 (1.63, 2.07)	1.56 (1.32,1.81)	1.57 (1.03, 2.10)	0.111	0.332	0.996
Minimum GSM of all plaques	87.41 (79.00,95.83)	78.62 (69.23,88.02)	75.80 (55.36,96.23)	0.204	0.306	0.805
Class (manual) of largest plaque	2.93 (2.80, 3.06)	2.97 (2.83, 3.12)	2.76 (2.40, 3.11)	0.692	0.366	0.265
Class (auto) of largest plaque	2.29 (2.15, 2.42)	2.20 (2.05, 2.35)	2.34 (2.02, 2.67)	0.420	0.747	0.420
Probability of stenosis >50%	5 (2.2, 6.9)	8 (4.6, 11.0)	3 (0.0, 6.1)	0.140	0.390	0.055

All data are frequencies or mean (95% confidence intervals). Model 3: age, sex, education, diabetes, total cholesterol, high density lipoprotein cholesterol, alcohol consumption, current smoking, hypertension, statin use.

Table 3. 6 **CIMT and plaque characteristics by ethnicity after adjustment for novel risk factors (Model 4).**

Variables	Ethnicity			P-value		
	EA (n = 330)	SA (n = 195)	AC (n = 122)	EA v SA	EA vs AC	SA vs AC
cIMT, mm	0.89 (0.86, 0.91)	0.89 (0.86, 0.91)	0.93 (0.90, 0.96)	0.943	0.043	0.058
Total plaque area, mm^2	5.34 (4.15,7.23)	5.55 (3.52,7.33)	3.73 (0.32, 5.1)	0.881	0.318	0.304
Maximum plaque Height, mm	3.67 (3.35,4.00)	3.28 (2.75,3.52)	3.91 (3.15,4.96)	0.285	0.594	0.295
Maximum plaque length, mm	12.2 (10.61,13.95)	12.1 (10.2,14.1)	13.1 (8.56, 17.7)	0.821	0.636	0.758
Average number of plaques per individual with plaque	1.80 (1.59, 2.01)	1.55 (1.30, 1.79)	1.53 (1.15, 2.31)	0.216	0.404	0.922
Minimum GSM of all plaques	87.12 (78.12, 94.12)	78.50 (69.12,87.87)	77.53 (57.37,101.6)	0.242	0.448	0.948
Class (manual) of largest plaque	2.80 (2.82, 3.07)	2.94 (2.80, 3.09)	2.70 (2.46, 3.24)	0.269	0.344	0.669
Class (auto) of largest plaque	2.34 (2.22, 2.46)	2.19 (2.05, 2.33)	2.20 (1.87, 2.53)	0.762	0.889	0.740
Probability of stenosis >50%	5 (2.7, 7.0)	6 (3.8, 9.2)	3 (0.1, 6.9)	0.275	0.523	0.673

All data are frequencies or mean (95% confidence intervals). Model 4: model 3 + NT pro BNP, CRP, IL6, troponin-T, LDL cholesterol (directly measured) instead of total cholesterol, total cholesterol in medium HDL instead of HDL-cholesterol, ApoB/ApoAI ratio, albumin, histidine, tyrosine, glutamine, docosahexaenoic acid, urinary albumin creatinine ratio, eGFR.

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Discussion

We found ethnic differences in the prevalence of carotid plaque in a population-based sample of people resident in West London, UK. People of AC ethnicity had a lower occurrence of carotid plaque than the other ethnic groups, while the burden of plaque in EA and SA was similar. The lack of difference between EA and SA was surprising considering the large excess of cardiovascular disease in SA discussed above, and our data for carotid plaque prevalence are also not consistent with previous estimates of excess CHD risk in SA in SABRE.(Tillin et al., 2013b) In those with plaque, plaque characteristics differed little between ethnic groups, in particular there was no evidence of SA having evidence of more lipid-rich or vulnerable plaques, as has been previously suggested based on data from coronary CT angiography.(Villadsen et al., 2017) Whether this reflects differences between the carotid and coronary circulation or the limitations of transcutaneous ultrasound assessment of plaque vulnerability in the carotid is unclear.

Ethnic differences in plaque prevalence were unexplained by disparities in ASCVD risk factors. It therefore remains to be explained why the AC group had a lower prevalence of carotid plaques than the other ethnic groups; however this observation is consistent with previous work, including in SABRE, showing lower risk of CHD in people of AC ethnicity in UK, - this was also unexplained by conventional ASCVD risk factors.(McKeigue et al., 1991, McKeigue et al., 1993) CIMT also differed by ethnicity, after adjustment for age and sex, CIMT was higher in AC compared with the other ethnic groups. This could be viewed as consistent with their higher risk of stroke but is inconsistent with their lower risk of CHD; this difference was attenuated after

adjustment for non-modifiable and modifiable risk factors and is likely to be mainly attributable to differences in ASCVD risk factors.

Better understanding and assessment of the prevalence of atherosclerosis and its relationship to cardiovascular risk factors in different ethnic groups is important. Such relationships may also provide insights into the pathogenesis of atherosclerosis in all ethnic groups. Our failure to identify factors explaining ethnic differences in carotid atherosclerotic plaque despite adjustment for ASCVD risk factors suggests that important determinants of ethnic differences in susceptibility to atherosclerosis remain to be identified. One potential explanation for the similar incidence of carotid disease between EA and SA subjects, despite the higher prevalence of cardiovascular disease in SA, could be the differential use of statins among these populations. In our study, statin use was reported as 68% among SA subjects, 48% among EA subjects, and 37% among AC subjects. Statins are known to lower cholesterol levels and stabilize plaques, potentially reducing the incidence and progression of carotid disease. Given the higher usage of statins among SA subjects compared to EA subjects, it is plausible that statins play a significant role in mitigating the expected higher prevalence of carotid disease in the SA population. Statins not only lower low-density lipoprotein (LDL) cholesterol but also have pleiotropic effects, such as improving endothelial function, reducing oxidative stress, and decreasing inflammation, all of which could contribute to a lower incidence of carotid plaque despite the higher overall cardiovascular risk in SA individuals. Our failure to identify factors explaining ethnic differences in carotid atherosclerotic plaque despite adjustment for ASCVD risk factors suggests that important determinants of ethnic differences in susceptibility to atherosclerosis remain to be identified. Mechanisms related to racism, population migration,(Patel et al., 2006) and socio-economic disadvantage could be involved.(Javed et al., 2022a) Racism

may impact the development of carotid disease through chronic stress, socioeconomic disadvantages, healthcare disparities, behavioural factors, and undefined biological pathways. Chronic stress from racism activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels, inflammation, and endothelial dysfunction, which are risk factors for atherosclerosis.(Yao et al., 2019) Socioeconomic disadvantages due to racism result in lower access to nutritious food, safe housing, and recreational opportunities, increasing cardiovascular risk. Additionally, racism limits access to quality healthcare, leading to delayed diagnoses and poorer management of cardiovascular conditions. Implicit biases among healthcare providers can result in miscommunication and mistrust, further exacerbating these disparities.(Panza et al., 2019, Williams and Rucker, 2000) Moreover, systemic racism may result in individuals from certain ethnic groups being denied access to healthcare or facing significant barriers to obtaining necessary medical services. This can lead to undiagnosed and untreated conditions, further increasing the risk of cardiovascular diseases, including carotid plaque development,(Javed et al., 2022a, Banerjee et al., 2021) but given the differences observed between minority ethnic groups in this study despite sharing some of these exposures, this question merits further study. We anticipate that there will be genetic differences between populations of different ancestry, but currently, there is little or no evidence to suggest that genetics makes a major contribution to ethnic differences in susceptibility to ASCVD.(Benjamin et al., 2015, Kuller, 2004)

Previous studies have examined ethnic differences in carotid atherosclerosis, although few have included SA people. A UK community-based study found higher CIMT and lower prevalence of plaque in AC compared with EA (Mackinnon et al., 2010) and this difference remained after adjustment for conventional ASCVD risk factors. Another UK-based study observed marginally higher CIMT in EA compared with SA

despite higher prevalence of ASCVD in SA.(Chahal et al., 2011) In the US, the Multi-Ethnic Study of Atherosclerosis found that CIMT was higher in people of African American ethnicity, but the risk of new plaque formation was lower in African American, Hispanic and Chinese ethnicities compared with White Americans after adjustment for traditional ASCVD risk factors.(Tattersall et al., 2014) The Diabetes Heart Study also found that African American people with T2DM had higher CIMT but lower prevalence of carotid plaque compared with those of European ancestry.(Freedman et al., 2005) In contrast, the Northern Manhattan Stroke study found similar maximum internal carotid artery plaque thickness (MICPT) in stroke-free African- and European- ethnicity individuals but lower MICPT in people of Hispanic ethnicity.(Sacco et al., 1997) A recent individual participant meta-analysis that compared the association of ASCVD risk factors with CIMT in different ethnicities from a range of countries, reported that high CIMT levels was highest amongst African American populations, similar in Asian, White and Hispanic people and lowest in African populations. In keeping with our findings, adjustment for risk factors only marginally attenuated these differences.(Nonterah et al., 2022) Overall, despite some inconsistencies, the results of these previous studies appear broadly in keeping with our findings.

As has been observed in some previous studies,(Mackinnon et al., 2010, Chahal et al., 2011, Tattersall et al., 2014) CIMT corresponded poorly with known risk differentials for ASCVD, especially CHD, in the ethnic groups. Plaque prevalence was consistent with the known lower risk of CHD in AC, but not with the elevated risk of ASCVD in SA or the elevated risk of stroke in AC.(Ebrahim et al., 1999, Prati et al., 2008) This raises questions about the reliability of CIMT and plaque as a screening tool for early detection of atherosclerosis *across* different ethnic groups. For CIMT it has previously been suggested that arterial wall remodelling in response to hemodynamic stresses

might complicate interpretation,(Bots et al., 1997b) but it is not obvious that this could explain the ethnic discordance between ASCVD risk and plaque prevalence, given the latter is generally considered a better predictor of ASCVD risk.(Inaba et al., 2012)

This study has limitations and strengths: it is cross-sectional so causal conclusions cannot be made with any confidence. Participants were drawn from a randomly selected population-based cohort but possible bias due to non-participation, attrition, missing data and residual confounding by unmeasured or imprecisely measured variables cannot be excluded. As might be expected in a population-based sample, the frequency of carotid plaque was quite low, particularly in AC, which will have limited our ability to detect small differences in plaque prevalence or characteristics, nevertheless the precision of the estimates was sufficient to exclude disparities in plaque prevalence in keeping with the magnitude of the elevated CVD risk in South Asians. Our categorization of ethnicity is crude and may obscure important differences within ethnic groups;(Bhopal, 2014) however our categories reflect the original study design and correspond to the broad ethnic groups in used by the UK classification scheme.(Office for National Statistics, 2015) AC participants mostly migrated between 1950 and 1960 (i.e. around the ages of 20 to 30), while most of the SA participants arrived in the UK in the 1970's (i.e. around 40 years old) and limited data was available about exposures, including childhood exposures and healthcare provision, that occurred prior to migration or extent of acculturation after migration. We included a comprehensive set of risk factors for ASCVD, but we acknowledge that including these risk factors, which potentially act as mediators of ethnic differences, could introduce bias.(VanderWeele and Vansteelandt, 2009) The study's strengths are first and foremost its community-based methodology and that it compares people of different ethnicities in the same location. SA and AC participants make up the majority of British

first-generation migrants and, unlike in some countries, universal health care, free at the point of use, is available in UK. This may lessen, though not abolish disadvantages in health access.(Nazroo et al., 2009) All examinations were conducted according to a strictly quality controlled methodology, as part of comprehensive phenotyping of this older age sample.

4 The impact of Carotid Atherosclerosis on global Cognitive function in a UK tri-ethnic prospective cohort study (SABRE: Southall and Brent Revisited) retrospective study

Abstract

Background Cognitive function has an important role in determining the quality of life of older adults. Cardiovascular disease is common in older people and may compromise cognitive performance; however, the extent to which this is related to carotid atherosclerosis is unclear.

Aims We investigated associations between carotid atherosclerosis and cognitive function and neuroimaging markers of brain health in a UK multi-ethnic community-based sample including people of European, South Asian, and African-Caribbean ethnicity.

Methods Carotid plaques and intima-media thickness (CIMT) were assessed using ultrasound in 985 people (mean age 73.2y, 56% male). Associations of carotid atherosclerosis with cognitive function (memory, executive function, language and The Community Screening Interview for Dementia (CSI-D) , a global measure of cognitive state) and neuroimaging measures (total brain volume, hippocampal volume, white matter (WM) lesion volume and coalescence score) were analysed using regression analyses, with and without adjustment for potential confounders using two models: 1) adjustment for age, sex, and ethnicity; 2) model 1 plus education, physical activity category, body mass index, hypertension, diabetes, total and high density lipoprotein cholesterol, atrial fibrillation, smoking, previous CVD, alcohol consumption, and presence of chronic kidney disease.

Results People with carotid plaque or higher CIMT had lower CSI-D score, poorer memory poorer executive function and higher WM lesion volume and coalescence. Language was poorer in people with plaque but was not correlated with cIMT. Associations with plaque were preserved after full adjustment (model 2) but relationships

for CIMT were attenuated. Associations with other plaque characteristics were generally unconvincing after adjustment.

Conclusions This multi-ethnic cohort study provides evidence that presence of carotid plaque, is associated with poorer cognitive function and brain health.

Introduction

Cognitive function has an important role in determining the quality of life of older adults and impaired cognitive function and dementias are major public health concerns. (Lynch, 2020) Cardiovascular disease (CVD) is common in older people and influences cognitive performance. For example, vascular dementia is the second most commonly diagnosed type of dementia after Alzheimer's disease in the elderly.(Skrobot et al., 2018) Two recent systematic reviews have examined the relationship between carotid atherosclerotic and cognition. Baradaran et al. (Sabayan et al., 2015, Romero et al., 2009b, Kearney-Schwartz et al., 2009a) found evidence of an association between carotid artery plaque and poorer cognition based on clinical diagnosis or cognitive testing, while as I reported in Chapter 2 (Anbar et al., 2022b) there was an adverse association between carotid atherosclerosis and a quantitative measure of cognitive performance, the Mini-Mental State Examination (MMSE), but the evidence base was limited and inconsistent. Neither review was able to account fully for confounding due to the disparate nature of the studies included. Moreover, there is inconsistent information about the association between carotid atherosclerosis and particular cognitive domains or neuroimaging markers of brain health, although associations between CVD and poorer performance in tests of memory, attention, processing speed and executive function have been reported.(Liu et al., 2021, Kawasaki et al., 2016b, Zhong et al., 2011a)

While carotid atherosclerosis is a well-recognised risk factor for ischaemic stroke,(Tendera et al., 2011) previous studies have also reported associations between carotid atherosclerosis (Piegza et al., 2022, Turk et al., 2008) or carotid stenosis (Muller et al., 2011) in the absence of stroke and neuroimaging markers of brain

health, such as atrophy or the presence of a white matter hyperintensity (WMH). The extent to which these associations reflect the direct consequences of carotid atherosclerotic disease as opposed to concomitant systemic atherosclerosis, cerebral small vessel disease, or some other process that accompanies carotid atherosclerosis remains unclear.(Jefferson et al., 2007, Romero et al., 2009a) Understanding these relationships may be important for understanding mechanisms and treatments, as some studies have reported that executive function, visuospatial episodic memory, and psychomotor speed improve after revascularization of carotid arteries.(Tendera et al., 2011) Another limitation of current evidence is that most investigations of atherosclerosis and cognitive function or brain health have been performed in European-origin populations. Studies in multi-ethnic populations have been small and infrequent.(Moroni et al., 2016b, Romero et al., 2009a) Ethnic differences in susceptibility to cardiovascular disease are well-recognised,(Schaich et al., 2022, Bothongo et al., 2022, Redwood and Gill, 2013) and vascular risk factors for dementia may not be generalizable to different ethnic groups.(Jefferson et al., 2007, Romero et al., 2009a).

The aim of this study therefore was to investigate cross-sectional associations between carotid atherosclerosis and cognitive function and brain health in a UK multi-ethnic community-based sample including people of European, South Asian, and African-Caribbean ethnicity.

Methods

Participants and study design

Detailed information about the Southall and Brent Revisited study (SABRE) has been published previously.(Tillin et al., 2012b, Al Saikhan et al., 2020b) SABRE was set up in 1988 as a tri-ethnic longitudinal cohort study to examine ethnic differences in chronic disease. It recruited predominantly European (EA), South Asian (SA) and African Caribbean (AC) participants living in West and North London; details have been previously described.(Tillin et al., 2012b) Approval for the current study was obtained from the NRES Committee London, Fulham (ref. 14/LO/0108).

For this study, we used data on 985 participants, who attended for clinical investigations (visit 3) which began in 2014 and ended in January 2018. All participants completed a health and lifestyle questionnaire.(Al Saikhan et al., 2020b) Information was recorded on age, sex, health, medical history, and medication. Participants' ethnicity was determined by interviewers based on grandparental origin and confirmed by participants. All participants were asked to refrain from alcohol, smoking, and caffeine for ≥12 h before clinic attendance. Height and weight were measured using a standardized protocol, body mass index (BMI) was calculated, and body fat percentage was measured using a Tanita BC 418 body composition analyzer. Seated brachial blood pressure (BP) was measured according to ESH guidelines.(O'Brien et al., 2005) The average of the second and third recordings was used as clinic BP. Alcohol consumption was categorised according to UK guidelines into none, ≤ 14 units per week or > 14 units per week. Physical activity measured as the total weekly energy (MJ) expended in sporting activities, cycling, walking, and in other strenuous activity during

leisure time was categorised based on ethnicity-appropriate criteria (Bryan et al., 2006) into: low (<1.5kcal/kg/day), moderate (≥1.5kcal/kg/day to <3kcal/kg/day), moderate to high (≥3kcal/kg/day to <6kcal/kg/day) and high (≥6kcal/kg/day) Coronary arterial disease was assessed using a combination of clinical history, diagnostic tests such as ECG, stress tests, and imaging studies like echocardiography . I undertook the critical task of data refinement, meticulously cleaning and organizing the information gathered by my colleagues. Specifically, I focused on selecting participants with plaques and conducted precise measurements for both plaques and intima-media thickness (IMT). Subsequently, I carried out comprehensive statistical analyses to derive meaningful insights from the data. Additionally, I wrote the first draft of the entire manuscript, taking responsibility for the subsequent writing and editing process. This involved synthesizing the research findings, methodologies, and results into a cohesive and well-articulated paper. Through my efforts, I aimed to enhance the overall clarity, coherence, and quality of the document, ensuring that it effectively communicates the significance of our research.

Carotid Ultrasound assessment

Carotid ultrasound scans were performed by an experienced sonographer as described in detail previously (Anbar et al., 2022a) using a protocol based on Stein et al.(Stein et al., 2008c) Scan were performed with a GE Vivid I Ultrasound system equipped with a 6-13 MHz broadband linear array transducer (12L-RS) along with a 3-lead ECG recording. The common carotid artery (CCA), internal carotid artery (ICA) and external carotid artery (ECA) were imaged bilaterally, and three-angle longitudinal views (lateral, posterior, and anterior) plus transverse views were saved as cine loops of 3-5 cardiac cycles. In addition to 2D-images, spectral-Doppler imaging, Colour and

Power doppler were recorded and used to assist with plaque identification and delineation. Quantitative analyses were performed offline using validated software (AMS II) that allowed automated measurement of CIMT, plaque area, categorisation of plaque based on the Grey-Weale score, plaque size and estimation of plaque grey-scale median (PGSM). cIMT is typically measured in diastole to reduce variability caused by the arterial wall's motion during the cardiac cycle. Measuring during diastole, when the heart is at rest, provides a more stable and reproducible measurement. from each of the 3 angles over the distal 1 cm length of each common carotid artery. The intima-media thickness in the internal and external carotid arteries was not assessed in keeping with guideline recommendations (Stein et al., 2008c). The mean CIMT from the far walls of right and left common carotid arteries (mean-mean) was calculated. Carotid plaque was defined as the presence of focal wall thickening at least 50% greater than that of the surrounding vessel wall or as a focal region with CIMT >1.5mm protruding into the lumen distinct from the adjacent boundary in any location in the extracranial carotid arteries.(Stein et al., 2008c). carotid stenosis >50% includes stenosis up to 100%. Comparing this range with a more significant threshold like 70% could provide deeper insights into the severity of stenosis. The choice of >50% is due to its recognition as a standard clinical threshold, but comparisons with a higher threshold (e.g., 70%) would offer granularity regarding the severity's impact on cognitive function.

Neuropsychological assessment

Cognitive function was assessed with a standardized neuropsychological test battery that has been validated for cross-cultural settings as previously described.(Park et al., 2017, Taylor et al., 2013) Clinically significant global cognitive impairment was identified using the Community Screening Instrument for Dementia (CSI-D),(Prince et al., 2011) and assessed three cognitive domains: memory (Consortium to Establish a Registry for Alzheimer's Disease (CERAD) total, immediate and delayed), executive function (digit span backward, colour trails part A and B) and language (Animal naming, Boston naming test). To generate a composite score for the CSI-D, a standard algorithm was applied.(Sosa et al., 2009) Raw neuropsychological test scores were standardized into *z*-scores for each ethnic group and averaged to create scores for specific cognitive domains, an exploratory principal components analysis having previously established that there was a single-factor solution for each cognitive domain in each ethnic group (data not shown). To prevent fatigue, trained staff conducted cognitive evaluations that lasted roughly 30 minutes early on the day of clinic attendance. Depression was assessed using the ten-item Geriatric Depression Scale (GDS). Dementia screening can be influenced by participants' education level, culture, and religious beliefs. To attempt to account for these influences we adjusted for education level in the statistical models. To address cultural sensitivity, we employed culturally sensitive screening tools and ensured that language barriers are minimized by providing translations or interpreters. Religious beliefs that may affect the perception and reporting of cognitive symptoms, were not accounted for in these analyses.

Neuroimaging sequences and analysis

All subjects underwent MRI examination at University College Hospital using a 3T MRI system (Philips Achieva, Eindhoven, Netherlands) with an 8 channel phased array head coil, following a previously described protocol (Sudre et al., 2018). The imaging protocol included a sagittal T1-weighted 3D TFE sequence with specific parameters (TR/TE/TI 7/3.2/836ms, flip-angle 18, voxel size 1mm3). Cortical gray matter was automatically parcellated into lobes using Geodesic Information Flows (GIF), and these outputs were utilized in the BaMoS algorithm for automatic white matter hyperintensity (WMH) segmentation.(Sudre et al., 2018) The BaMoS algorithm employed unsupervised hierarchical model selection, enabling accurate identification and delineation of WMH. Brain tissue segmentation, involving cortical gray matter parcellation and erasure of skull signal, was also performed using the GIF algorithm.(Cardoso et al., 2015) The methodology included a multi-atlas segmentation technique, STEPS (Similarity and Truth Estimation for Propagated Segmentations), for segmenting various brain structures, including hippocampal volumes.

Non-periventricular lesion classification, referring to lesions not extending beyond 25% of the ventricular border, was automatically conducted by assessing their confluency level. Additionally, a comprehensive amalgamation score (CS) was computed, considering the ratio of lesions in each confluency category relative to the total WMH volume and removing lesions with percentage of lesion border along ventricles >25% in 1st (most periventricular) layer. This global coalescence score provides a metric for evaluating the overall clustering and merging of WMH within the brain.(McPhillie et al., 2021)

Statistical analyses

Analyses were performed with Stata v.17.0 and 18.0 (StataCorp, College Station, TX, USA). Continuous data describing the sample were summarised as means and standard deviations (SD) or median (interquartile range) for skewed data, and categorical data as counts and percentages. Normality was assessed through frequency histograms, QQ plots and Shapiro-Wilk tests. multilinear regression modelling was used to examine the association of measures of carotid atherosclerosis and cognitive outcomes. glm was used to examine the association between measures of carotid atherosclerosis and neuroimaging outcomes using a log link function and a gamma family distribution. The rationale behind selecting this approach was the need to examine the association between continuous (exposure) variables and a continuous outcome where the relationship is not linear and the residuals do not follow a normal distribution and may be heteroscedastic, i.e. violating some assumptions of ordinary linear regression. The utilization of the log link function effectively converts the linear predictor into a logarithmic scale, thereby guaranteeing that the predicted values remain non-negative. This is particularly crucial in situations where the outcome data exhibits positive skewness and consists solely of non-negative values. To accommodate these specific characteristics, the gamma family distribution was employed. The utilization of robust standard errors was employed in order to accommodate the potential presence of heteroscedasticity. The aforementioned methodology offers a resilient and efficacious approach for modelling, while tackling the complexities posed by non-linearity, non-normal data distributions and heteroscedasticity.

Results were summarised as regression coefficients (95% confidence intervals). Two models were used: 1) minimal adjustment for age, sex, and ethnicity; 2) full confounder adjustment i.e., model 1 plus education, physical activity category, BMI, HTN, diabetes, total and HDL cholesterol, atrial fibrillation, smoking, CVD (i.e. CHD, stroke,

or heart failure), alcohol consumption category, presence of chronic kidney disease and depression. Confounders were chosen based on prior knowledge drawn from the literature. The same adjustment strategy was used for neuroimaging outcome, with the addition of the total brain volume which is a strong predictor of volumetric neuroimaging outcomes, and its inclusion will therefore increase the precision of estimates.

The possibility of effect modification by sex was looked for in all models by including a sex interaction term, if this was not statistically significant both sexes were pooled for analysis, otherwise we planned that results for both sexes would be presented separately. In all cases there was no evidence of modification by sex so only pooled data are presented below. The possible existence of nonlinear relationships beyond those accounted for by glm was investigated fitting fractional polynomials but there was no convincing evidence in any model for more complex non-linear relationships, so these were not analysed further.

Analyses were performed using complete case analysis which is valid under the assumption that missingness was independent of outcomes. Statistical inference was based on a combination of p-values, effect sizes and CI. The disproportionate sample sizes could potentially affect the results due to differences in statistical power. To mitigate this, we use the following approaches: Weight the Analysis: We employ statistical techniques to weight the samples so that each ethnic group is appropriately represented. Stratified Analysis: We conduct stratified analyses to examine the results within each ethnic group separately.

Results

Participant characteristics are shown in Table 4.1. The average age was 73 years and 56% of participants were male. The ethnicity of participants was 44% European, 33%

South Asian and 23% African Caribbean. 24% of participants had diabetes and 59% had hypertension.

Table 4.1 Characteristics of participants.

Variables	N	Mean/%	SD [IQR]
Age, y	985	73.2	6.7
Male sex	553	56%	
Ethnicity			
European	437	44%	
South Asian	326	33%	
African Caribbean	228	23%	
Systolic blood pressure, mmHg	985	141.1	18.1
Diastolic blood pressure, mmHg	985	79.3	10.7
Heart rate, bpm	985	67.4	11.4
Height, cm	984	165.3	9.0
Body mass index, kg/m^2	985	27.9	4.7
Fat percent	957	32.5	8.2
Total cholesterol, mmol/l	962	4.6	1.1
High density lipoprotein cholesterol, mmol/l		962	1.5 0.4
Triglycerides, mmol/l		962	1.3 [0.7]
Glycated haemoglobin, mmol/mol		953	40.5 9.6

Diabetes mellitus	242	24.4%	
Coronary Heart Disease	124	13.1%	
Stroke	15	1.6%	
Hypertension	568	58.9%	
Chronic kidney disease	161	16.8%	
Urinary albumin: creatinine ratio	954	0.06	0.01
Alcohol consumption			
None	373	37.6%	
≤ 14 units per week	539	54.3%	
> 14 units per week	80	8.1%	
Physical activity category			
Low	236	32.07%	
Moderate	261	35.46%	
Moderate to high	193	26.22%	
High	46	6.25%	
Current smoker	27	2.7%	
Presence of any carotid plaques	144	14.5%	
Right side	87		
Left side	88		
Plaque area, mm^2	126	38.6	26.9
Plaque Grayscale Median	126	84.0	31.4

Carotid intima-media thickness, mm	928	0.89	0.21

Carotid atherosclerosis and cognitive function

A comparison of cognitive function by presence or absence of plaque is shown in (Figure 4.1A&B) Global cognitive function, memory and executive function were lower in people with carotid plaques but there was little difference in language performance.

When people with and without carotid stenosis >50% were compared only executive function was convincingly lower in those with carotid stenosis. All other cognitive measures were lower in people with stenosis, but due to the limited number of people with carotid stenosis, the estimates were imprecise and consequently the evidence of a difference was unconvincing.

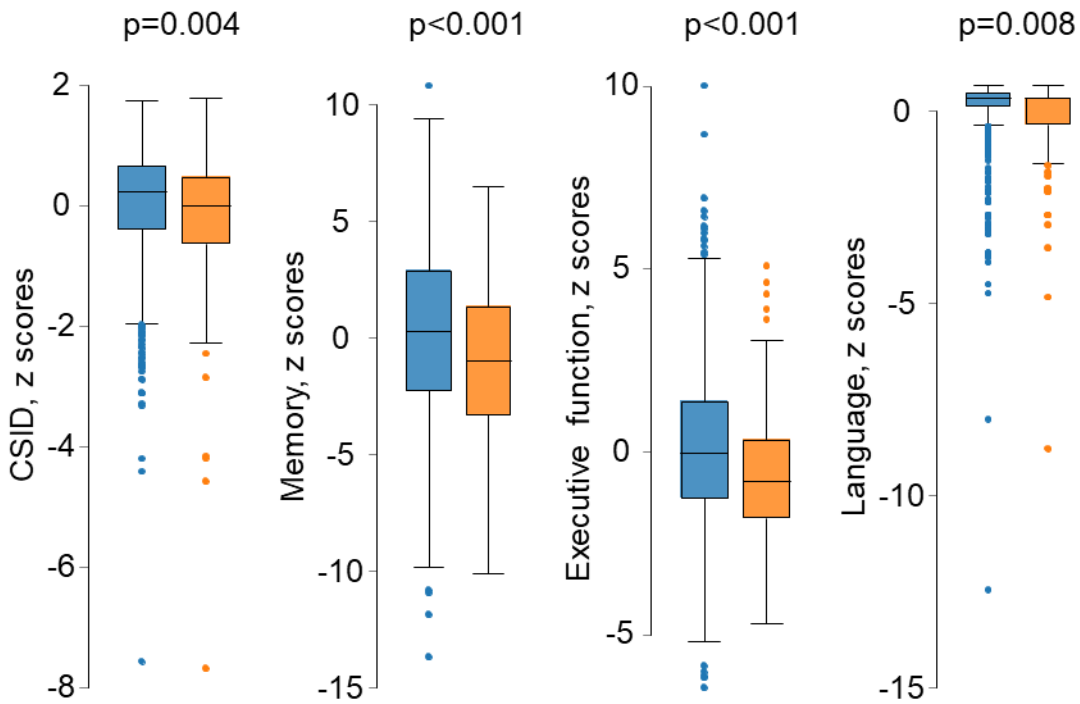

Figure 4.1(A) Comparison of cognitive function by presence or absence of plaque. People with plaques (orange) and without (blue). Abbreviations: CSID – Community Screening Instrument for Dementia.

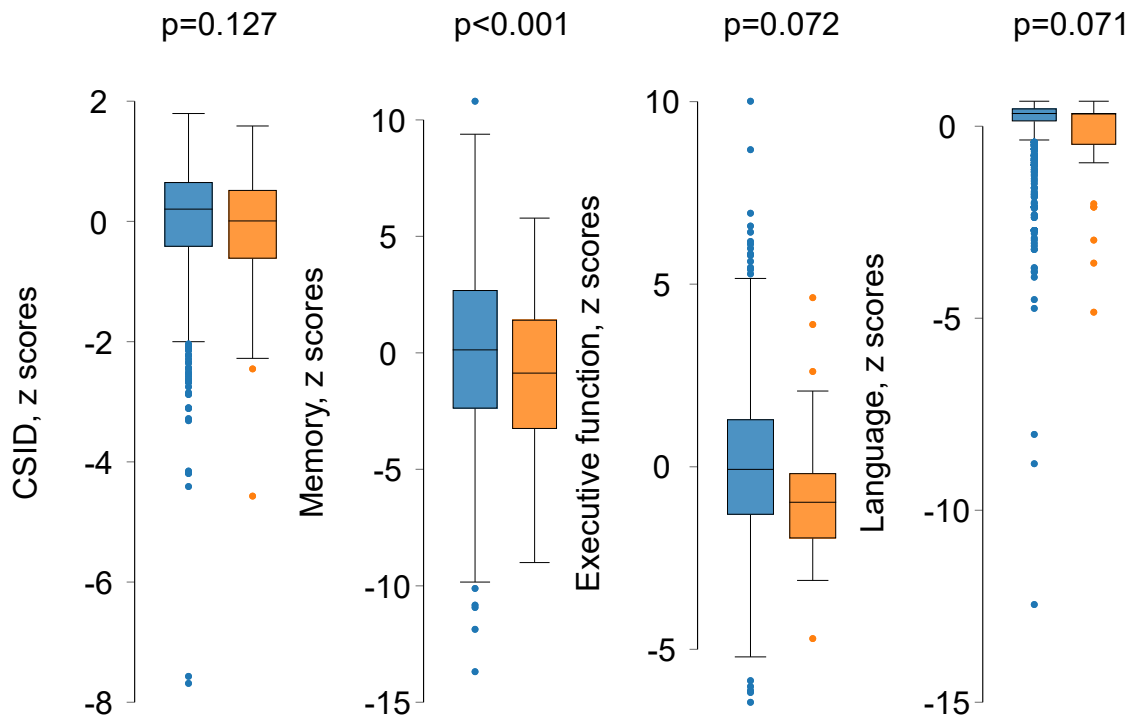

Figure 4.2(B) Comparison of cognitive function by presence or absence of plaque. People with plaques (orange) and without (blue). Abbreviations: CSID – Community Screening Instrument for Dementia.

(Table 4.2) presents the correlation analysis between plaque characteristics and cognitive functional domains. The results reveal important insights into the relationship between these variables. Regarding global cognition, no significant correlations were found with any of the plaque characteristics, including CIMT, plaque area, plaque number, minimum GSM, class (manual), and class (auto). However, when examining specific cognitive domains, such as memory, a negative correlation was observed with CIMT, plaque area, and plaque number, indicating that individuals with higher CIMT, larger plaque area, and more plaques tended to exhibit poorer memory performance. Similarly, executive function/attention showed negative correlations with CIMT, plaque

area, and plaque number, suggesting that greater plaque burden was associated with lower executive function and attention. In contrast, there were no significant correlations between language and any of the plaque characteristics. These findings highlight the domain-specific associations between plaque characteristics and cognitive function, emphasizing the potential impact of plaque burden on memory and executive function/attention.

Table 4. 2 Spearman correlation coefficients (r_s) between cIMT, plaque characteristics and cognitive functional domains

Cognitive domain	cIMT, mm	Plaque area, mm^2	#plaques+0	#plaques	Minimum PGSM	Class (manual)	Class (auto)
CSID	r_s = -0.071 p = 0.032	r_s = -0.084 p = 0.009	r_s = -0.086 p = 0.008	r_s = 0.109 p = 0.241	r_s = -0.021 p = 0.819	r_s = -0.053 p = 0.590	r_s = 0.037 p = 0.713
Executive function/ attention	r_s = -0.097 p = 0.003	r_s = -0.128 p < 0.001	r_s = -0.127 p < 0.001	r_s = 0.120 p = 0.206	r_s =0.043 p = 0.666	r_s = -0.157 p = 0.149	r_s = -0.029 p = 0.756
Language	r_s =-0.052 p= 0.875	r_s = -0.082 p = 0.011	r_s = -0.083 p = 0.011	r_s = 0.096 p = 0.306	r_s =-0.013 p= 0.886	r_s =-0.179 p= 0.079	r_s =-0.053 p= 0.563
Memory	r_s = -0.120 p = 0.003	r_s = -0.110 p < 0.001	r_s =-0.111 p < 0.001	r_s = 0.167 p = 0.075	r_s = 0.058 p = 0.532	r_s = -0.168 p = 0.096	r_s = -0.011 p = 0.902

Abbreviations: cIMT, carotid intima media thickness; CSID, Community Screening Instrument for Dementia; #plaques, numbers of plaques in only people with plaque; #plaques+0, number of plaques in all participants (i.e. includes those without plaque coded as zero); PGSM, plaque grey-scale median. Bold values were interpreted as showing evidence of correlation**.**

Figure (4.3A-4.4B-4.5C) displays the results of various regression analysis models as forest plots. All correlations between cognitive metrics and carotid atherosclerosis weakened and became inconclusive after adjustment (model 1 or model 2), with only the association with presence of carotid plaque remaining statistically significant.

Carotid atherosclerosis and Neuroimaging

Figure 4.2A shows a comparison of neuroimaging biomarkers by presence or absence of plaque without adjustment for confounding factors. WMH lesion volume and CS were lower in people with plaque, but total brain volume and hippocampal volume did not differ. When people with and without carotid stenosis >50 % were compared (Figure 4.2B), there were no clear differences in neuroimaging biomarkers, but the limited number of people with carotid stenosis meant that estimates were imprecise, and it was difficult to draw firm conclusions.

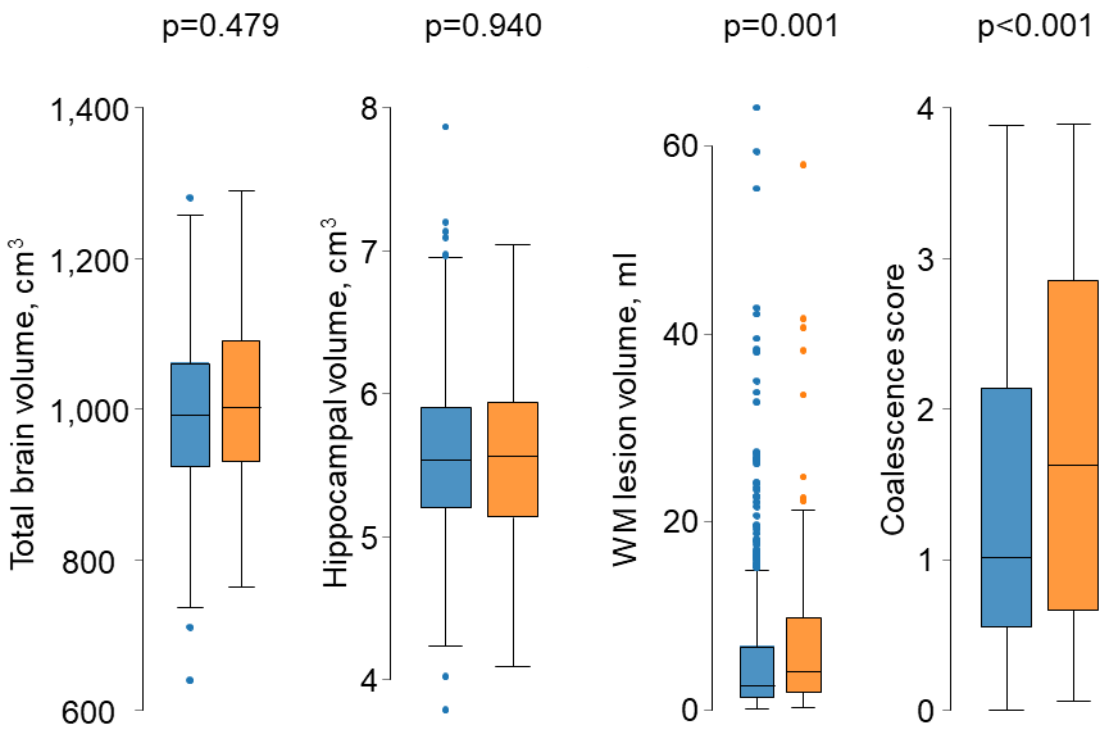

Figure 4.3A Comparison of neuroimaging biomarkers by presence or absence of plaque. People with plaques (orange) and without (blue). WM – white matter.

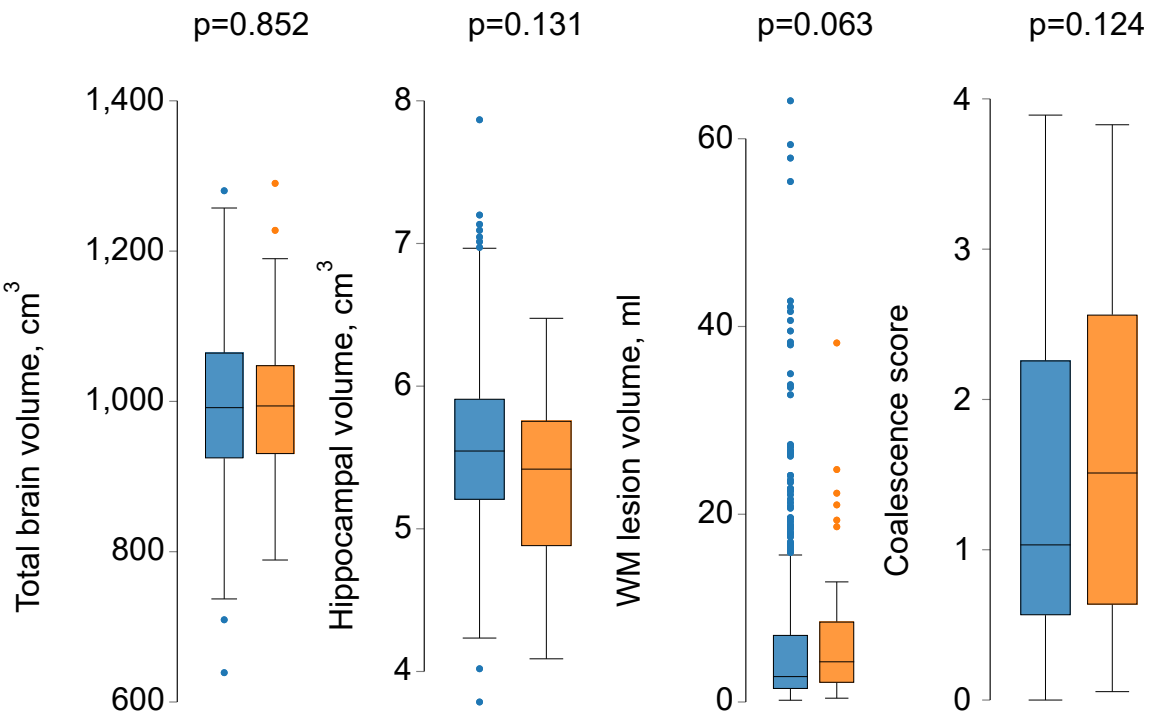

Figure 4.4B Comparison of neuroimaging biomarkers by presence or absence of stenosis >50%. People with stenosis (orange) and without (blue). WM – white matter.

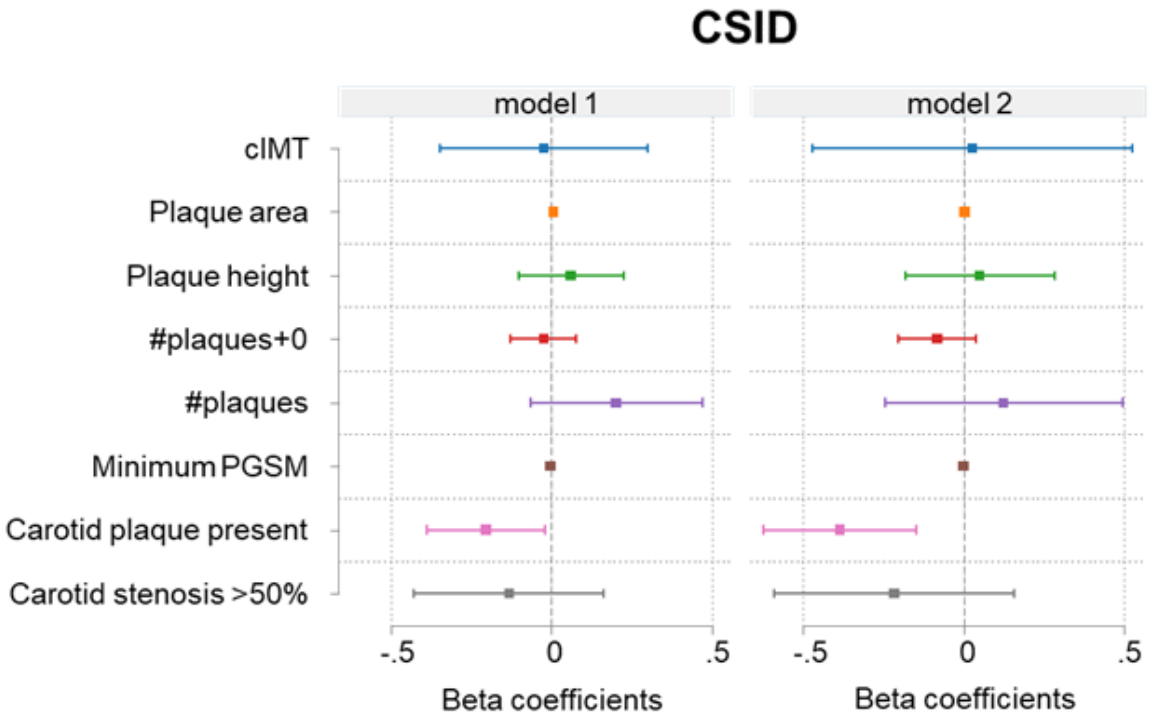

Figure 4.5 Forest plots summarising the association between measures of carotid atherosclerosis and CSID after adjustment for age, sex ethnicity (model 1), and model 1 plus education, physical activity category, BMI, HTN, diabetes, total and HDL cholesterol, atrial fibrillation, smoking, existing CVD (i.e. coronary heart disease, stroke, or heart failure), alcohol consumption category, presence of chronic kidney disease and depression (model 2). Abbreviations as in Table 4.2.

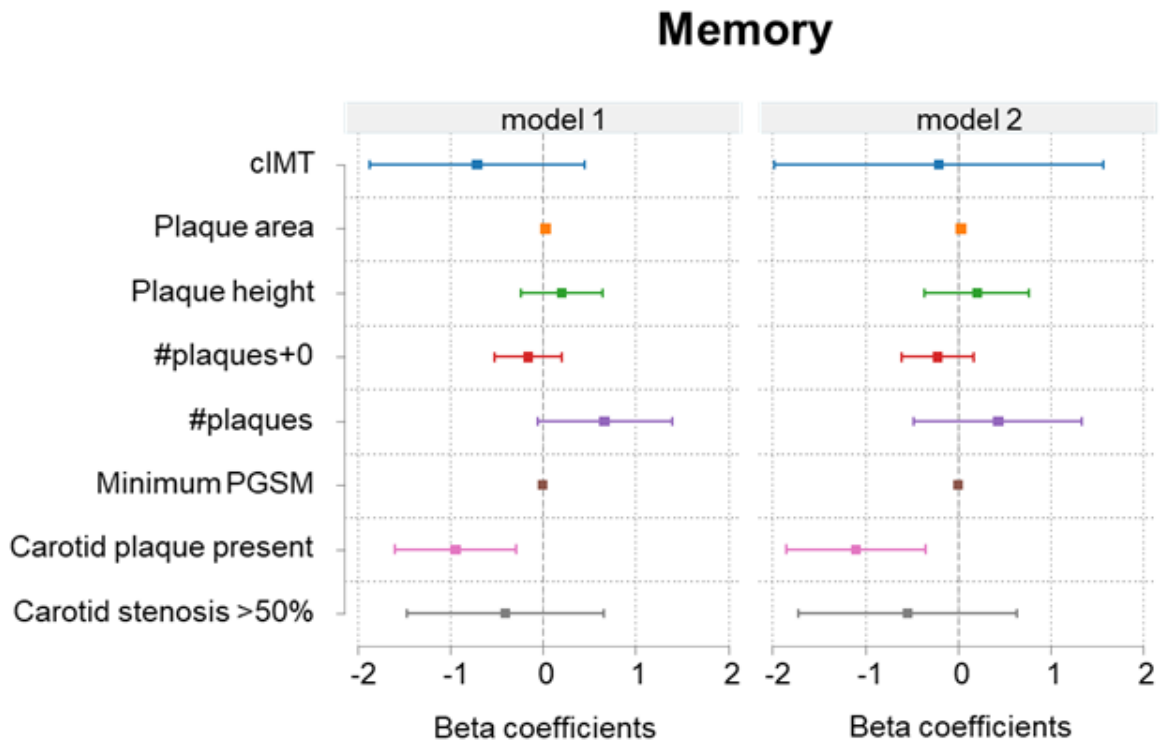

Figure 4.6 Forest plots summarising the association between measures of carotid atherosclerosis and memory after adjustment for age, sex ethnicity (model 1), and model 1 plus education, physical activity category, BMI, HTN, diabetes, total and HDL cholesterol, atrial fibrillation, smoking, existing CVD (i.e. coronary heart disease, stroke, or heart failure), alcohol consumption category, presence of chronic kidney disease and depression (model 2). Abbreviations as in Table 4.2.

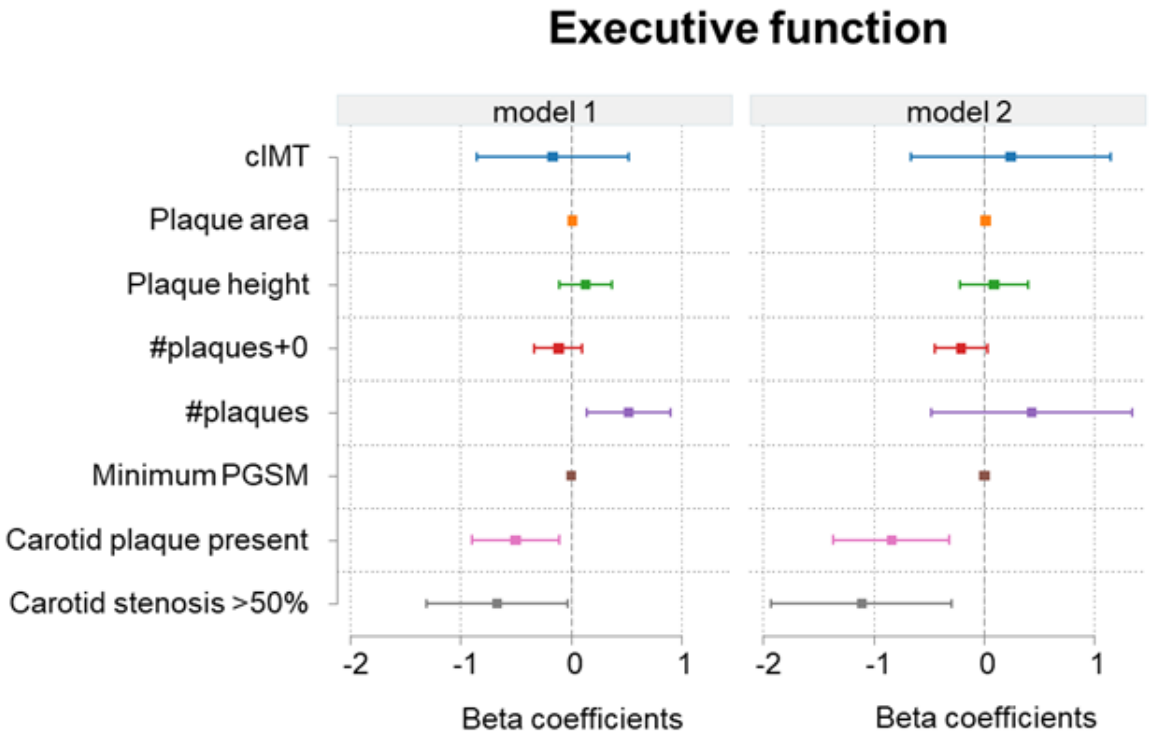

Figure 4.7 Forest plots summarising the association between measures of carotid atherosclerosis and executive function after adjustment for age, sex ethnicity (model 1), and model 1 plus education, physical activity category, BMI, HTN, diabetes, total and HDL cholesterol, atrial fibrillation, smoking, existing CVD (i.e. coronary heart disease, stroke, or heart failure), alcohol consumption category, presence of chronic kidney disease and depression (model 2). Abbreviations as in Table 4.2.

Table 4.3 shows correlations between measurements of brain volume and plaque characteristics such CIMT, plaque area, plaque number, minimum GSM, and class. The results showed that these plaque features and brain volume had only weak relationships. The relationships between CS and CIMT, plaque area, and plaque number were weak positive associations, with the correlations with CIMT and plaque area being statistically significant. Although the relationships between sum of all lesions as proportion of TIV when the border along ventricles is less than 25% of the overall lesion border in the 4th (most juxtacortical) layer and CIMT and plaque area were positive, they were not statistically significant. Strong positive correlations were seen between Overall coalescence score when removing lesions with percentage of lesion border along ventricles > 25% and plaque area and plaque number, with the latter two correlations being statistically significant. Overall coalescence score when removing lesions with percentage of lesion border along ventricles > 25% showed mild positive associations with CIMT. white matter lesion volume revealed marginally significant positive relationships with CIMT, plaque area, and plaque number. The correlations between CIMT and plaque area were statistically significant. Plaque area and plaque number showed weak negative relationships with overall lesion volume, with the correlation with plaque area being statistically significant. Overall, these findings imply that there are weak correlations between brain volume measures and various plaque characteristics, with the correlation between these specific plaque characteristics and brain volume changing in severity.

Table 4. 3 Spearman correlation coefficients (r_s) between cIMT / plaque characteristics and brain volumes and WMH measurements

Neuroimaging measure	cIMT, mm	Plaque area, mm^2	#plaques+0	#plaques	Minimum PGSM	Class (manual)	Class (auto)
Coalescence score	r_s = 0.097 p = 0.014	r_s = -0.144 p = 0.157	r_s = 0.100 p = 0.008	r_s = -0.100 p = 0.353	r_s = 0.193 p = 0.520	r_s = 0.013 p = 0.899	r_s = -0.054 p = 0.503
Hippocampal volume	r_s = -0.068 p = 0.065	r_s = -0.060 p = 0.553	r_s = -0.004 p = 0.915	r_s = -0.038 p = 0.709	r_s = -0.149 p = 0.146	r_s = -0.182 p = 0.110	r_s = -0.177 p = 0.080
Total brain volume	r_s = 0.004 p = 0.899	r_s = 0.144 p = 0.156	r_s = 0.036 p = 0.336	r_s = 0.093 p = 0.362	r_s = -0.013 p = 0.893	r_s = -0.230 p = 0.308	r_s = 0.100 p = 0.323
WM lesion volume	r_s = 0.082 p = 0.026	r_s = -0.088 p = 0.393	r_s = 0.100 p = 0.006	r_s = -0.133 p = 0.197	r_s = 0.295 p = 0.021	r_s = 0.040 p = 0.614	r_s = -0.073 p = 0.463

Abbreviations as in Table 4.2.

Figure 4.6A, 4.7B, 4.8C, and 4.9D depicts the findings from the various regression analysis models. For total brain volume CIMT, presence of carotid plaque and carotid stenosis >50% showed evidence of association with smaller brain volume in model 1 (age, sex and ethnicity adjusted) but all associations were attenuated once full adjustment for all potential confounders was performed (model 2). For hippocampal volume there was some evidence that greater plaque height was associated with smaller hippocampal volume, there were no other convincing associations. For WM lesion volume presence of carotid plaque was associated with greater lesion volume in both model 1 and 2. There was also an inverse association between number of plaques (#plaques) and WM lesion volume but this was not seen when people with no plaques were included and it is possible that this was a chance finding. Coalescence score

was higher in people with plaques but otherwise there were no convincing associations.

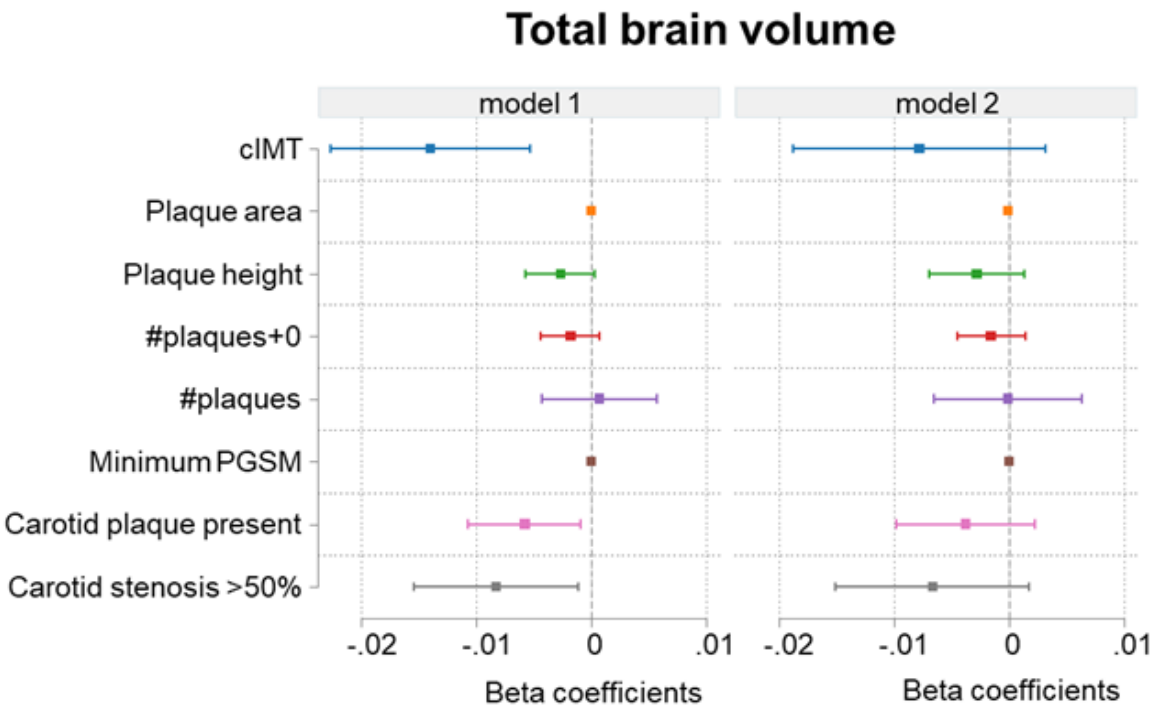

Figure 4. 8**(A) Total brain volume. Forest plots summarising the associations between measures of carotid atherosclerosis and neuroimaging measures after adjustment for age, sex ethnicity (model 1) and model 1plus education, physical activity category, BMI, HTN, diabetes, total and HDL cholesterol, atrial fibrillation, smoking, existing CVD (i.e. coronary heart disease, stroke, or heart failure), alcohol consumption category, presence of chronic kidney disease and depression. Abbreviations as in Table 4.2.**

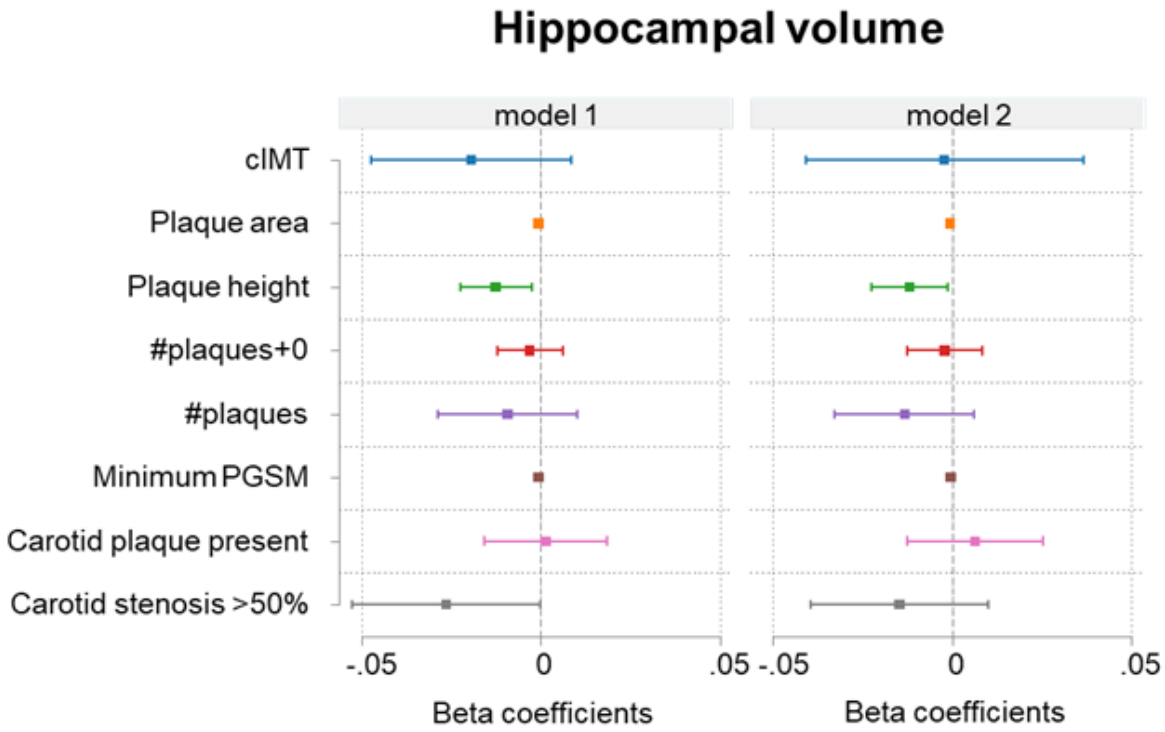

Figure 4. 9**(B) Hippocampal volume. Forest plots summarising the associations between measures of carotid atherosclerosis and neuroimaging measures after adjustment for age, sex ethnicity (model 1) and model 1plus education, physical activity category, BMI, HTN, diabetes, total and HDL cholesterol, atrial fibrillation, smoking, existing CVD (i.e. coronary heart disease, stroke, or heart failure), alcohol consumption category, presence of chronic kidney disease and depression. Abbreviations as in Table 4.2.**

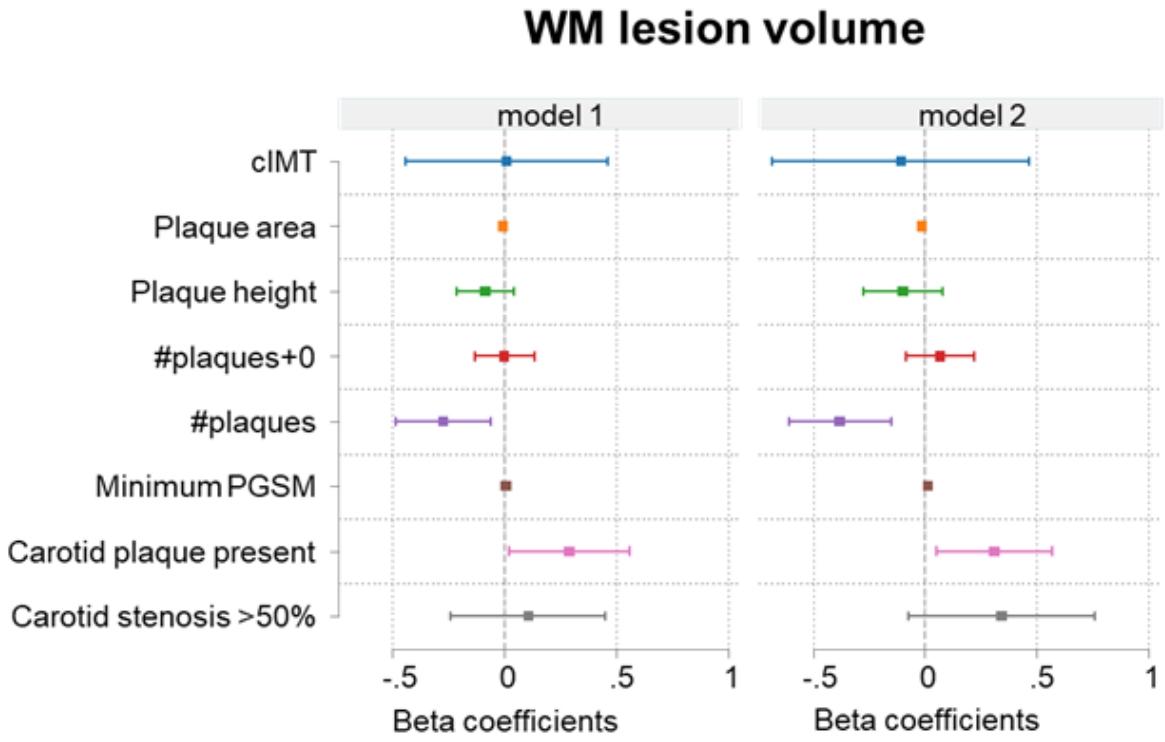

Figure 4. 10 (C) WM lesion volume Forest plots summarising the associations between measures of carotid atherosclerosis and neuroimaging measures after adjustment for age, sex ethnicity (model 1) and model 1plus education, physical activity category, BMI, HTN, diabetes, total and HDL cholesterol, atrial fibrillation, smoking, existing CVD (i.e. coronary heart disease, stroke, or heart failure), alcohol consumption category, presence of chronic kidney disease and depression. Abbreviations as in Table 4.2.

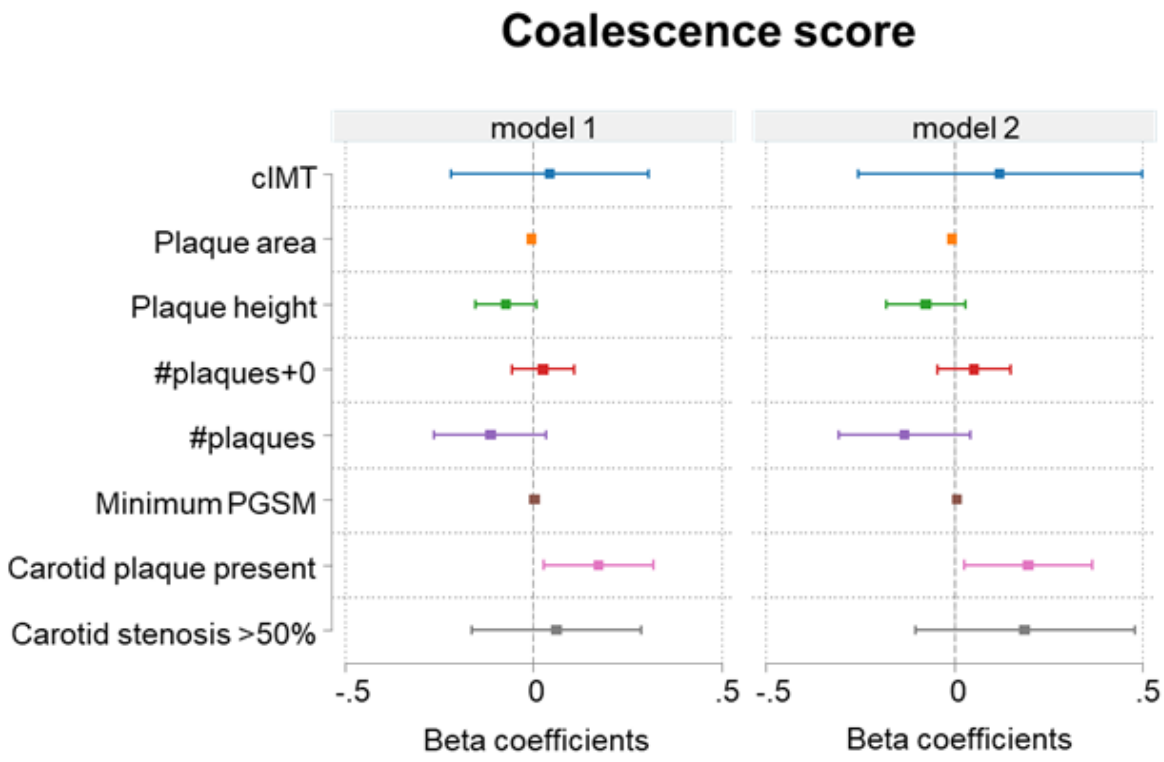

Figure 4. 11 (D) Coalescence score) Forest plots summarising the associations between measures of carotid atherosclerosis and neuroimaging measures after adjustment for age, sex ethnicity (model 1) and model 1plus education, physical activity category, BMI, HTN, diabetes, total and HDL cholesterol, atrial fibrillation, smoking, existing CVD (i.e. coronary heart disease, stroke, or heart failure), alcohol consumption category, presence of chronic kidney disease and depression. Abbreviations as in Table 4.2.

Discussion

We investigated associations between measures of carotid atherosclerosis and cognitive performance and neuroimaging measures of brain health in a multi-ethnic population cohort. In unadjusted analyses, several measures of carotid atherosclerosis were associated with poorer cognition, including impaired executive function and memory, but following adjustment for potential confounders, particularly age, most associations except for associations with presence of plaque were substantially attenuated or abolished. Presence of plaque was associated with increased WM lesion volume and increased WM lesion coalescence, but there was no convincing evidence of associations between cIMT and any neuroimaging measure of brain health once confounding had been accounted for. The more robust relationship between plaque and various outcomes may indicate that plaque is a more definitive indicator of carotid atherosclerosis than cIMT, which in part may reflect an adaptive response to local transmural pressure.(Ebrahim et al., 1999, Bots et al., 1997b)

Our findings can be compared with previous research examining associations between cognitive impairment and carotid atherosclerosis. A study conducted by Auperin et al. (Auperin et al., 1996a) did not identify any statistically significant correlations between carotid atherosclerosis and cognitive function in women; however, associations were observed between carotid plaque and mini-mental state examination scores (MMSE) and Digit Symbol Substitution Test (DSST) scores in men. The Cardiovascular Health Study (Johnston et al., 2004) found that presence of plaque was associated with lower performance on MMSE and DSST, but that this relationship was attenuated when accounting for risk factors related to vascular disease. Similarly, correlations between cIMT and decreased MMSE and DSST scores were weakened

when vascular risk factors were taken into consideration. In another study of individuals diagnosed with cardiovascular disease (Muller et al., 2007) higher carotid intima-media thickness (cIMT) was observed to be associated with poorer memory, but no correlations were observed in relation to processing or executive function; however, this study did not fully account for potentially confounding risk factors. Whitehall II (Singh-Manoux et al., 2008b) reported that cIMT showed no discernible correlation with cognitive state and memory. Another study (Gardener et al., 2017) also found no correlation between carotid plaque burden and cognition. Variability in study samples, cognitive testing methods and severity of carotid atherosclerosis probably contribute to some differences between studies. Another potential source of inter-study difference is the extent of cognitive reserve.(Stern, 2012) The neural implementation of cognition involves two key components: neural reserve, reflecting inter-individual differences in cognitive processing within a healthy brain, and neural compensation, encompassing adaptive changes in cognitive processing to address the challenges posed by brain pathology. Together, these components contribute to cognitive reserve, i.e. an individual's capacity to maintain cognitive function in the presence of neurological damage or pathology,(Stern, 2009, Stern, 2002) which may mitigate the effects of cerebrovascular disease and underly differential associations between the extent of cerebrovascular disease in an individual and its functional consequences. Cognitive reserve is likely to differ between different populations or samples, and this may contribute to differences between studies since cognitive reserve is influenced by many factors.(Corbo et al., 2023) These include education level and participation in intellectual and physical activities and social engagement throughout the lifespan. (Pettigrew and Soldan, 2019)

We observed that carotid plaques were linked to lower total brain volume in line with a prior study,(Ammirati et al., 2020) but this relationship was attenuated after full adjustment for risk factors. We also observed associations between the presence of carotid plaque and WM lesion volume that were independent of risk factors. This is consistent with the findings of a systematic review and meta-analysis,(Moroni et al., 2016a) which observed a 42% increased probability of WMH in individuals with carotid atherosclerosis in comparison to those without. However, Moroni et al., noted that the association between carotid atherosclerosis and brain outcomes could be attributable to shared risk factors that were not accounted for in their analysis. Our findings suggest that associations of WM lesion volume with presence of plaque cannot be fully accounted for by measured confounders. Another study (Romero et al., 2009c) also observed no association between common carotid CIMT and WMH, total brain volume or hippocampal volume after adjustment for risk factors, although the intime-media thickness of the internal carotid artery was associated with WMH and total brain volume. In the Northern Manhattan study (Della-Morte et al., 2018, Thurston et al., 2023) an intima-media thickness measure that was a composite of the intima media thickness of the common carotid artery, the bulb and the internal carotid was associated with WMH volume even after adjusting for risk factors; however they reported that associations for CIMT were not significant after adjustment. In our study of older people, the internal carotid artery was infrequently visualised, and it was not feasible to measure the intima-media thickness of the internal carotid artery reliably. It seems plausible that differences in method of assessment of carotid artery intima-media thickness, (composite intima-media thickness vs. CIMT) could also contribute to differences between studies. The other factor that could contribute to between study differences is varying degrees of cognitive reserve. as discussed above.

Our study has strengths and limitations. Strengths include that it: 1) uses a multi-ethnic population-based sample that includes the two major ethnic minorities in the UK; 2) carotid atherosclerosis was measured using standardised ultrasound protocols, which included assessment of plaque characteristics including PGSM and echogenicity; 3) cognition was assessed using domain-specific cognitive tests that have been validated in ethnic minority participants; 4) detailed brain imaging and analysis was performed; and comprehensive adjustment for possible confounders was possible due to the detailed phenotyping that was undertaken during the clinic visit. Limitations include cohort attrition which may have introduced bias and reduced the representativeness of the sample, the possible presence of residual or unmeasured confounding despite extensive phenotyping, the use of multiple comparisons which increases the likelihood of false discovery, and the cross-sectional design which precludes causal inference.

This cross-sectional study of a multi-ethnic cohort of individuals resident in UK, provides evidence that presence of carotid plaque, is associated with poorer cognitive function and brain health. Associations with CIMT or plaque characteristics were unconvincing once confounding had been accounted for. Whether subclinical atherosclerosis poses different risk at different ages and whether different locations, and or intensifying risk factor management can contribute to halting further cognitive impairment needs further exploration.

5 THE IMPACT OF CAROTID ARTERY ATHEROSCLEROSIS ON COGNITIVE FUNCTION IN THE MRC NATIONAL SURVEY OF HEALTH AND DEVELOPMENT (NSHD: THE BRITISH 1946 BIRTH COHORT). retrospective study

Abstract

Background Carotid artery atherosclerosis is implicated in cognitive decline. This chapter explores the association between measures of carotid artery atherosclerosis and subsequent cognitive function in the MRC National Survey of Health and Development (NSHD), a British birth cohort born in1946.

Methods 1,565 participants in NSHD had carotid atherosclerosis examined using ultrasound as part of a comprehensive clinic-based assessment at age 60-64 and subsequently, at age 69 cognitive performance was assessed again in the same individuals during a home visit. Analyses were performed using Mann Whitney rank tests, Spearman's correlation coefficients and multivariable regression analysis. Results are presented with 95% confidence intervals, and a complete case analysis was conducted for statistical inferences.

Results There was no convincing evidence of differences in cognitive performance at 69 in people with and without plaque in unadjusted analyses. Neither was there convincing evidence for correlations between plaque characteristics and cognitive performance. There was evidence of a weak correlation between higher CIMT and poorer memory at age 60. There was also evidence of correlation between higher carotid distensibility and better memory and visual search speed at age 60. At age 69 higher carotid distensibility correlated with poorer visual search speed and global cognition. After adjustment for confounders presence of plaque was associated with poorer visual search speed at age 60 but there were no other convincing associations. This association remained after adjustment for childhood cognition. There was no evidence of an association between carotid atherosclerosis and memory at age 69 or visual

search speed at age 69 adjusted for confounders, childhood cognition and performance at age 60.

Conclusions Contrary to expectations, this investigation within the MRC National Survey of Health and Development did not find strong or convincing links between carotid artery atherosclerosis and cognitive decline. There were some associations that were statistically significant, but these may represent chance findings given the multiple associations examined.

Introduction

The link between cardiovascular (CV) health and cognitive decline is a crucial issue at a time when the world's population is aging.(Samieri et al., 2018) Information acquisition, processing, storage, and utilization all depend on cognitive function, a term which refers to a collection of mental skills and abilities. Performance of cognitive tasks depends on memory, attention, linguistic abilities, problem-solving, and decision-making, to name just a few.(Kiely, 2014) Millions of individuals worldwide suffer from forms of cognitive impairment, putting a strain on patients, families, and healthcare systems.(Livingston et al., 2017) In addition to vascular cognitive impairment (VCI), other forms of cognitive impairment and dementia, such as Alzheimer's disease, are related to CV risk factors,(Gorelick et al., 2011b) probably reflecting multiple interlinked mechanisms linked to CV risk rather than a standalone disorder.(Desideri and Bocale, 2021) In Chapter 3, I showed using a systematic review and meta-analysis that there was inconsistent evidence that carotid artery atherosclerosis was linked to cognitive impairment.(Anbar et al., 2022b) This conclusion is consistent with that of others (Fresnais et al., 2021, Ihle-Hansen et al., 2021) showing that gaps persist in our understanding of the ways in which carotid artery atherosclerosis influences cognitive function.

Much of the current evidence on links between atherosclerosis and cognitive function is based on cross-sectional studies. Longitudinal investigations with extended follow-up durations may be required to capture the gradual evolution of cognitive impairment over time, as highlighted by the few longitudinal studies included in the Systematic Review and Meta-Analysis Chapter. Addressing these research gaps is important, as

it promises a more profound understanding of this complex link and the development of pragmatic approaches to preserve cognitive health in aging populations.

The primary objective of this chapter was to elucidate the relationship between carotid artery atherosclerosis and subsequent cognitive performance in a birth cohort of older age people in UK who had also undergone cognitive assessment in youth and repeated assessment of some cognitive tests at age 60-64 and 68-70.

Methods

Participants

The Medical Research Council National Survey of Health and Development (NSHD) is a National Birth Cohort that recruited 5,362 people born in the same week of 1946 in England, Scotland or Wales,(Wadsworth et al., 2006) and subsequently followed their health and development across the entire lifespan up to the present day (https://nshd.mrc.ac.uk/). Data have been gathered at regular intervals during the participants' lifetimes, including information from medical examinations, interviews, questionnaires, imaging and biological samples.

A total of 1565 participants were analysed from the 23rd follow-up conducted between 2006-2010 when they were aged 60-64. Further follow-ups were conducted as the participants aged, specifically at ages 68 and 70, to gather additional data. This longitudinal approach aimed to capture changes over time. clinical evaluations, including carotid ultrasound, were performed, and subsequently, following a post questionnaire at age 68, participants also underwent a follow-up home visit including tests of cognitive function when they were aged 68-70. Participants without ultrasound imaging

scans or cognitive function tests were excluded from the analysis (Figure 5.1). Ethical approval for the studies was obtained from the NRES Queen Square REC (14/LO/1073) and Scotland A REC (14/SS/ 1009). Research was conducted in accordance with the Helsinki Declaration and written, informed consent was obtained from the study member for each component of data collection. I undertook the critical task of data refinement, meticulously cleaning and organizing the information gathered by my colleagues. Specifically, I focused on selecting participants with plaques and conducted precise measurements for both plaques and intima-media thickness (IMT). Subsequently, I carried out comprehensive statistical analyses to derive meaningful insights from the data. Additionally, I wrote the first draft of the entire manuscript, taking responsibility for the subsequent writing and editing process. This involved synthesizing the research findings, methodologies, and results into a cohesive and well-articulated paper. Through my efforts, I aimed to enhance the overall clarity, coherence, and quality of the document, ensuring that it effectively communicates the significance of our research.

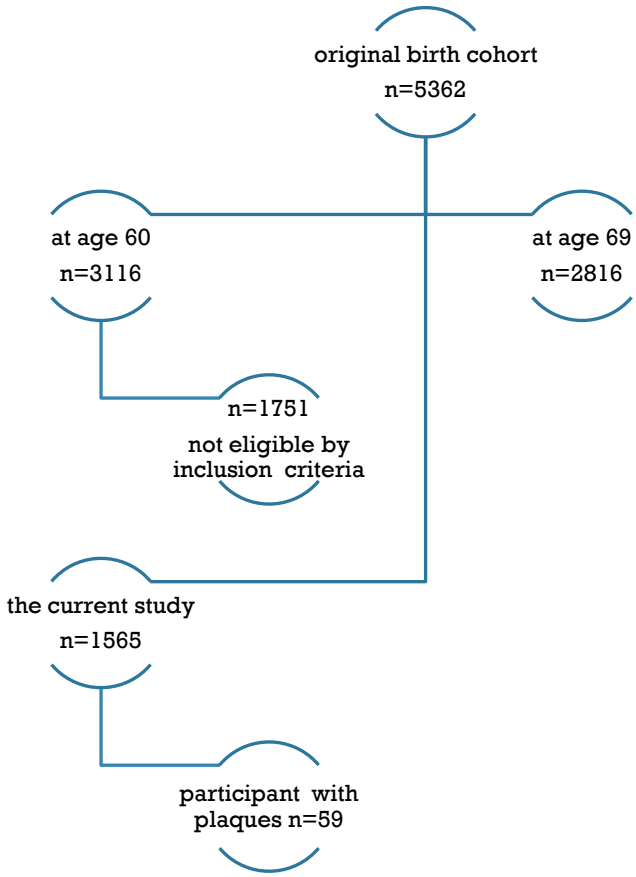

FIGURE 5. 1 FLOW DIAGRAM FOR NATIONAL SURVEY OF HEALTH AND DEVELOPMENT DATA USED IN THIS STUDY.

Investigations

Information on socio-demographic or socio-economic factors, medication or medical conditions, was collected from questionnaires in 2009 & 2015.

Common Carotid Intimal Medial Thickness and Carotid Plaque

B-mode ultrasound imaging was employed for evaluation of carotid intima-media thickness (CIMT), specifically focusing on the common carotid artery (CCA). in 2009 & 2015 Carotid ultrasounds were conducted by trained sonographers with expertise in vascular imaging by team member. During ultrasonography scans, six images per individual were captured, providing comprehensive coverage of the artery wall from three distinct angles on both the left and right sides. Certified sonographers conducted all measurements using the GE Vivid-I ultrasound system equipped with a high-resolution transducer (12MHz), adhering to a standardized imaging protocol. The CCA images were subjected to offline plaque measurement of CIMT using the Carotid Analyser (Iowa City, Iowa), which allows semi-automatic edge detection of the echogenic lines of the intima–media complex. A measure termed ‘carotid artery distensibility’ was derived from the same images and arterial segments used for CIMT measurement using the software. This was calculated as:

$$\frac{D_{max} - D_{min}}{D_{min}} \%$$

where D_{max} and D_{min} are the maximum and minimum diameters respectively over the cardiac cycle. This measure does not correspond to the usual definition of distensibility which is calculated per unit pressure change but corresponds to strain. We have used

the device's terminology throughout, but interpretations have been made assuming that this is a measure of strain, which is related to arterial stiffness. This can be regarded as related to atherosclerosis in some circumstances but is not a direct measure of it.(Cecelja et al., 2011)

Both CIMT and distensibility measurements were conducted by two readers at the central vascular laboratory of the Institute of Child Health, London. Within and between reader reliability was excellent (ICC > 0.9). Shear wave elastography, a method for measuring tissue elasticity, was not used due to its limited availability at the time of study. Instead, traditional methods were employed to ensure consistency and comparability with existing data.(Masi et al., 2014).

Cognitive function

Cognitive function was formally assessed when participants were 60-64 and 68-79 years old. Earlier assessments of intellectual ability based on the National Foundation for Educational Research tests were also conducted when participants were aged 8 to 26 years old. This longitudinal data collection provides a comprehensive view of cognitive changes over time using verbal and nonverbal aptitude tests created by the National Foundation for Educational Research. The tests comprised:

1. At age 8: nonverbal reasoning, pronunciation, vocabulary, and reading comprehension (sentence completion).
2. At age 11, verbal and nonverbal intelligence (series completion), addition, multiplication, subtraction, and division skills, as well as pronunciation and vocabulary skills comparable to those at age 8.

3. At age 15, Group Ability Test AH4 (verbal and nonverbal intelligence), Watts-Vernon Reading Test (sentence completion), and mathematics (arithmetic, geometry, trigonometry, and algebra)
4. At age 26, the Watts-Vernon Reading Test (as administered at age 15, but with an additional 10 harder questions to avoid a ceiling effect).

Scores were standardized to a mean of 0 and a standard deviation of 1 so that they could be averaged to give an overall cognitive function score for childhood, adolescence, and early adulthood.

Age 60-64

At age 60-64 the study used a variety of cognitive tests to evaluate trends in verbal memory, letter search speed, and reaction time. To test short-term verbal memory, participants in the Verbal Memory Test had to recollect words from a list of 15 items three times in a minute. The Letter Search Speed Test measured letter search speed by having participants quickly find and cross out the letters P and W in a 30 by 20 matrix within one minute. In the Simple Reaction Time Test, participants were timed on how quickly they pressed a button in response to a signal. The result was the mean reaction time across 20 trials. In the Choice Response Time Test, participants had to quickly push buttons that represented the numbers 1 through 4, with 40 trials total. The result was the mean response time for trials that were accurate. Together, these exams gave a complete evaluation of cognitive functioning.(Masi et al., 2018)

Age 68-70

The cognitive state of individuals at age 69-70 was assessed using a validated version of the Addenbrooke's Cognitive Examination-III (ACE-III), a comprehensive cognitive exam that evaluates attention/orientation, verbal fluency, memory, language, and

visuospatial skills. In addition, verbal episodic memory, motor speed and processing speed were assessed using same tests as at age 60-64.

Statistical analyses

The statistical analyses were carried out using Stata version 17.0 and 18.0. Continuous data was summarised using means and standard deviations (SD) or medians and interquartile ranges for skewed data. Categorical data were presented as counts and percentages. To assess the relationships between various cognitive domains (including global cognition, memory, executive functioning, and language (including short-term verbal memory (memory) at ages 60 and 69, visual search speed at ages 60 and 69, and a global measure of ACE-III at age 69) and carotid artery characteristics, we calculated Spearman's rank correlation coefficients (r_s) along with associated p-values.

We visually represented the comparison of different cognitive outcomes based on the presence or absence of plaque using box plots. To statistically evaluate these differences, we employed Mann-Whitney U tests, which are suitable for non-normally distributed data.

In further analyses, we utilized glm models to explore the associations between cognitive functioning outcomes (including global cognition, memory, executive functioning, and language) and various measures of carotid atherosclerosis with adjustment for potential confounders. Exposure measures included the presence of plaques, carotid stenosis >50%, the number of plaques, total plaque area, lowest GSM of all plaques, and CIMT. 4 models were used: model 1 involved minimal adjustments for a limited set of potential confounding factors, namely age and gender. In model 2, we performed adjustments including other potential confounding variables: educational

attainment, childhood social class, smoking status, glycosylated haemoglobin (HbA1c) levels, diabetes, alcohol consumption, body mass index (BMI), total cholesterol, triglycerides, hypertension, and hypertension medication.

For Model 3 was an extension of Model 2 where we adjusted for childhood cognition. This accounts for differences in cognition in early life and can be interpreted as modelling the change in cognition from this period. Model 4 also adjusted for cognition at age 60-64 so can be interpreted as a change model over the age period 60-64 to 68-70, i.e. approximately a 6-8 year period. Models 3 and 4 can provide valuable insights into the trajectory of cognitive decline in relation to atherosclerosis at age 60-64. The selection of confounding factors was based on prior knowledge based on relevant literature. Additionally, we explored the potential effect modification by sex in all our models by including a sex interaction term. However, in all cases, we found no substantial gender-related effects, so only pooled data is shown.

Regression results were summarized as regression coefficients accompanied by 95% confidence intervals. We ensured that our statistical models adhered to crucial assumptions, such as the normal distribution of residuals, homoskedasticity, and the absence of multicollinearity. In cases where homoskedasticity assumptions were not met, we applied robust regression using the White-Huber Sandwich Estimator.

For our primary analysis, we conducted a complete case analysis (listwise deletion), assuming that the missing data were independent of the outcomes. Statistical inferences were based on a combination of factors, including p-values, effect sizes, and confidence intervals.

Results

Table 5.1 provides an overview of the characteristics of the participants. The cohort consisted of 1565 individuals, (mean age was 63.2 years, 48% male). Slightly more than half had hypertension, 6.4% had diabetes and 8.7% were current smokers. Figures (5.2 A-F) show a simple comparison of cognitive measures at age 68-70 by presence of plaque at age 60-64.

TABLE 1.1 SAMPLE CHARACTERISTICS AT AGE 60-64

Variables	N	Mean/%	SD
Age, y	1565	63.2	14.8
Male sex	753	48%	
Height, m	1438	1.6	0.08
Weight, kg	409	77	14
Body mass index, kg/m^2	1565	27.9	4.5
Moderate physical activity	1056	67.5%	
Total cholesterol, mmol/l	1565	9.6	17.2
Triglycerides, mmol/l	1565	6.8	22.7
HbA1c, mmol/mol	1565	201.5	314.2
Hypertension	934	59.6%	
Diabetes mellitus	100	6.4%	
Coronary artery bypass grafting (CABG)	14	1%	
Any stroke or transient ischaemic attack	35	2%	

Childhood cognition Z score	1447	0.21	0.79
Educational attainment			
No qualifications	298	19.7%	
Vocational only	176	11.3%	
A level	494	31.5%	
ACE-III: visuospatial at 69	1151	15.6	1.8
ACE-III: memory at 69	1157	23.9	2.6
ACE-III: attention at 69	1156	16.8	1.8
ACE-III: language at 69	1147	25.3	1.0
ACE-III: total score (100max) at 69	1144	92.3	5.4
Visual letter search speed at 60 (Max 600)	1543	271.1	69.7
Visual letter search speed at 69 (Max 600)	1364	266.3	71.3
Word list memory test at 60 (Max 45)	1540	24.9	6.0
Word list memory test at 69 (Max 45)	1565	18.8	11.7
Global cognition at age 69 (Max100)	1144	92.3	5.4
Current smoker	131	8.7%	

Presence of one or more carotid plaques	65	3.8%	
Carotid artery distensibility, %	1557	6.74	1.7
Carotid intima-media thick-ness, mm	1565	0.68	0.1

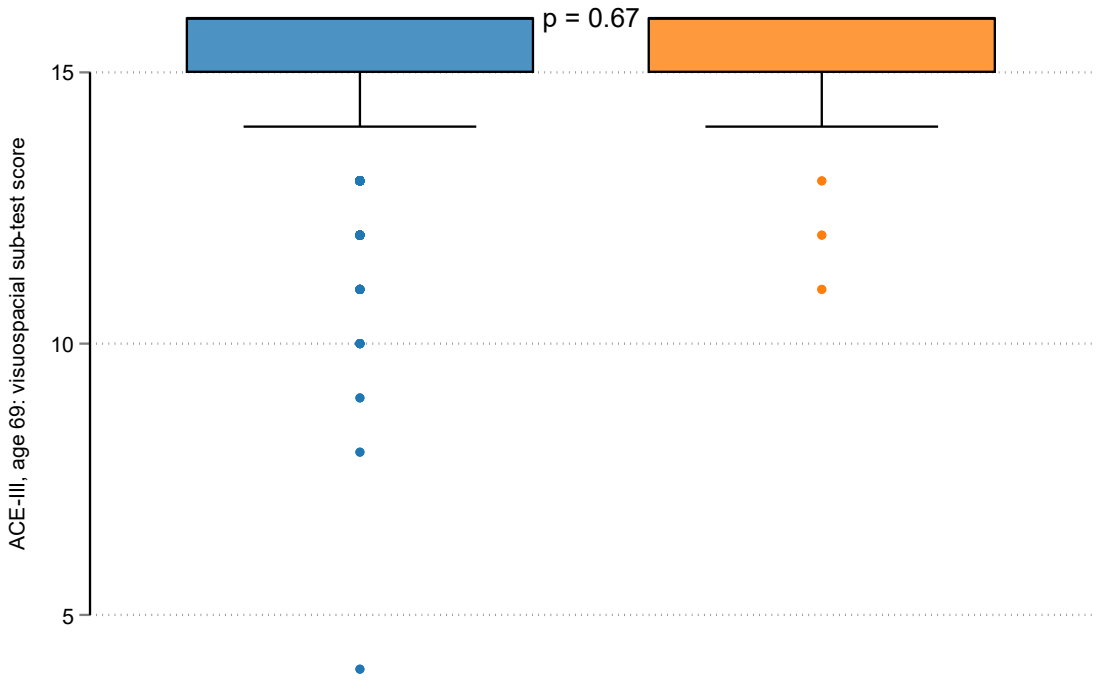

FIGURE 5. 2 A) COMPARISON OF ACEIII (VISUOSPATIAL SUBSET) AT AGE 68-70 BY PRESENCE OF PLAQUE AT AGE 60-64. PEOPLE WITHOUT PLAQUES (BLUE) AND WITH (ORANGE).

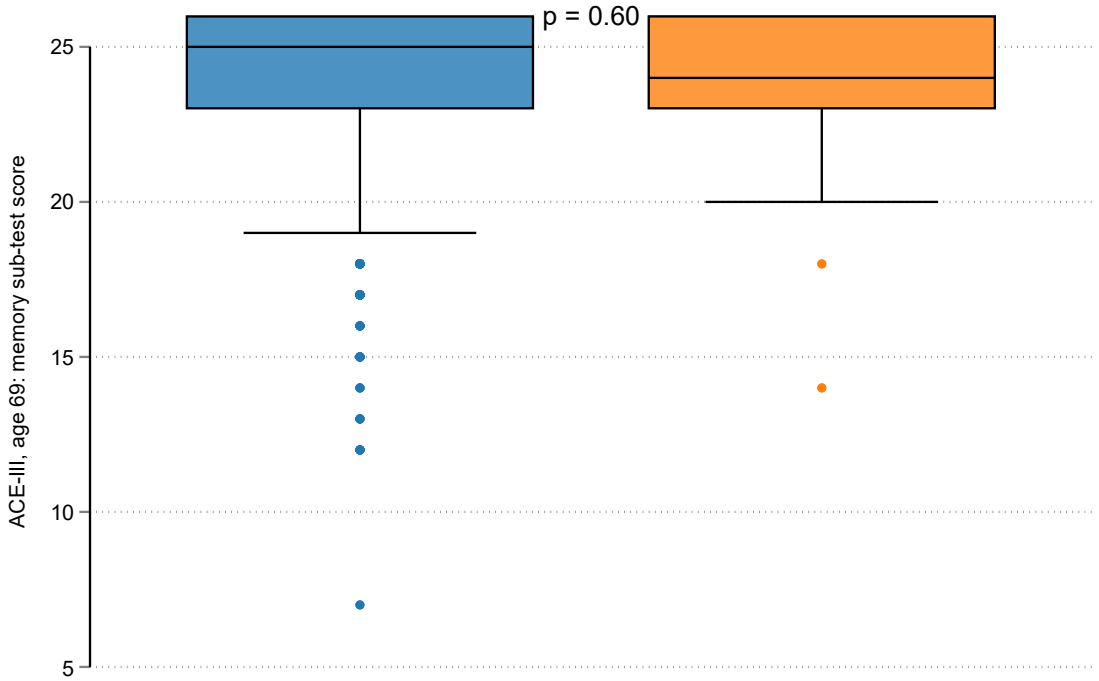

FIGURE 5.2 B) COMPARISON OF ACEIII (MEMORY SUBSET) AT AGE 68-70 BY PRESENCE OF PLAQUE AT AGE 60-64. PEOPLE WITHOUT PLAQUES (BLUE) AND WITH (ORANGE).

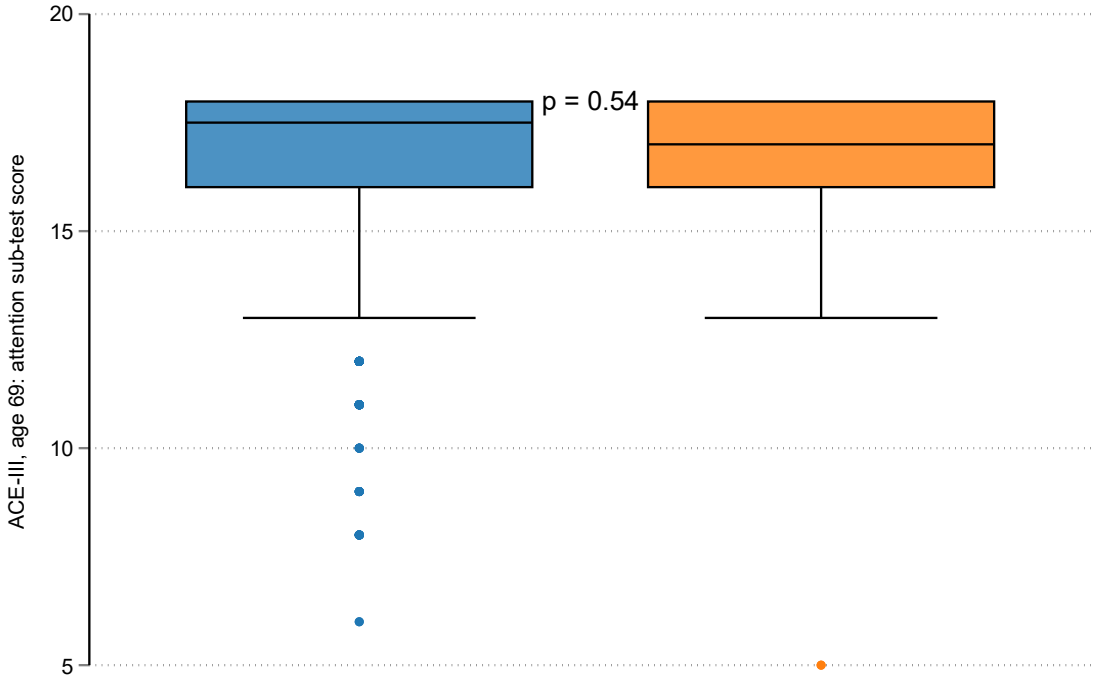

FIGURE 5. 2 C) COMPARISON OF ACEIII (ATTENTION SUBSET) AT AGE 68-70 BY PRESENCE OF PLAQUE AT AGE 60-64. PEOPLE WITHOUT PLAQUES (BLUE) AND WITH (ORANGE).

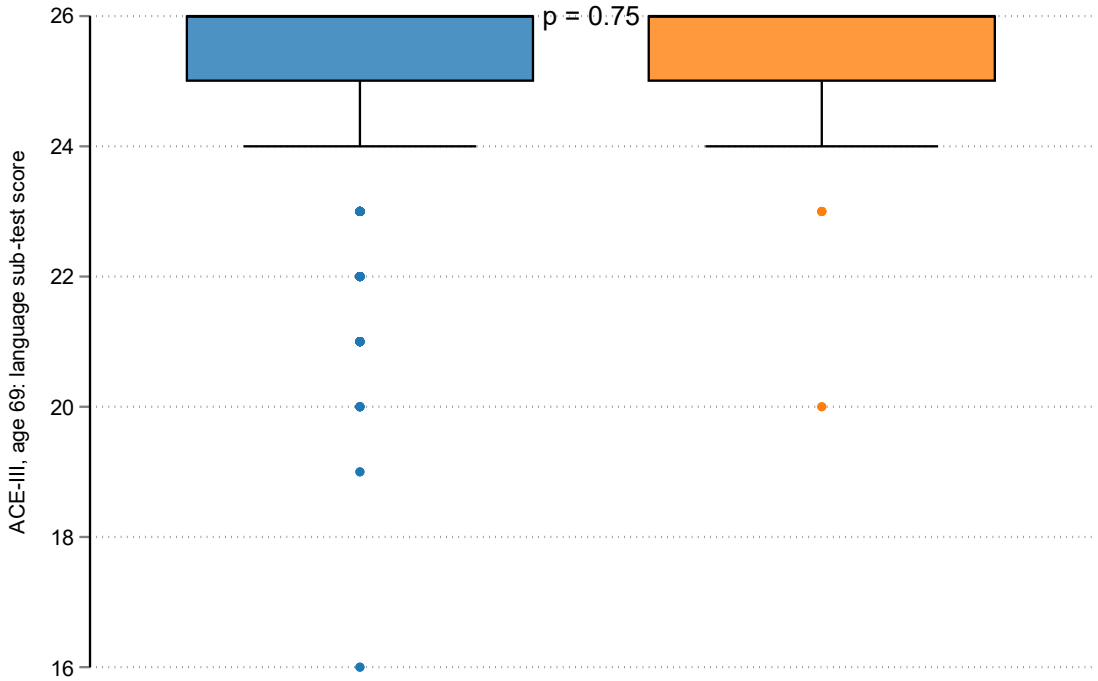

FIGURE 5. 2 D) COMPARISON OF ACEIII (LANGUAGE SUBSET) AT AGE 68-70 BY PRESENCE OF PLAQUE AT AGE 60-64. PEOPLE WITHOUT PLAQUES (BLUE) AND WITH (ORANGE).

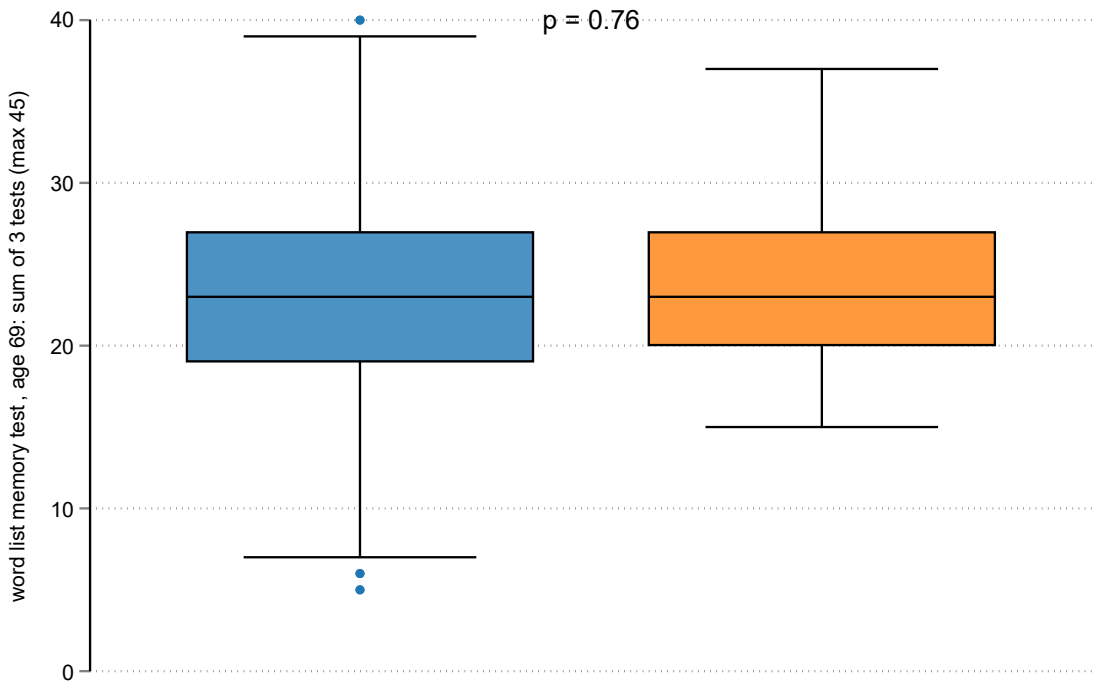

FIGURE 5. 2 E) COMPARISON OF WORD LIST MEMORY TEST AT AGE 68-70 BY PRESENCE OF PLAQUE AT AGE 60-64. PEOPLE WITHOUT PLAQUES (BLUE) AND WITH (ORANGE).

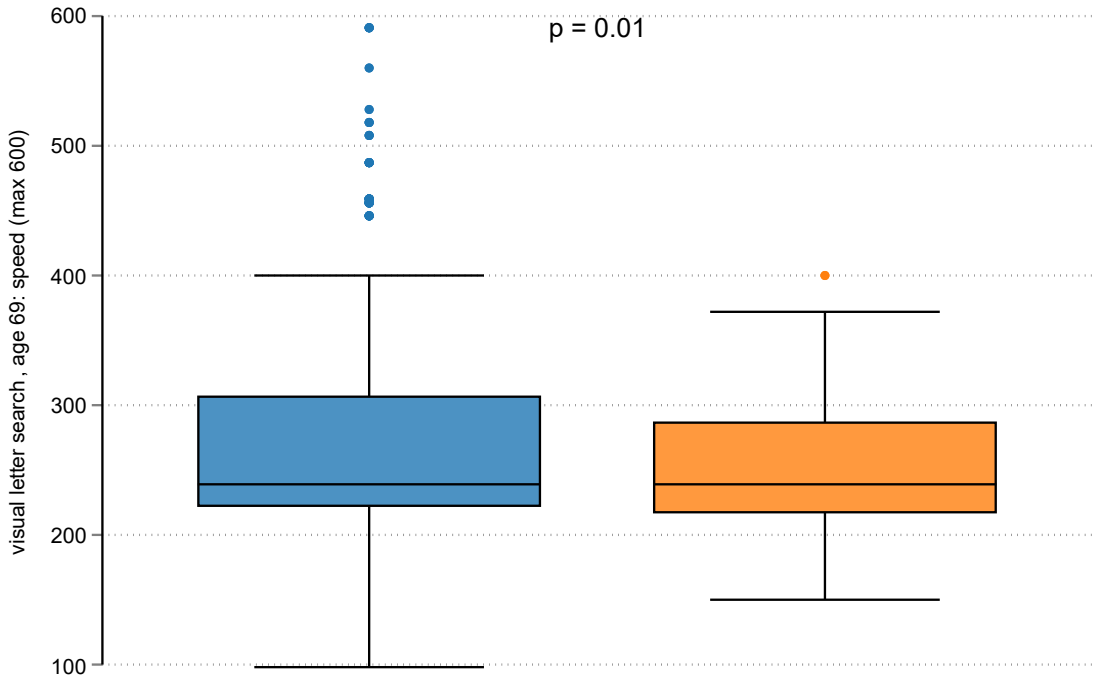

FIGURE 5. 2 F) COMPARISON OF VISUAL LETTER SEARCH AT AGE 68-70 BY PRESENCE OF PLAQUE AT AGE 60-64. PEOPLE WITHOUT PLAQUES (BLUE) AND WITH (ORANGE).

Table 5.2 shows rank correlations between plaque characteristics, CIMT, carotid distensibility and cognitive performance measures. With the exception of memory performance at age 60 which showed a weak negative connection (r_S = -0.067, p = 0.013) with CIMT, there were no convincing correlations with measures of carotid atherosclerosis. Carotid artery distensibility, (the inverse of carotid artery stiffness) correlated with better member and visual search speed at age 60, although the coefficients were weak (<0.01). In contrast, carotid artery distensibility at age 60 was inversely correlated with visual search speed and ACE-III global cognitive performance at age 69, although again the correlations were weak.

TABLE 5.2 SPEARMAN CORRELATION COEFFICIENTS FOR THE RELATIONSHIP BETWEEN PLAQUE CHARACTERISTICS, CIMT AND CAROTID DISTENSIBILITY WITH COGNITIVE FUNCTIONAL DOMAINS

Cognitive domain	Plaque area	Plaque height	Plaque length	GSM	CIMT	Carotid distensibility
Memory at 60	r_s = -0.081 p = 0.56	r_s = -0.022 p = 0.88	r_s = -0.201 p = 0.12	r_s = -0.251 p = 0.11	r_s = - 0.067 p = 0.01	r_s = 0.080 p = 0.002
Visual search speed, age 60	r_s = -0.198 p = 0.14	r_s = -0.148 p = 0.28	r_s = -0.053 p = 0.66	r_s = -0.016 p = 0.89	r_s = -0.011 p = 0.66	r_s = -0.066 p = 0.01
Memory at 69	r_s = -0.057 p = 0.66	r_s = 0.312 p = 0.79	r_s = -0.038 p = 0.83	r_s = 0.001 p > 0.99	r_s = -0.021 p = 0.24	r_s = 0.004 p = 0.87
Visual search speed, age 69	r_s = -0.182 p = 0.21	r_s = -0.108 p = 0.49	r_s = -0.039 p = 0.81	r_s = -0.597 p = 0.71	r_s = -0.003 p = 0.96	r_s = -0.055 p = 0.045
Global measure ACE-III age 69	r_s = 0.124 p = 0.48	r_s = 0.178 p = 0.28	r_s = 0.093 p = 0.59	r_s = -0.169 p = 0.38	r_s = -0.039 p = 0.16	r_s = -0.063 p = 0.032

Abbreviations: CIMT, common carotid artery intima media thickness, GSM, grey scale median.

Associations between measures of carotid atherosclerosis and cognitive function with adjustment for potential confounding

The analysis of the relationship between measures of carotid atherosclerosis, global cognition at 69, and memory at both ages 60-64 and 69 in figures (5.3 A-E) did not reveal any convincing associations with measures of carotid atherosclerosis in either Model 1 (minimal adjustment) or Model 2 (full adjustment). Presence of plaque which was associated with reduced visual search speed at age 60. It should be noted however that in some cases the estimates were not very precise, and the confidence intervals were compatible with moderate effect sizes. Carotid distensibility (strain) was positively associated with memory at age 60 and inversely with visual search speed at age 69 even after full adjustment for confounding (model 2), but no convincing associations were observed with memory at age 69 or visual search speed at age 60.

In Model 3, which incorporates adjustments for child cognition and can be viewed as a crude measure of cognitive decline since childhood, we observed no convincing associations between cognitive measures and carotid atherosclerosis except for a negative association between presence of plaque and visual search speed at age 60. The direction and magnitude of the association between plaque and visual search speed at age 69 was similar but the relationship was not statistically significant. Higher carotid distensibility was associated with greater preservation of memory at age 60, but a greater decline in visual search speed at age 69.

In model 4 which assesses decline in cognitive performance between age 60 and 69, and for which only memory and visual search speed data were available, there was no convincing evidence of any associations with carotid atherosclerosis. There was a weak negative relationship between carotid distensibility and visual search speed.

In this analysis, we conducted a regression study to explore the relationships between carotid intima-media thickness (CIMT) and plaque characteristics with cognitive performance. The model was adjusted for age and sex (Model 1), and the results are presented in Table 5.3. I investigated various cognitive domains, including Memory (at ages 60 and 69), Visual Search Speed (at ages 60 and 69), and Global Measure ACE-III (at age 69). The plaque characteristics under examination were Plaque Area, Plaque Height, Plaque Length, Presence of Plaque, CIMT, and Carotid Distensibility. For each cognitive domain and plaque characteristic, the regression coefficient (β), along with its 95% confidence interval in parentheses is shown. The tables follow a similar structure for other cognitive domains, plaque characteristics, and age groups, offering a comprehensive overview of the relationships between carotid measures and cognitive performance in the specified model. In Table 5.4, the regression analysis was expanded by including further revisions to Model 2. This model adjusted for education, childhood socioeconomic class, smoking, HbA1c levels, diabetes, alcohol use, BMI, total cholesterol, triglycerides, hypertension, and hypertension medication. Table 5.5 extends Model 3's analysis by including childhood cognition as an extra adjustment and with this adjustment the model can be considered as a measure of change in cognition since childhood. The relationships between carotid measurements and cognitive function are investigated for a variety of cognitive domains and plaque types. Finally, Table 5.6 displays the findings of Model 4, which includes performance at age 60 as an extra adjustment. This final model (which is limited to memory and visual search speed as outcomes since these were the only two domains that were measured at 60 and 69) can be interpreted as a model of change over the period 60 to 69.

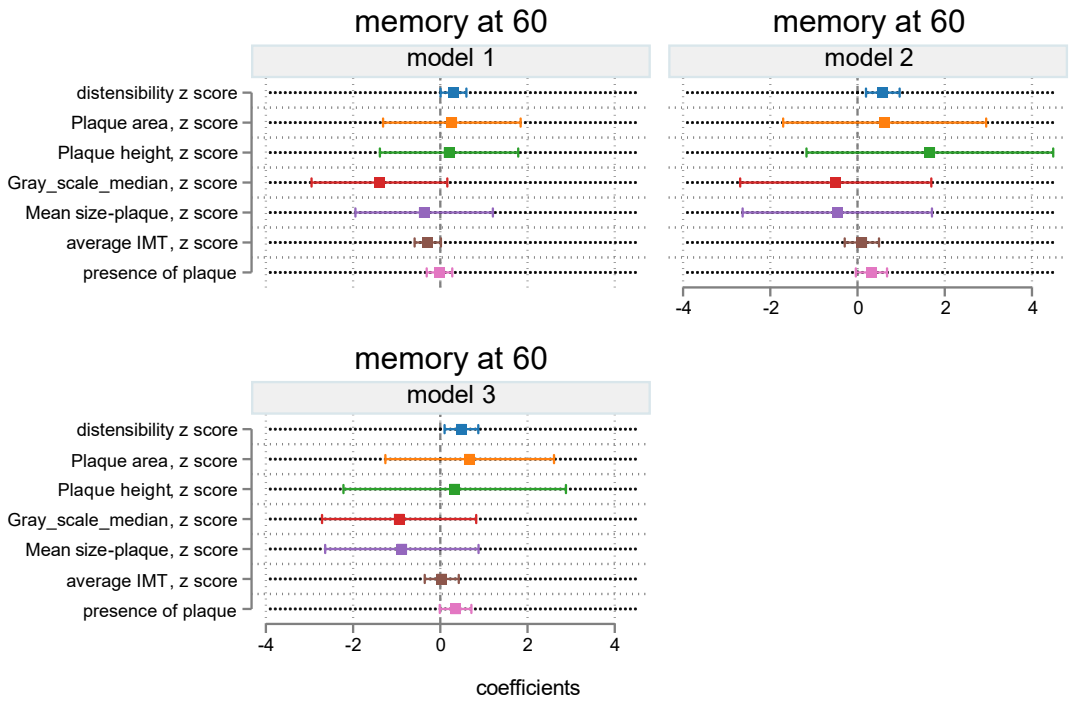

FIGURE 5.3 A) FOREST PLOTS OF THE STANDARDIZED REGRESSION COEFFICIENTS BETWEEN MEASURES OF CAROTID ATHEROSCLEROSIS AND MEMORY AT AGE 60.

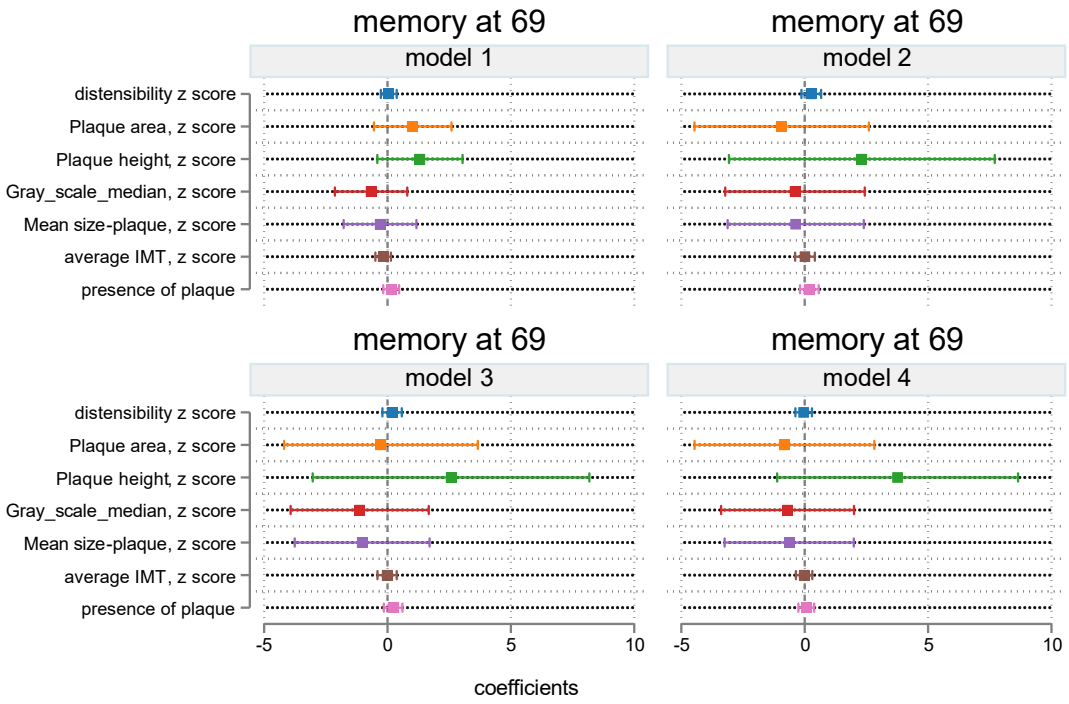

FIGURE 5.3 B) FOREST PLOTS OF THE STANDARDIZED REGRESSION COEFFICIENTS BETWEEN MEASURES OF CAROTID ATHEROSCLEROSIS AND MEMORY AT AGE 69.

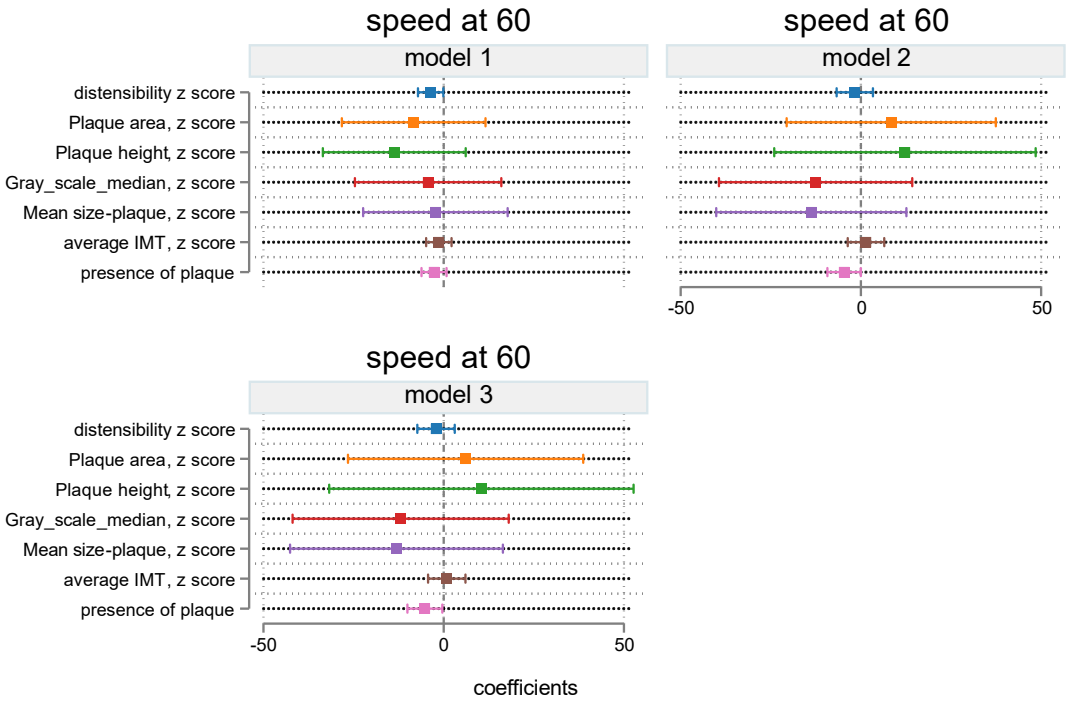

FIGURE 5.3 C) FOREST PLOTS OF THE STANDARDIZED REGRESSION COEFFICIENTS BETWEEN MEASURES OF CAROTID ATHEROSCLEROSIS AND VISUAL SEARCH SPEED AT AGE 60.

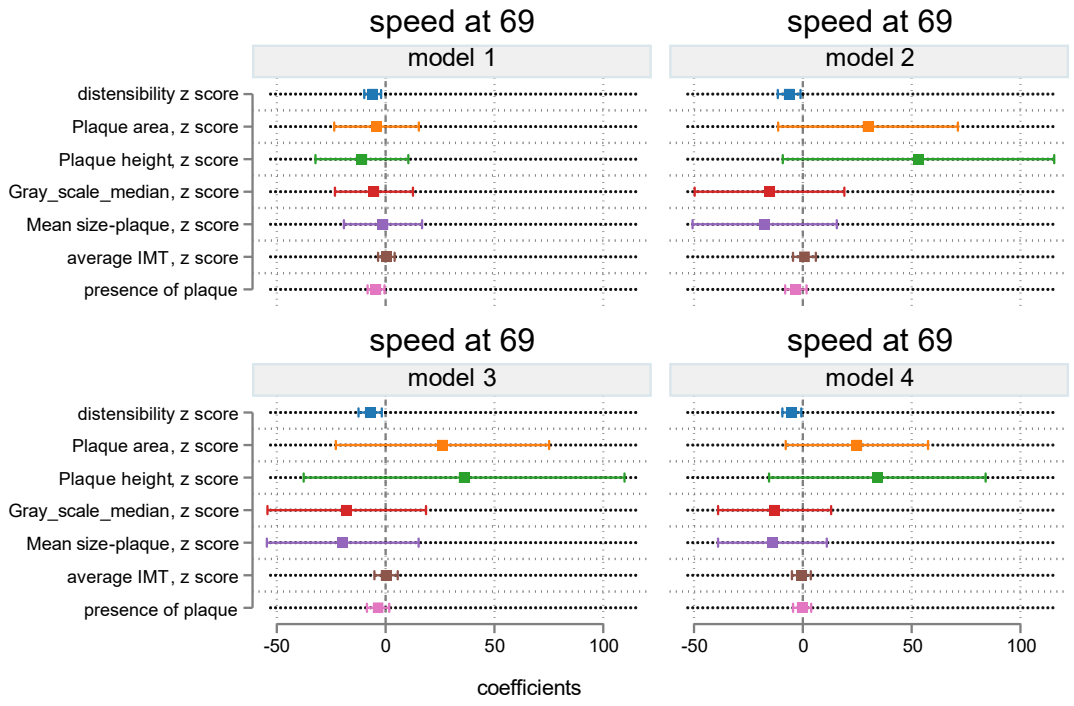

FIGURE 5.3 D) FOREST PLOTS OF THE STANDARDIZED REGRESSION COEFFICIENTS BETWEEN MEASURES OF CAROTID ATHEROSCLEROSIS AND VISUAL SEARCH SPEED AT AGE 69.

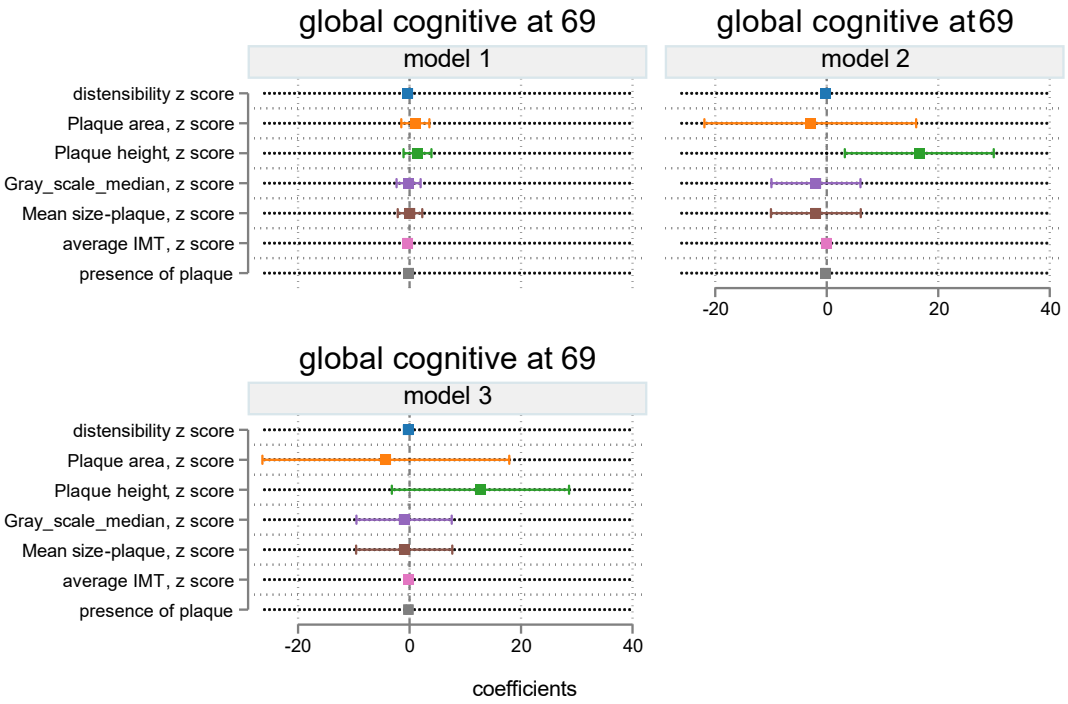

FIGURE 5.3 E) FOREST PLOTS OF THE STANDARDIZED REGRESSION COEFFICIENTS BETWEEN MEASURES OF CAROTID ATHEROSCLEROSIS AND GLOBAL COGNITION (ACE-III) AT AGE 69.

TABLE 5.3 REGRESSION COEFFICIENTS, B, (95% CONFIDENCE INTERVAL) AND P VALUES FOR ASSOCIATIONS OF CAROTID INTIMA-MEDIA AND PLAQUE CHARACTERISTICS WITH COGNITIVE PERFORMANCE AFTER ADJUSTMENT (MODEL 1: AGE, SEX).

Cognitive domain	Plaque area	Plaque height	Plaque length	Presence of plaque	CIMT	Carotid Distensibility
Memory, age 60	β = 0.0 (-0.0, 0.1) p = 0.736	β = 0.1 (-0.8, 1.1) p = 0.806	β = -0.1 (-0.4, 0.2) p = 0.516	β = -0.0 (-1.6, 1.4) p = 0.900	β = -2.2 (-4.5, 0.1) p = 0.061	β = 0.7 (0.0, 0.3) p = 0.040
Memory, age 69	β = 0.0 (-0.0, 0.1) p = 0.176	β = 0.8 (-0.2, 1.7) p = 0.132	β = 0.0 (-0.2, 0.2) p = 0.996	β = 0.7 (-0.8, 2.7) p = 0.326	β = -1.5 (-3.8, 1.0) p = 0.269	β = 0.0 (-0.1, 0.21) p = 0.756
Visual search speed, age 60	β = -0.5 (-1.8, 0.7) p = 0.406	β = -8.5 (-21.8, 3.7) p = 0.106	β = 0.16 (-3.8, 4.1) p = 0.956	β = -14.0 (-1.8, 0.7) p = 0.406	β = -10.5 (-38.8, 16.9) p = 0.453	β = -2.1 (-4.1, -0.0) p = 0.044
Visual search speed, age 69	β = -0.2 (-1.5, 0.9) p = 0.667	β = -7.5 (-21.8, 6.7) p = 0.306	β = 0.3 (-3.1, 3.7) p = 0.840	β = -23.5 (-43.8, -2.9) p = 0.026	β = 2.5 (-27.8, 32.0) p = 0.866	β = -3.5 (-5.8, -1.2) p = 0.003
Global measure ACE-III age 69	β = 0.1 (-0.1, 0.2) p = 0.407	β = 0.9 (-0.7, 2.6) p = 0.257	β = 0.0 (-0.4, 0.5) p = 0.864	β = -0.7 (-2.5, 1.1) p = 0.472	β = -2.5 (-4.9, 0.1) p = 0.063	β = -0.2 (-0.4, 0.0) p = 0.071
Abbreviations as in Table 5.2						

TABEL 5.4 REGRESSION COEFFICIENTS, B, (95% CONFIDENCE INTERVAL) AND P VALUES FOR ASSOCIATIONS OF CAROTID INTIMA-MEDIA AND PLAQUE CHARACTERISTICS WITH COGNITIVE PERFORMANCE AFTER ADJUSTMENT (MODEL 2: MODEL 1 + EDUCATION, CHILDHOOD SOCIAL CLASS, SMOKING, HBA1C LEVELS, DIABETES, ALCOHOL CONSUMPTION, BMI, TOTAL CHOLESTEROL, TRIGLYCERIDES, HYPERTENSION, AND HYPERTENSION MEDICATION)

Cognitive do-main	Plaque area	Plaque height	Plaque length	Presence of plaque	CIMT	Carotid Distensibility
Memory at 60	β = 0.0 (-0.1, 0.1) p = 0.581	β = 1.0 (-0.8, 2.7) p = 0.234	β = -0.1 (-0.8, 0.4) p = 0.673	β = 1.5 (-0.2, 3.5) p = 0.080	β = 0.7 (-2.2, 3.7) p = 0.619	β = 0.3 (0.1, 0.5) p = 0.003
Memory at 69	β = -0.0 (-0.2, 0.1) p = 0.586	β = 1.5 (-2.0, 5.0) p = 0.376	β = -0.3 (-1.0, 0.3) p = 0.286	β = 0.9 (-0.9, 2.9) p = 0.326	β = 0.0 (-3.0, 3.2) p = 0.966	β = 0.1 (-0.0, 0.3) p = 0.196
Visual search speed, age 60	β = 0.5 (-1.3, 2.4) p = 0.55	β = 8.0 (-15.8, 31.7) p = 0.486	β = 1.9 (-5.2, 9.7) p = 0.546	β = -24.5 (-48.8, -0.11) p = 0.040	β = 11.5 (-28.8, 50.7) p = 0.584	β = -0.9 (-3.8, 1.9) p = 0.506
Visual search speed, age 69	β = 1.9 (-0.8, 4.7) p = 0.140	β = 33.6 (-6.8, 75.7) p = 0.085	β = 4.2 (-4.8, 12.8) p = 0.296	β = -16.5 (-42.8, 9.0) p = 0.206	β = 5.7 (-35.8, 46.7) p = 0.709	β = -3.5 (-6.7, -0.6) p = 0.018
Global measure ACE-III age 69	β = -0.2 (-1.4, 1.0) p = 0.717	β = 10.9 (2.1, 19.6) p = 0.023	β = -1.3 (-4.1, 1.6) p = 0.313	β = -1.0 (-3.1, 1.1) p = 0.357	β = -0.6 (-3.7, 2.4) p = 0.678	β = -0.13 (-0.4, 0.1) p = 0.273
Abbreviations as in Table 5.2						

TABLE 5.5 REGRESSION COEFFICIENTS, B, (95% CONFIDENCE INTERVAL) AND P VALUES FOR ASSOCIATIONS OF CAROTID INTIMA-MEDIA AND PLAQUE CHARACTERISTICS WITH COGNITIVE PERFORMANCE AFTER ADJUSTMENT (MODEL 3: MODEL 2 + CHILDHOOD COGNITION).

Cognitive domain	Plaque area	Plaque height	Plaque length	Presence of plaque	CIMT	Carotid Distensibility
Memory at 60	β = 0.2 (-1.4, 1.8) p = 0.789	β = -0.5 (-1.8, 0.7) p = 0.406	β = 0.0 (-0.4, 0.6) p = 0.738	β = 1.8 (-0.0, 3.7) p = 0.058	β = -0.5 (-1.8, 0.7) p = 0.406	β = 0.2 (0.0, 0.5) p = 0.014
Memory at 69	β = -0.0 (-0.2, 0.2) p = 0.883	β = 1.5 (-1.9, 5.7) p = 0.334	β = -0.1 (-1.0, 0.6) p = 0.612	β = 1.1 (-0.8, 3.1) p = 0.236	β = -0.1 (-3.1, 2.9) p = 0.936	β = 0.1 (-0.1, 0.3) p = 0.336
Visual search speed, age 60	β = 0.3 (-1.7, 2.4) p = 0.69	β = -6.5 (-20.8, 34.7) p = 0.606	β = 1.5 (-7.2, 10.2) p = 0.796	β = -27.5 (-52.8, -2.7) p = 0.034	β = 6.5 (-33.8, 46.7) p = 0.746	β = -1.2 (-4.8, 1.7) p = 0.426
Visual search speed, age 69	β = 1.5 (-1.4, 4.7) p = 0.256	β = 23.5 (-24.4, 71.7) p = 0.306	β = 3.8 (-6.8, 14.7) p = 0.456	β = -18.5 (-45.8, 8.7) p = 0.146	β = 1.5 (-40.1, 43.7) p = 0.940	β = -4.1 (-7.8, -1.7) p = 0.009
Global measure ACE-III age 69	β = -0.3 (-1.7, 1.2) p = 0.622	β = 8.3 (-2.1, 18.8) p = 0.090	β = -1.6 (-4.7, 1.5) p = 0.226	β = -1.0 (-3.1, 1.0) p = 0.321	β = -1.0 (-4.0, 2.0) p = 0.507	β = -0.16 (-0.4, 0.1) p = 0.164
Abbreviations as in Table 5.2						

TABLE 5.6. REGRESSION COEFFICIENTS, B, (95% CONFIDENCE INTERVAL) AND P VALUES FOR ASSOCIATIONS OF CAROTID INTIMA-MEDIA AND PLAQUE CHARACTERISTICS WITH COGNITIVE PERFORMANCE AFTER ADJUSTMENT (MODEL 4: MODEL 3 + PERFORMANCE AT AGE 60).

Cognitive domain	Plaque area	Plaque height	Plaque length	Presence of plaque	CIMT	Carotid Distensibility
Memory at 69	β = -0.1 (-0.3, 0.2) p = 0.626	β = 2.5 (-0.7, 5.7) p = 0.116	β = -0.3 (-1.1, 0.4) p = 0.370	β = 0.3 (-1.3, 2.0) p = 0.696	β = -0.2 (-2.8, 2.4) p = 0.889	β = -0.0 (-0.2, 0.2) p = 0.805
Visual search speed, age 69	β = 1.6 (-0.5, 3.7) p = 0.121	β = 22.4 (-10.2, 55.0) p = 0.156	β = 4.2 (-3.2, 11.5) p = 0.236	β = -1.7 (-23.5, 20.1) p = 0.879	β = -5.2 (-39.0, 28.6) p = 0.763	β = -2.9 (-5.5, -0.4) p = 0.023
Abbreviations as in Table 5.2						

Discussion

In this study, the primary objective was to investigate whether there was an association between the presence of carotid artery atherosclerosis and subsequent cognitive function in participants in NSHD, as previously explored in this thesis in a cross-sectional analysis in SABRE. In addition, I wanted to determine whether individuals with carotid plaques showed evidence of a decline in cognitive function compared to their counterparts without such plaques. This was possible due to the availability of assessments of cognitive ability in childhood and, in some cases, repeat measures of cognitive tests at age 60-64 (abbreviated as age 60) and 68-70 (abbreviated as age 69).

Unlike in SABRE, comparison of people with and without plaque in unadjusted comparisons showed little difference in cognitive performance. This is probably largely due to the small variation in age in NSHD (who were all born in a single week of1946), since age was a major confounder in SABRE. There was little evidence of a correlation between plaque measures and measures of cognitive performance at either age 60 or age 69. A weak negative association between CIMT and memory at 60, although plausible, should be viewed in the light of the multiple comparisons undertaken and the possibility of false positive discovery. Further analysis including adjustment for potential confounders revealed few convincing associations. An association between presence of plaque and poorer visual search speed at age 60 is mechanistically credible but could be a chance finding given the multiple associations examined.

These generally negative findings contrast to some extent with a prior longitudinal study. Zhong et al. (Zhong et al., 2012b) reported an association between CIMT at baseline and incidence of cognitive impairment over 10 years of follow-up, although

no association with presence of plaque was observed in their study, consistent with our observations.

While not a direct measure of carotid atherosclerosis, our study did reveal an inverse correlation between carotid distensibility and memory function in individuals aged 60, in line with the work of Duncombe et al.(Wadsworth et al., 2006) This finding suggests a potential connection between reduced carotid distensibility, a crude measure of arterial stiffness, and cognitive impairment in the realm of memory function. Nevertheless, it must be acknowledged that the carotid distensibility measure provided by the Carotid Analyser software is not really a measure of distensibility but a measure of strain (normalized length change), so this measure will also be influenced by the distending carotid pulse pressure. No other significant associations were observed between plaque variables and memory performance at age 69, visual search speed at both ages 60 and 69, or the overall cognitive measure at age 69, which is consistent with prior research by others.(Wendell et al., 2012, Wolf, 2012)

It is conceivable that additional variables, such as genetic predisposition, or cerebrovascular ailments, which are not assessed in this particular investigation could potentially exert a more pronounced influence on the manifestation of cognitive impairment, as suggested by Falk.(Falk, 2006) Furthermore, it is acknowledged that cognitive decline is a complex phenomenon influenced by various factors, both vascular and non-vascular that could contribute to variable findings between different cohorts.(Insull, 2009, Libby et al., 2002)

The interpretation of the findings of this study should be undertaken within the framework of various limitations. The study was performed in a British birth cohort with attendees tending to be biased toward healthy individuals. Nevertheless, the sample

remains reasonably representative of people born in UK in the post-war period.(Stafford et al., 2013) It is also important to acknowledge that the generalizability of the findings to other populations or ethnic groups may be restricted, as indicated by Mackinnon et al.(Mackinnon et al., 2004) It is also relevant that only 4% of individual had carotid plaques and the change in cognition performance over the follow-up over a median of 6 years of follow-up was evident (see Table 5.1), but not large. This restriction of range of exposure and outcome will have limited the ability to detect small or subtle effects of carotid atherosclerosis on cognitive performance. For example, most results for ACE-III, although consistent with a null effect, are also frequently compatible with reductions of 2 to 4 ACE-III points based on the 95% confidence intervals (e.g. Table 5.5). Future investigations encompassing larger and more heterogeneous cohorts would be valuable.

The study also has strengths. First and foremost, the study made use of data derived from the MRC National Survey of Health and Development (NSHD), which is the oldest national birth cohort study in the United Kingdom and made use of meticulously standardized measures and assessments, such as ultrasound imaging, cognitive tests, and questionnaires performed at age 60 and 69.

In conclusion this study found no compelling evidence for a strong association between carotid atherosclerosis and cognitive decline. Some suggestive findings with respect to carotid distensibility should be explored further using more conventional measures of carotid artery stiffness and elastic properties.

Chapter 6 General discussion

In the last chapter in my thesis, we aim to discuss briefly the main findings and clinical implications of the work presented in the thesis.

In chapter 2 we performed a systematic review which identified 31 studies investigating the relationship between carotid atherosclerosis and MMSE scores. we found inconsistent evidence of a cross-sectional association between carotid artery atherosclerosis and poorer MMSE scores, with only 15 out of the 31 studies showing some evidence of an association. The discrepancies in findings may be attributable to factors such as sample size, and limitations of the MMSE in detecting mild cognitive impairment A significant benefit of longitudinal study over cross-sectional research is its ability to trace changes over time within individuals and show causality. Some of the problems they address include selection bias and whether cognitive deterioration as evaluated by the MMSE occurs before or after carotid artery disease. Improved control over confounding factors, including drug usage or lifestyle changes, is another benefit of longitudinal research. Therefore, the incorporation of longitudinal data would improve comprehension and the capacity to make trustworthy inferences regarding the correlation between MMSE scores and carotid artery atherosclerosis.

Based on this analysis it appeared that evidence for an association between carotid atherosclerosis and cognitive impairment was inconclusive, and further research was needed to elucidate underlying mechanisms and perhaps identify specific subgroups

that may be more vulnerable. This knowledge, in turn, may have implications for preventive strategies and targeted interventions in populations at risk for cardiovascular and cognitive health challenges.

In chapter 3 we investigated ethnic differences in carotid atherosclerosis among Europeans (EA), South Asians (SA), and African Caribbeans (AC) in the Southall and Brent Revisited (SABRE) cohort. Previous studies had revealed disparities in ASCVD risk among these ethnic groups. Specifically, while South Asians had a higher risk of CHD, African Caribbeans exhibited a lower risk of CHD, but a higher risk of stroke compared to Europeans. I observed that prevalence of any plaque was similar in Europeans and South Asian participants, but lower in African Caribbean participants; adjustments for known risk factors had minimal effects on the observed ethnic differences in carotid atherosclerosis and these ethnic differences remain largely unexplained. This underscores the need for further research to identify additional factors influencing atherosclerosis in different ethnic groups. Future research directions could focus on novel factors beyond traditional risk factors that may contribute to ethnic differences in carotid atherosclerosis. These could include more nuanced assessment of socio-economic factors, migration history, and exposure to racism in addition to exploring potential genetic influences on ethnic disparities in susceptibility to ASCVD. While carotid ultrasound is a relatively cheap and non-invasive method to assess atherosclerosis, The similarity in plaque burden observed between South Asians and Europeans, despite their distinct ASCVD risk profiles, raises significant concerns about the utility of carotid ultrasound as a reliable screening tool for risk assessment in these populations. This scepticism is further supported by a 2016 study published in the International Journal of Cardiology, which demonstrated that Intima-Media Thickness (IMT), as measured by carotid ultrasound, is not a reliable marker for coronary artery

disease (CAD) when compared to histology.(Meershoek et al., 2016) These findings suggest that while carotid ultrasound can provide valuable insights, its effectiveness in accurately assessing ASCVD risk across different ethnic groups is questionable, particularly regarding the use of IMT as a marker for atherosclerosis. Therefore, there is a need to explore more reliable and nuanced markers that better reflect the underlying atherosclerotic burden and predict cardiovascular events across diverse populations.

In chapter 4 we aimed to investigate the cross-sectional associations between carotid atherosclerosis, cognitive function, and brain health in SABRE. The findings revealed that the presence of carotid plaque was associated with poorer cognitive function, particularly in measures of global cognitive performance, memory, and executive function/attention in unadjusted analyses. However, after comprehensive adjustment for potential confounders, most associations, except for the association with presence of plaque, were substantially attenuated or abolished.

In terms of neuroimaging measures, the study observed associations between the presence of carotid plaque and increased white matter lesion volume and coalescence. However, after full adjustment for risk factors, the relationship with total brain volume was attenuated. This suggests that while the presence of plaque may be independently associated with some vascular neuroimaging outcomes, these associations can be confounded by other factors, such as cardiovascular risk factors. This study contributes to the growing body of literature on the relationship between carotid atherosclerosis, cognitive function, and brain health. The associations observed, particularly with carotid plaque, emphasize the need for further research to elucidate the

underlying mechanisms and potential interventions to mitigate cognitive decline in older adults.

In Chapter 5, I used the NSHD study to investigate the potential correlation between carotid artery atherosclerosis and change in cognitive function in a cohort of older individuals who had repeat measures of cognition including in childhood. Despite a thorough exploration of various indicators of carotid atherosclerosis, including plaque characteristics and arterial measures, our findings did not reveal convincing or consistent correlations with cognitive performance across different domains once confounders were accounted for.

The differences between findings in the two cohorts studied merits consideration since the SABRE and NSHD cohorts provide contrasting demographic and epidemiological insights into carotid plaque incidence and cardiovascular risk assessment. The two samples differ in several respects:

Age Disparity: the mean age in the SABRE cohort was slightly older (average age = 73.2 years) compared to the MRC cohort (average = 63 years at the time of carotid ultrasound). This age difference may contribute to the lower incidence of carotid plaque in NSHD. It is also noteworthy that, as a birth cohort, NSHD had much less variation in age than SABRE. This can be seen as a strength in that the influence of age is minimised but a weakness in that the variation in various exposure and outcomes may be smaller.

Carotid plaque incidence: SABRE demonstrates a higher prevalence of carotid plaque, correlating with the increased age and prolonged exposure to more adverse risk factors for atherosclerosis.

Even allowing for differences in the cohorts studied, our findings highlight that Carotid Intima-Media Thickness (CIMT) has limited value in assessing risk for cognitive impairment. This aligns with the broader body of research suggesting that traditional CVD risk factors (e.g., hypertension, cholesterol levels, smoking) are more predictive of cognitive decline and cardiovascular events. The findings underscore that these established risk factors should remain the focus of risk assessment and management strategies.

Future Research Directions

Functional/Histological Assessment: future research should focus on detailed assessments of carotid plaque, including elastography, histology, and identifying novel high-risk features of plaques, to provide a more comprehensive risk evaluation. For example, replacing CIMT with arterial stiffness measurements using shear wave elastography could offer more accurate insights into vascular health and risk stratification.

Inclusion of pathological data: integrating cerebrovascular and neurodegenerative pathology data could enhance understanding of the link between cardiovascular health and cognitive function. This approach would provide a more holistic view of the contributory disease processes and their interactions.

Longitudinal Designs and Broader Assessments: future research using longitudinal designs with longer follow-up, broader cognitive assessments throughout life,(Venketasubramanian, 2024) and larger sample sizes could provide a more comprehensive understanding of the dynamic interplay between carotid atherosclerosis and cognitive decline. Additionally, considering the multifaceted nature of cognitive function,

incorporating a richer set of social and psychological factors in future investigations may further elucidate the intricacies of this relationship.

In conclusion, the thesis provides new information about the links between carotid artery atherosclerosis, cognitive function, and brain health. While specific associations varied, and conclusive evidence was often elusive, the findings underscore the need for ongoing research to unravel the complexities of this relationship. Ultimately, the knowledge gained from these studies may guide personalized strategies for preventing and managing cardiovascular and cognitive diseases across diverse populations.

References

AARTSEN, M. J., MARTIN, M. & ZIMPRICH, D. 2004. Gender Differences in Level and Change in Cognitive Functioning: Results from the Longitudinal Aging Study Amsterdam. *Gerontology,* 50**,** 35-8.

AL SAIKHAN, L., ALOBAIDA, M., BHUVA, A., CHATURVEDI, N., HEASMAN, J., HUGHES, A. D., JONES, S., EASTWOOD, S., MANISTY, C., MARCH, K., GHOSH, A. K., MAYET, J., OGUNTADE, A., TILLIN, T., WILLIAMS, S., WRIGHT, A. & PARK, C. 2020a. Imaging Protocol, Feasibility, and Reproducibility of Cardiovascular Phenotyping in a Large Tri-Ethnic Population-Based Study of Older People: The Southall and Brent Revisited (SABRE) Study. *Front Cardiovasc Med,* 7**,** 591946.

AL SAIKHAN, L., ALOBAIDA, M., BHUVA, A., CHATURVEDI, N., HEASMAN, J., HUGHES, A. D., JONES, S., EASTWOOD, S., MANISTY, C., MARCH, K., GHOSH, A. K., MAYET, J., OGUNTADE, A., TILLIN, T., WILLIAMS, S., WRIGHT, A. & PARK, C. 2020b. Imaging Protocol, Feasibility, and Reproducibility of Cardiovascular Phenotyping in a Large Tri-Ethnic Population-Based Study of Older People: The Southall and Brent Revisited (SABRE) Study. *Frontiers in Cardiovascular Medicine,* 7.

ALAM, U., ASGHAR, O., AZMI, S. & MALIK, R. A. 2014. Chapter 15 - General aspects of diabetes mellitus. *In:* ZOCHODNE, D. W. & MALIK, R. A. (eds.) *Handbook of Clinical Neurology.* Elsevier.

ALBERT, M. A., GLYNN, R. J., BURING, J. & RIDKER, P. M. 2006. Impact of Traditional and Novel Risk Factors on the Relationship Between Socioeconomic Status and Incident Cardiovascular Events. *Circulation,* 114**,** 2619-2626.

ALEXANDROV, A. V. 2007. The Spencer's Curve: Clinical Implications of a Classic Hemodynamic Model. *Journal of Neuroimaging,* 17**,** 6-10.

ALHUSAINI, S., KARAMA, S., NGUYEN, T. V., THIEL, A., BERNHARDT, B. C., COX, S. R., CORLEY, J., TAYLOR, A., EVANS, A. C., STAR, J. M., BASTIN, M. E., WARDLAW, J. M., DEARY, I. J. & DUCHARME, S. 2018. Association between carotid atheroma and cerebral cortex structure at age 73 years. *Ann Neurol,* 84**,** 576-587.

ALSHEIKH-ALI, A. A., KITSIOS, G. D., BALK, E. M., LAU, J. & IP, S. 2010. The vulnerable atherosclerotic plaque: scope of the literature. *Ann Intern Med,* 153**,** 387-95.

ALTMAN, D. G. & BLAND, J. M. 2003. Statistics Notes - Interaction revisited: the difference between two estimates. *BMJ,* 326**,** 219-219.

AMMIRATI, E., MORONI, F., MAGNONI, M., ROCCA, M. A., MESSINA, R., ANZALONE, N., DE FILIPPIS, C., SCOTTI, I., BESANA, F., SPAGNOLO, P., RIMOLDI, O. E., CHIESA, R., FALINI, A., FILIPPI, M. & CAMICI, P. G. 2020. Extent and characteristics of carotid plaques and brain parenchymal loss in asymptomatic patients with no indication for revascularization. *IJC Heart & Vasculature,* 30**,** 100619.

ANAND SONIA, S., EIKELBOOM JOHN, W., DYAL, L., BOSCH, J., NEUMANN, C., WIDIMSKY, P., AVEZUM ALVARO, A., PROBSTFIELD, J., COOK BRUNS, N., FOX KEITH, A. A., BHATT DEEPAK, L., CONNOLLY STUART, J., YUSUF, S. & NULL, N. 2019. Rivaroxaban Plus Aspirin Versus Aspirin in Relation to Vascular Risk in the COMPASS Trial. *Journal of the American College of Cardiology,* 73**,** 3271-3280.

ANBAR, R., CHATURVEDI, N., EASTWOOD, S. V., TILLIN, T. & HUGHES, A. D. 2022a. Carotid atherosclerosis in people of European, South Asian and African Caribbean ethnicity in the Southall and Brent revisited study (SABRE). *Front Cardiovasc Med,* 9**,** 1002820.

ANBAR, R., SULTAN, S. R., AL SAIKHAN, L., ALKHARAIJI, M., CHATURVEDI, N., HARDY, R., RICHARDS, M. & HUGHES, A. 2022b. Is carotid artery atherosclerosis associated with poor cognitive function assessed using the Mini-Mental State Examination? A systematic review and meta-analysis. *BMJ Open,* 12**,** e055131.

ANDO, J. & YAMAMOTO, K. 2009. Vascular mechanobiology endothelial cell responses to fluid shear stress. *Circulation Journal,* 73**,** 1983-1992.

ARNETT, D. K., BLUMENTHAL, R. S., ALBERT, M. A., BUROKER, A. B., GOLDBERGER, Z. D., HAHN, E. J., HIMMELFARB, C. D., KHERA, A., LLOYD-JONES, D., MCEVOY, J. W., MICHOS, E. D., MIEDEMA, M.

D., MUÑOZ, D., SMITH, S. C., VIRANI, S. S., WILLIAMS, K. A., YEBOAH, J. & ZIAEIAN, B. 2019. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation,* 140**,** e596-e646.

ASSMANN, G., CULLEN, P., JOSSA, F., LEWIS, B. & MANCINI, M. 1999. Coronary Heart Disease: Reducing the Risk. *Arteriosclerosis, Thrombosis, and Vascular Biology,* 19**,** 1819-1824.

AUPERIN, A., BERR, C., BONITHON-KOPP, C., TOUBOUL, P.-J., RUELLAND, I., DUCIMETIERE, P. & ALPEROVITCH, A. 1996a. Ultrasonographic assessment of carotid wall characteristics and cognitive functions in a community sample of 59-to 71-year-olds. *Stroke,* 27**,** 1290-1295.

AUPERIN, A., BERR, C., BONITHON-KOPP, C., TOUBOUL, P. J., RUELLAND, I., DUCIMETIERE, P. & ALPEROVITCH, A. 1996b. Ultrasonographic assessment of carotid wall characteristics and cognitive functions in a community sample of 59- to 71-year-olds. The EVA Study Group. *Stroke,* 27**,** 1290-5.

BALAKUMAR, P., MAUNG-U, K. & JAGADEESH, G. 2016. Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacological Research,* 113**,** 600-609.

BANERJEE, S., AAYSHA CADER, F., GULATI, M. & CAPERS, Q. 2021. Racism and Cardiology: A Global Call to Action. *CJC Open,* 3**,** S165-S173.

BARNETT, H. J., TAYLOR, D. W., ELIASZIW, M., FOX, A. J., FERGUSON, G. G., HAYNES, R. B., RANKIN, R. N., CLAGETT, G. P., HACHINSKI, V. C. & SACKETT, D. L. 1998. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *New England Journal of Medicine,* 339**,** 1415-1425.

BASITH, S., MANAVALAN, B., SHIN, T. H., PARK, C. B., LEE, W. S., KIM, J. & LEE, G. 2022. The Impact of Fine Particulate Matter 2.5 on the Cardiovascular System: A Review of the Invisible Killer. *Nanomaterials (Basel),* 12.

BAZZANO, L. A., HE, J., MUNTNER, P., VUPPUTURI, S. & WHELTON, P. K. 2003. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Annals of internal medicine,* 138**,** 891-897.

BEERI, M. S., RAVONA-SPRINGER, R., SILVERMAN, J. M. & HAROUTUNIAN, V. 2009. The effects of cardiovascular risk factors on cognitive compromise. *Dialogues in clinical neuroscience,* 11**,** 201.

BENJAMIN, I., BROWN, N., BURKE, G., CORREA, A., HOUSER, S. R., JONES, D. W., LOSCALZO, J., VASAN, R. S. & WHITMAN, G. R. 2015. American Heart Association Cardiovascular Genome-Phenome Study: foundational basis and program. *Circulation,* 131**,** 100-12.

BENTZON, J. F., OTSUKA, F., VIRMANI, R. & FALK, E. 2014. Mechanisms of Plaque Formation and Rupture. *Circulation Research,* 114**,** 1852-1866.

BHOPAL, R. S. 2014. *Migration, ethnicity, race, and health in multicultural societies,* Oxford, Oxford University Press.

BIASI, G. M., SAMPAOLO, A., MINGAZZINI, P., DE AMICIS, P., EL-BARGHOUTY, N. & NICOLAIDES, A. N. 1999. Computer analysis of ultrasonic plaque echolucency in identifying high risk carotid bifurcation lesions. *Eur J Vasc Endovasc Surg,* 17**,** 476-9.

BJORNSDOTTIR, G., SIGURDSSON, S., STURLAUGSDOTTIR, R., GUDMUNDSDOTTIR, A., EIRIKSDOTTIR, G., THORSSON, B., ASPELUND, T., GUSTAVSSON, T., LAUNER, L. J., HARRIS, T. B. & GUDNASON, V. 2018. Longitudinal Changes in Size and Composition of Carotid Artery Plaques Using Ultrasound: Adaptation and Validation of Methods (Inter- and Intraobserver Variability). *Journal for Vascular Ultrasound,* 38**,** 198-208.

BOCK, R. & LUSBY, R. 1992. Carotid plaque morphology and interpretation of the echolucent lesion. *Labs KH, Jager KA, FitzGerald DE, Woodcock JP, Neuerberg-Heusler D, eds. Diagnostic Vascular Ultrasound. London, UK: Edward Arnold,* 21**,** 254-263.

BOTHONGO, P. L. K., JITLAL, M., PARRY, E., WATERS, S., FOOTE, I. F., WATSON, C. J., CUZICK, J., GIOVANNONI, G., DOBSON, R., NOYCE, A. J., MUKADAM, N., BESTWICK, J. P. & MARSHALL, C.

R. 2022. Dementia risk in a diverse population: A single-region nested case-control study in the East End of London. *Lancet Reg Health Eur,* 15**,** 100321.

BOTS, M. L., DE JONG, P. T. V. M., HOFMAN, A. & GROBBEE, D. E. 1997a. Left, Right, Near or Far Wall Common Carotid Intima-Media Thickness Measurements: Associations with Cardiovascular Disease and Lower Extremity Arterial Atherosclerosis. *Journal of Clinical Epidemiology,* 50**,** 801-807.

BOTS, M. L., HOFMAN, A. & GROBBEE, D. E. 1997b. Increased common carotid intima-media thickness. Adaptive response or a reflection of atherosclerosis? Findings from the Rotterdam Study. *Stroke,* 28**,** 2442-7.

BRETELER, M. M. [New York, NY] :.

BRETELER, M. M. B., CLAUS, J. J., GROBBEE, D. E. & HOFMAN, A. 1994. Cardiovascular disease and distribution of cognitive function in elderly people: The Rotterdam study. *British Medical Journal,* 308**,** 1604-1608.

BRYAN, S. N., TREMBLAY, M. S., PEREZ, C. E., ARDERN, C. I. & KATZMARZYK, P. T. 2006. Physical activity and ethnicity: evidence from the Canadian Community Health Survey. *Can J Public Health,* 97**,** 271-6.

BURATTI, L., BALESTRINI, S., ALTAMURA, C., VITICCHI, G., FALSETTI, L., LUZZI, S., PROVINCIALI, L., VERNIERI, F. & SILVESTRINI, M. 2015. Markers for the Risk of Progression from Mild Cognitive Impairment to Alzheimer's Disease. *Journal of Alzheimer's Disease,* 45**,** 883-890.

BURATTI, L., BALUCANI, C., VITICCHI, G., FALSETTI, L., ALTAMURA, C., AVITABILE, E., PROVINCIALI, L., VERNIERI, F. & SILVESTRINI, M. 2014. Cognitive deterioration in bilateral asymptomatic severe carotid stenosis. *Stroke,* 45**,** 2072-2077.

CALOGERO, E., FABIANI, I., PUGLIESE, N. R., SANTINI, V., GHIADONI, L., DI STEFANO, R., GALETTA, F., SARTUCCI, F., PENNO, G., BERCHIOLLI, R., FERRARI, M., CIONI, D., NAPOLI, V., DE CATERINA, R., DI BELLO, V. & CARAMELLA, D. 2018. Three-Dimensional Echographic Evaluation of Carotid Artery Disease. *J Cardiovasc Echogr,* 28**,** 218-227.

CAPLAN, L. R. & HENNERICI, M. 1998. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. *Archives of neurology,* 55**,** 1475-1482.

CAPPABIANCA, S., SOMMA, F., NEGRO, A., ROTONDO, M., SCUOTTO, A. & ROTONDO, A. 2016. Extracranial internal carotid artery: anatomical variations in asymptomatic patients. *Surgical and radiologic anatomy (English ed.),* 38**,** 893-902.

CARCAILLON, L., PLICHART, M., ZUREIK, M., ROUAUD, O., MAJED, B., RITCHIE, K., TZOURIO, C., DARTIGUES, J. F. & EMPANA, J. P. 2015. Carotid plaque as a predictor of dementia in older adults: the Three-City Study. *Alzheimer's & Dementia,* 11**,** 239-48.

CARDOSO, M. J., MODAT, M., WOLZ, R., MELBOURNE, A., CASH, D., RUECKERT, D. & OURSELIN, S. 2015. Geodesic Information Flows: Spatially-Variant Graphs and Their Application to Segmentation and Fusion. *IEEE Trans Med Imaging,* 34**,** 1976-88.

CARLSSON, C. M., NONDAHL, D. M., KLEIN, B. E., MCBRIDE, P. E., SAGER, M. A., SCHUBERT, C. R., KLEIN, R. & CRUICKSHANKS, K. J. 2009. Increased atherogenic lipoproteins are associated with cognitive impairment: effects of statins and subclinical atherosclerosis. *Alzheimer Dis Assoc Disord,* 23**,** 11-7.

CARPENTER, M., SINCLAIR, H. & KUNADIAN, V. 2016. Carotid Intima Media Thickness and Its Utility as a Predictor of Cardiovascular Disease. *Cardiology in review,* 24**,** 70-75.

CARR, S., FARB, A., PEARCE, W. H., VIRMANI, R. & YAO, J. S. T. 1996. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. *Journal of Vascular Surgery,* 23**,** 755-766.

CECELJA, M., JIANG, B., BEVAN, L., FROST, M. L., SPECTOR, T. D. & CHOWIENCZYK, P. J. 2011. Arterial stiffening relates to arterial calcification but not to noncalcified atheroma in women. A twin study. *J Am Coll Cardiol,* 57**,** 1480-6.

CHAHAL, N. S., LIM, T. K., JAIN, P., CHAMBERS, J. C., KOONER, J. S. & SENIOR, R. 2011. Does subclinical atherosclerosis burden identify the increased risk of cardiovascular disease mortality among United Kingdom Indian Asians? A population study. *Am Heart J,* 162**,** 460-6.

CHANDRA, A., STONE, C. R., LI, W. A., GENG, X. & DING, Y. 2017. The cerebral circulation and cerebrovascular disease II: Pathogenesis of cerebrovascular disease. *Brain Circ,* 3**,** 57-65.

CHAYTOR, N. & SCHMITTER-EDGECOMBE, M. 2003. The ecological validity of neuropsychological tests: a review of the literature on everyday cognitive skills. *Neuropsychol Rev,* 13**,** 181-97.

CIRES-DROUET, R. S., MOZAFARIAN, M., ALI, A., SIKDAR, S. & LAL, B. K. 2017. Imaging of high-risk carotid plaques: ultrasound. *Semin Vasc Surg,* 30**,** 44-53.

CISMARU, G., SERBAN, T. & TIRPE, A. 2021. Ultrasound Methods in the Evaluation of Atherosclerosis: From Pathophysiology to Clinic. *Biomedicines,* 9.

CLARK, A. M., DESMEULES, M., LUO, W., DUNCAN, A. S. & WIELGOSZ, A. 2009. Socioeconomic status and cardiovascular disease: risks and implications for care. *Nature Reviews Cardiology,* 6**,** 712-722.

COBBLE, M. & BALE, B. 2010. Carotid intima-media thickness: knowledge and application to everyday practice. *Postgraduate medicine,* 122**,** 10-18.

COBZEANU, B. M., BALDEA, V., COSTAN, V. V., COBZEANU, M. D., PALADE, O. D., GHEORGHE, L., RADULESCU, L., SEVERIN, F., LUPASCU URSULESCU, C., BANDOL, G., MARTU, C., ROSU, A. M. & COBZEANU, M. L. 2023. Anatomical Variants of Internal Carotid Artery—Results from a Retrospective Study. *Medicina,* 59**,** 1057.

COLLINS, G. S. & ALTMAN, D. G. 2010. An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. *BMJ,* 340**,** c2442-c2442.

CORBO, I., MARSELLI, G., DI CIERO, V. & CASAGRANDE, M. 2023. The protective role of cognitive reserve in mild cognitive impairment: A systematic review. *Journal of Clinical Medicine,* 12**,** 1759.

CRIQUI, M. H. & ABOYANS, V. 2015. Epidemiology of peripheral artery disease. *Circulation research,* 116**,** 1509-1526.

CUMMINGS, P. 2009. The relative merits of risk ratios and odds ratios. *Arch Pediatr Adolesc Med,* 163**,** 438-45.

DAHLOF, B. 2010. Cardiovascular Disease Risk Factors: Epidemiology and Risk Assessment. *The American journal of cardiology,* 105**,** 3A-9A.

DAVIS, P. H., DAWSON, J. D., RILEY, W. A. & LAUER, R. M. 2001. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation,* 104**,** 2815-9.

DE KORTE, C. L., HANSEN, H. H. & VAN DER STEEN, A. F. 2011. Vascular ultrasound for atherosclerosis imaging. *Interface focus,* 1**,** 565-575.

DE LA TORRE, J. C. 2016. Cerebral Perfusion Enhancing Interventions: A New Strategy for the Prevention of Alzheimer Dementia. *Brain Pathol,* 26**,** 618-31.

DEATON, C., FROELICHER, E. S., WU, L. H., HO, C., SHISHANI, K. & JAARSMA, T. 2011. The global burden of cardiovascular disease. *European Journal of Cardiovascular Nursing,* 10**,** S5-S13.

DELLA-MORTE, D., DONG, C., MARKERT, M. S., ELKIND, M. S. V., SACCO, R. L., WRIGHT, C. B. & RUNDEK, T. 2018. Carotid Intima-Media Thickness Is Associated With White Matter Hyperintensities. *Stroke,* 49**,** 304-311.

DESIDERI, G. & BOCALE, R. 2021. Correlation between cardiovascular risk factors and cognitive decline. *Eur Heart J Suppl,* 23**,** E73-e76.

DEWEESE, J. A., MAY, A. G., LIPCHIK, E. O. & ROB, C. G. 1970. Anatomic and hemodynamic correlations in carotid artery stenosis. *Stroke,* 1**,** 149-57.

DIAS, E. D. M., GIOLLO, L. T., MARTINELLI, D. D., MAZETI, C., JUNIOR, H. M., VILELA-MARTIN, J. F. & YUGAR-TOLEDO, J. C. 2012. Carotid intima-media thickness is associated with cognitive deficiency in hypertensive patients with elevated central systolic blood pressure. *Cardiovascular Ultrasound,* 10.

DONNAN, G. A., DAVIS, S., CHAMBERS, B. R. & GATES, P. 1998. Surgery for prevention of stroke. *The Lancet,* 351**,** 1372-1373.

EASTWOOD, S. V., TILLIN, T., DEHBI, H. M., WRIGHT, A., FOROUHI, N. G., GODSLAND, I., WHINCUP, P., SATTAR, N., HUGHES, A. D. & CHATURVEDI, N. 2015. Ethnic differences in associations between fat deposition and incident diabetes and underlying mechanisms: the SABRE study. *Obesity (Silver Spring),* 23**,** 699-706.

EBRAHIM, S., PAPACOSTA, O., WHINCUP, P., WANNAMETHEE, G., WALKER, M., NICOLAIDES, A. N., DHANJIL, S., GRIFFIN, M., BELCARO, G., RUMLEY, A. & LOWE, G. D. 1999. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. *Stroke,* 30**,** 841-50.

EL-BARGHOUTY, N., LEVINE, T., LADVA, S., FLANAGAN, A. & NICOLAIDES, A. 1996. Histological verification of computerised carotid plaque characterisation. *European journal of vascular and endovascular surgery,* 11**,** 414-416.

EL-KATTAN, M. M., ZAKARIA, Y. A., EL-FAYOMY, N., HELMY, S. M., KHAIRY, H. M., RAMZY, G. M. & EL-JAAFARY, S. I. 2009. Peripheral arterial disease and cognition. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery,* 46**,** 311-322.

ERHARDT, L. 2009. Cigarette smoking: an undertreated risk factor for cardiovascular disease. *Atherosclerosis,* 205**,** 23-32.

ERIKSEN, A., TILLIN, T., O'CONNOR, L., BRAGE, S., HUGHES, A., MAYET, J., MCKEIGUE, P., WHINCUP, P., CHATURVEDI, N. & FOROUHI, N. G. 2015. The Impact of Health Behaviours on Incident Cardiovascular Disease in Europeans and South Asians - A Prospective Analysis in the UK SABRE Study. *PLoS One,* 10**,** e0117364.

FABER, R. A. 2009. The Neuropsychiatric Mental Status Examination. *SEMIN NEUROL,* 29**,** 185-193.

FALK, E. 2006. Pathogenesis of atherosclerosis. *Journal of the American College of cardiology,* 47**,** C7-C12.

FALSETTI, L., VITICCHI, G., BURATTI, L., GRIGIONI, F., CAPUCCI, A. & SILVESTRINI, M. 2018. Interactions between Atrial Fibrillation, Cardiovascular Risk Factors, and ApoE Genotype in Promoting Cognitive Decline in Patients with Alzheimer's Disease: A Prospective Cohort Study. *Journal of Alzheimer's Disease,* 62**,** 713-725.

FARINA, D., LOMBARDI, D., BERTULETTI, M., PALUMBO, G., ZORZA, I. & RAVANELLI, M. 2019. An additional challenge for head and neck radiologists: anatomic variants posing a surgical risk – a pictorial review. *Insights into Imaging,* 10**,** 112.

FERNANDES, M., KEERTHIRAJ, B., MAHALE, A. R., KUMAR, A. & DUDEKULA, A. 2016. Evaluation of carotid arteries in stroke patients using color Doppler sonography: A prospective study conducted in a tertiary care hospital in South India. *Int J Appl Basic Med Res,* 6**,** 38-44.

FERNÁNDEZ-ALVAREZ, V., LINARES SÁNCHEZ, M., LÓPEZ ALVAREZ, F., SUÁREZ NIETO, C., MÄKITIE, A. A., OLSEN, K. D. & FERLITO, A. 2022. Evaluation of Intima-Media Thickness and Arterial Stiffness as Early Ultrasound Biomarkers of Carotid Artery Atherosclerosis. *Cardiology and Therapy,* 11**,** 231-247.

FESKE, S. K. 2021. Ischemic Stroke. *The American Journal of Medicine,* 134**,** 1457-1464.

FLAHERTY, M. L., KISSELA, B., KHOURY, J. C., ALWELL, K., MOOMAW, C. J., WOO, D., KHATRI, P., FERIOLI, S., ADEOYE, O., BRODERICK, J. P. & KLEINDORFER, D. 2012. Carotid Artery Stenosis as a Cause of Stroke. *Neuroepidemiology,* 40**,** 36-41.

FREEDMAN, B. I., HSU, F. C., LANGEFELD, C. D., RICH, S. S., HERRINGTON, D. M., CARR, J. J., XU, J., BOWDEN, D. W. & WAGENKNECHT, L. E. 2005. The impact of ethnicity and sex on subclinical cardiovascular disease: the Diabetes Heart Study. *Diabetologia,* 48**,** 2511-2518.

FRESNAIS, D., HUMBLE, M. B., BEJEROT, S., MEEHAN, A. & FURE, B. 2021. The Association between Carotid Intima-Media Thickness and Cognitive Impairment: A Systematic Review and Meta-Analysis. *Dementia and Geriatric Cognitive Disorders,* 50**,** 305-317.

FUCHS, F. D. & WHELTON, P. K. 2020. High Blood Pressure and Cardiovascular Disease. *Hypertension,* 75**,** 285-292.

GARCIA, J. & KHANG-LOON, H. 1996. Carotid atherosclerosis. Definition, pathogenesis, and clinical significance. *Neuroimaging clinics of North America,* 6**,** 801-810.

GARDENER, H., CAUNCA, M. R., DONG, C., CHEUNG, Y. K., ELKIND, M. S., SACCO, R. L., RUNDEK, T. & WRIGHT, C. B. 2017. Ultrasound markers of carotid atherosclerosis and cognition: the Northern Manhattan Study. *Stroke,* 48**,** 1855-1861.

GIANNOUKAS, A., CHABOK, M., SPANOS, K. & NICOLAIDES, A. 2016. Screening for asymptomatic carotid plaques with ultrasound. *European Journal of Vascular and Endovascular Surgery,* 52**,** 309-312.

GILBERT, R. T. 2004. Management of dyslipidaemia. *Heart,* 90**,** 949.

GIMBRONE, M. A., JR. & GARCÍA-CARDEÑA, G. 2016. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ Res,* 118**,** 620-36.

GOFF, D. C., JR., LLOYD-JONES, D. M., BENNETT, G., COADY, S., D'AGOSTINO, R. B., GIBBONS, R., GREENLAND, P., LACKLAND, D. T., LEVY, D., O'DONNELL, C. J., ROBINSON, J. G., SCHWARTZ, J. S., SHERO, S. T., SMITH, S. C., JR., SORLIE, P., STONE, N. J., WILSON, P. W., JORDAN, H. S., NEVO, L., WNEK, J., ANDERSON, J. L., HALPERIN, J. L., ALBERT, N. M., BOZKURT, B., BRINDIS, R. G., CURTIS, L. H., DEMETS, D., HOCHMAN, J. S., KOVACS, R. J., OHMAN, E. M., PRESSLER, S. J., SELLKE, F. W., SHEN, W. K., SMITH, S. C., JR., TOMASELLI, G. F. & AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION TASK FORCE ON PRACTICE, G. 2014. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation,* 129**,** S49-73.

GOFUR, E. M. & SINGH, P. 2021. Anatomy, back, vertebral canal blood supply. *StatPearls [Internet]*.

GOLDENBERG, I., JONAS, M., TENENBAUM, A., BOYKO, V., MATETZKY, S., SHOTAN, A., BEHAR, S., REICHER-REISS, H. & GROUP, B. I. P. S. 2003. Current smoking, smoking cessation, and the risk of sudden cardiac death in patients with coronary artery disease. *Archives of internal medicine,* 163**,** 2301-2305.

GOLLEDGE, J., GREENHALGH, R. M. & DAVIES, A. H. 2000. The Symptomatic Carotid Plaque. *Stroke,* 31**,** 774-781.

GORELICK, P. B., SCUTERI, A., BLACK, S. E., DECARLI, C., GREENBERG, S. M., IADECOLA, C., LAUNER, L. J., LAURENT, S., LOPEZ, O. L. & NYENHUIS, D. 2011a. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *stroke,* 42**,** 2672-2713.

GORELICK, P. B., SCUTERI, A., BLACK, S. E., DECARLI, C., GREENBERG, S. M., IADECOLA, C., LAUNER, L. J., LAURENT, S., LOPEZ, O. L., NYENHUIS, D., PETERSEN, R. C., SCHNEIDER, J. A., TZOURIO, C., ARNETT, D. K., BENNETT, D. A., CHUI, H. C., HIGASHIDA, R. T., LINDQUIST, R., NILSSON, P. M., ROMAN, G. C., SELLKE, F. W. & SESHADRI, S. 2011b. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke,* 42**,** 2672-713.

GORNIK, H. L. & BECKMAN, J. A. 2005. Peripheral arterial disease. *Circulation,* 111**,** e169-e172.

GRANT, R. L. 2014. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ,* 348**,** f7450-f7450.

GRAY-WEALE, A. C., GRAHAM, J. C., BURNETT, J. R., BYRNE, K. & LUSBY, R. J. 1988. Carotid artery atheroma: comparison of preoperative B-mode ultrasound appearance with carotid endarterectomy specimen pathology. *J Cardiovasc Surg (Torino),* 29**,** 676-81.

GREENLAND, P., ALPERT, J. S., BELLER, G. A., BENJAMIN, E. J., BUDOFF, M. J., FAYAD, Z. A., FOSTER, E., HLATKY, M. A., HODGSON, J. M., KUSHNER, F. G., LAUER, M. S., SHAW, L. J., SMITH, S. C., JR., TAYLOR, A. J., WEINTRAUB, W. S., WENGER, N. K., JACOBS, A. K., SMITH, S. C., JR., ANDERSON, J. L., ALBERT, N., BULLER, C. E., CREAGER, M. A., ETTINGER, S. M., GUYTON, R. A., HALPERIN, J. L., HOCHMAN, J. S., KUSHNER, F. G., NISHIMURA, R., OHMAN, E. M., PAGE, R. L., STEVENSON,

W. G., TARKINGTON, L. G., YANCY, C. W., AMERICAN COLLEGE OF CARDIOLOGY, F. & AMERICAN HEART, A. 2010. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol,* 56**,** e50-103.

GRODSTEIN, F. 2007. Cardiovascular risk factors and cognitive function. *Alzheimer's & dementia,* 3**,** S16-S22.

GRØNHOLDT, M.-L. M. 1999. Ultrasound and Lipoproteins as Predictors of Lipid-Rich, Rupture-Prone Plaques in the Carotid Artery. *Arteriosclerosis, Thrombosis, and Vascular Biology,* 19**,** 2-13.

GROUP, E. C. S. T. C. 1998. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *The Lancet,* 351**,** 1379-1387.

GUPTA, A., BARADARAN, H., SCHWEITZER, A. D., KAMEL, H., PANDYA, A., DELGADO, D., DUNNING, A., MUSHLIN, A. I. & SANELLI, P. C. 2013. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke,* 44**,** 3071-7.

GUPTA, R. & GUPTHA, S. 2010. Strategies for initial management of hypertension. *Indian J Med Res,* 132**,** 531-42.

HAJAR, R. 2017. Risk factors for coronary artery disease: historical perspectives. *Heart views: the official journal of the Gulf Heart Association,* 18**,** 109.

HALEY, A. P., FORMAN, D. E., POPPAS, A., HOTH, K. F., GUNSTAD, J., JEFFERSON, A. L., PAUL, R. H., LER, A. S., SWEET, L. H. & COHEN, R. A. 2007. Carotid artery intima-media thickness and cognition in cardiovascular disease. *International Journal of Cardiology,* 121**,** 148-54.

HANKEY, G. J., NORMAN, P. E. & EIKELBOOM, J. W. 2006. Medical treatment of peripheral arterial disease. *Jama,* 295**,** 547-553.

HAVRANEK, E. P., MUJAHID, M. S., BARR, D. A., BLAIR, I. V., COHEN, M. S., CRUZ-FLORES, S., DAVEY-SMITH, G., DENNISON-HIMMELFARB, C. R., LAUER, M. S., LOCKWOOD, D. W., ROSAL, M. & YANCY, C. W. 2015. Social Determinants of Risk and Outcomes for Cardiovascular Disease. *Circulation,* 132**,** 873-898.

HEISS, W. D. 2014. PET imaging in ischemic cerebrovascular disease: current status and future directions. *Neurosci Bull,* 30**,** 713-32.

HELLINGS, W. E., PEETERS, W., MOLL, F. L., PIERS, S. R. D., SETTEN, J. V., SPEK, P. J. V. D., VRIES, J.-P. P. M. D., SELDENRIJK, K. A., BRUIN, P. C. D., VINK, A., VELEMA, E., KLEIJN, D. P. V. D. & PASTERKAMP, G. 2010. Composition of Carotid Atherosclerotic Plaque Is Associated With Cardiovascular Outcome. *Circulation,* 121**,** 1941-1950.

HENDRIKSE, J., VAN RAAMT, A. F., VAN DER GRAAF, Y., MALI, W. P. & VAN DER GROND, J. 2005. Distribution of cerebral blood flow in the circle of Willis. *Radiology,* 235**,** 184-189.

HERTZER, N. R., BEVEN, E. G., YOUNG, J. R., O'HARA, P. J., RUSCHHAUPT 3RD, W., GRAOR, R. A., DEWOLFE, V. G. & MALJOVEC, L. C. 1984. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Annals of surgery,* 199**,** 223.

HOFMAN, A., OTT, A., BRETELER, M. M., BOTS, M. L., SLOOTER, A. J., VAN HARSKAMP, F., VAN DUIJN, C. N., VAN BROECKHOVEN, C. & GROBBEE, D. E. 1997. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *The Lancet,* 349**,** 151-154.

HONG, Y. M. 2010. Atherosclerotic cardiovascular disease beginning in childhood. *Korean Circ J,* 40**,** 1-9.

IHLE-HANSEN, H., IHLE-HANSEN, H., SANDSET, E. C. & HAGBERG, G. 2021. Subclinical Carotid Artery Atherosclerosis and Cognitive Function: A Mini-Review. *Front Neurol,* 12**,** 705043.

IHNATSENKA, B. & BOEZAART, A. P. 2010. Ultrasound: Basic understanding and learning the language. *Int J Shoulder Surg,* 4**,** 55-62.

INABA, Y., CHEN, J. A. & BERGMANN, S. R. 2012. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis,* 220**,** 128-33.

INSULL, W. 2009. The Pathology of Atherosclerosis: Plaque Development and Plaque Responses to Medical Treatment. *The American Journal of Medicine,* 122**,** S3-S14.

JASHARI, F., IBRAHIMI, P., BAJRAKTARI, G., GRONLUND, C., WESTER, P. & HENEIN, M. Y. 2016. Carotid plaque echogenicity predicts cerebrovascular symptoms: a systematic review and meta-analysis. *Eur J Neurol,* 23**,** 1241-7.

JASHARI, F., IBRAHIMI, P., NICOLL, R., BAJRAKTARI, G., WESTER, P. & HENEIN, M. Y. 2013. Coronary and carotid atherosclerosis: Similarities and differences. *Atherosclerosis,* 227**,** 193-200.

JAVED, Z., HAISUM MAQSOOD, M., YAHYA, T., AMIN, Z., ACQUAH, I., VALERO-ELIZONDO, J., ANDRIENI, J., DUBEY, P., JACKSON, R. K., DAFFIN, M. A., CAINZOS-ACHIRICA, M., HYDER, A. A. & NASIR, K. 2022a. Race, Racism, and Cardiovascular Health: Applying a Social Determinants of Health Framework to Racial/Ethnic Disparities in Cardiovascular Disease. *Circulation: Cardiovascular Quality and Outcomes,* 15.

JAVED, Z., MAQSOOD, M. H., YAHYA, T., AMIN, Z., ACQUAH, I., VALERO-ELIZONDO, J., ANDRIENI, J., DUBEY, P., JACKSON, R. K., DAFFIN, M. A., CAINZOS-ACHIRICA, M., HYDER, A. A. & NASIR, K. 2022b. Race, Racism, and Cardiovascular Health: Applying a Social Determinants of Health Framework to Racial/Ethnic Disparities in Cardiovascular Disease. *Circulation: Cardiovascular Quality and Outcomes,* 15**,** e007917.

JEFFERSON, A., MASSARO, J., WOLF, P., SESHADRI, S., AU, R., VASAN, R., LARSON, M., MEIGS, J., KEANEY, J. & LIPINSKA, I. 2007. Inflammatory biomarkers are associated with total brain volume: the Framingham Heart Study. *Neurology,* 68**,** 1032-1038.

JELLINGER, K. A. 2013. Pathology and pathogenesis of vascular cognitive impairment—a critical update. *Frontiers in aging neuroscience,* 5**,** 45821.

JOHNSTON, S. C., O'MEARA, E. S., MANOLIO, T. A., LEFKOWITZ, D., O'LEARY, D. H., GOLDSTEIN, S., CARLSON, M. C., FRIED, L. P. & LONGSTRETH JR, W. 2004. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. *Annals of internal medicine,* 140**,** 237-247.

JONES, S., TILLIN, T., PARK, C., WILLIAMS, S., RAPALA, A., AL SAIKHAN, L., EASTWOOD, S. V., RICHARDS, M., HUGHES, A. D. & CHATURVEDI, N. 2020a. Cohort Profile Update: Southall and Brent Revisited (SABRE) study: a UK population-based comparison of cardiovascular disease and diabetes in people of European, South Asian and African Caribbean heritage. *International journal of epidemiology,* 49**,** 1441-1442e.

JONES, S., TILLIN, T., PARK, C., WILLIAMS, S., RAPALA, A., AL SAIKHAN, L., EASTWOOD, S. V., RICHARDS, M., HUGHES, A. D. & CHATURVEDI, N. 2020b. Cohort Profile Update: Southall and Brent Revisited (SABRE) study: a UK population-based comparison of cardiovascular disease and diabetes in people of European, South Asian and African Caribbean heritage. *Int J Epidemiol,* 49**,** 1441-1442e.

KALARIA, R. N. 2012. Cerebrovascular Disease and Mechanisms of Cognitive Impairment. *Stroke,* 43**,** 2526-2534.

KAPLOVITCH, E., EIKELBOOM, J. W., DYAL, L., ABOYANS, V., ABOLA, M. T., VERHAMME, P., AVEZUM, A., FOX, K. A. A., BERKOWITZ, S. D., BANGDIWALA, S. I., YUSUF, S. & ANAND, S. S. 2021. Rivaroxaban and Aspirin in Patients With Symptomatic Lower Extremity Peripheral Artery Disease: A Subanalysis of the COMPASS Randomized Clinical Trial. *JAMA Cardiology,* 6**,** 21-29.

KAWASAKI, M., ARAI, Y., HIRATA, T., TAKAYAMA, M., ABE, Y., NIIMURA, H., MIMURA, M., TAKEBAYASHI, T. & HIROSE, N. 2016a. Carotid atherosclerosis, cytomegalovirus infection, and cognitive decline in the very old: a community-based prospective cohort study. *Age,* 38**,** 1-13.

KAWASAKI, M., ARAI, Y., TAKAYAMA, M., HIRATA, T., TAKAYAMA, M., ABE, Y., NIIMURA, H., MIMURA, M., TAKEBAYASHI, T. & HIROSE, N. 2016b. Carotid atherosclerosis, cytomegalovirus infection,

and cognitive decline in the very old: a community-based prospective cohort study. *Age,* 38**,** 1-13.

KEANEY JR, J. F. 2000. Atherosclerosis: from lesion formation to plaque activation and endothelial dysfunction. *Molecular aspects of medicine,* 21**,** 99-166.

KEARNEY-SCHWARTZ, A., ROSSIGNOL, P., BRACARD, S., FELBLINGER, J., FAY, R., BOIVIN, J.-M., LECOMPTE, T., LACOLLEY, P., BENETOS, A. & ZANNAD, F. 2009a. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. *Stroke,* 40**,** 1229-1236.

KEARNEY-SCHWARTZ, A., ROSSIGNOL, P., BRACARD, S., FELBLINGER, J., FAY, R., BOIVIN, J. M., LECOMPTE, T., LACOLLEY, P., BENETOS, A. & ZANNAD, F. 2009b. Vascular Structure and Function Is Correlated to Cognitive Performance and White Matter Hyperintensities in Older Hypertensive Patients With Subjective Memory Complaints. *Stroke,* 40**,** 1229-1236.

KELLER, H., MEIER, W. & KUMPE, D. 1976. Noninvasive angiography for the diagnosis of vertebral artery disease using Doppler ultrasound (vertebral artery Doppler). *Stroke,* 7**,** 364-369.

KIELY, K. M. 2014. Cognitive Function. *In:* MICHALOS, A. C. (ed.) *Encyclopedia of Quality of Life and Well-Being Research.* Dordrecht: Springer Netherlands.

KNOPMAN, D. S. 2007. Cerebrovascular disease and dementia. *Br J Radiol,* 80 Spec No 2**,** S121-7.

KNOPMAN, D. S. & PETERSEN, R. C. 2014. Mild cognitive impairment and mild dementia: a clinical perspective. *Mayo Clin Proc,* 89**,** 1452-9.

KOKUBO, Y., WATANABE, M., HIGASHIYAMA, A., NAKAO, Y. M., NAKAMURA, F. & MIYAMOTO, Y. 2018. Impact of Intima-Media Thickness Progression in the Common Carotid Arteries on the Risk of Incident Cardiovascular Disease in the Suita Study. *J Am Heart Assoc,* 7.

KOMULAINEN, P., KIVIPELTO, M., LAKKA, T. A., HASSINEN, M., HELKALA, E.-L., PATJA, K., NISSINEN, A. & RAURAMAA, R. 2007a. Carotid intima-media thickness and cognitive function in elderly women: a population-based study. *Neuroepidemiology,* 28**,** 207-213.

KOMULAINEN, P., KIVIPELTO, M., LAKKA, T. A., HASSINEN, M., HELKALA, E. L., PATJA, K., NISSINEN, A. & RAURAMAA, R. 2007b. Carotid intima-media thickness and cognitive function in elderly women: A population-based study. *Neuroepidemiology,* 28**,** 207-213.

KRAWISZ, A. K., CARROLL, B. J. & SECEMSKY, E. A. 2021. Risk Stratification and Management of Extracranial Carotid Artery Disease. *Cardiol Clin,* 39**,** 539-549.

KRISTENSEN, T., HOVIND, P., IVERSEN, H. K. & ANDERSEN, U. B. 2018. Screening with doppler ultrasound for carotid artery stenosis in patients with stroke or transient ischaemic attack. *Clinical Physiology and Functional Imaging,* 38**,** 617-621.

KULLER, L. H. 2004. Ethnic differences in atherosclerosis, cardiovascular disease and lipid metabolism. *Curr Opin Lipidol,* 15**,** 109-13.

LACKLAND, D. T., ROCCELLA, E. J., DEUTSCH, A. F., FORNAGE, M., GEORGE, M. G., HOWARD, G., KISSELA, B. M., KITTNER, S. J., LICHTMAN, J. H., LISABETH, L. D., SCHWAMM, L. H., SMITH, E. E. & TOWFIGHI, A. 2014. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke,* 45**,** 315-53.

LAI, M. M. Y., SHARMAN, M. J., AMES, D. J., ELLIS, K. A., COX, K. L., HEPWORTH, G., DESMOND, P., CYARTO, E. V., MARTINS, R. N., MASTERS, C. L. & LAUTENSCHLAGER, N. T. 2020. Relationship of established cardiovascular risk factors and peripheral biomarkers on cognitive function in adults at risk of cognitive deterioration. *Journal of Alzheimer's disease,* 74**,** 163-171.

LAL, B. K., BEACH, K. W. & SUMNER, D. S. 2011. Intracranial collateralization determines hemodynamic forces for carotid plaque disruption. *Journal of Vascular Surgery,* 54**,** 1461-1471.

LATTIMORE, J. O.-D. L., CELERMAJER DAVID, S. & WILCOX, I. 2003. Obstructive sleep apnea and cardiovascular disease. *Journal of the American College of Cardiology,* 41**,** 1429-1437.

LERITZ, E. C., MCGLINCHEY, R. E., KELLISON, I., RUDOLPH, J. L. & MILBERG, W. P. 2011. Cardiovascular Disease Risk Factors and Cognition in the Elderly. *Curr Cardiovasc Risk Rep,* 5**,** 407-412.

LESZEK, J., MIKHAYLENKO, E. V., BELOUSOV, D. M., KOUTSOURAKI, E., SZCZECHOWIAK, K., KOBUSIAK-PROKOPOWICZ, M., MYSIAK, A., DINIZ, B. S., SOMASUNDARAM, S. G., KIRKLAND, C. E. & ALIEV, G. 2021. The Links between Cardiovascular Diseases and Alzheimer's Disease. *Curr Neuropharmacol,* 19**,** 152-169.

LEVENSON, J. W., SKERRETT, P. J. & GAZIANO, J. M. 2002. Reducing the global burden of cardiovascular disease: the role of risk factors. *Preventive cardiology,* 5**,** 188-199.

LI, Y., ZHENG, S., ZHANG, J., WANG, F., LIU, X. & HE, W. 2021a. Advance ultrasound techniques for the assessment of plaque vulnerability in symptomatic and asymptomatic carotid stenosis: a multimodal ultrasound study. *Cardiovasc Diagn Ther,* 11**,** 28-38.

LI, Z., LIN, L., WU, H., YAN, L., WANG, H., YANG, H. & LI, H. 2021b. Global, Regional, and National Death, and Disability-Adjusted Life-Years (DALYs) for Cardiovascular Disease in 2017 and Trends and Risk Analysis From 1990 to 2017 Using the Global Burden of Disease Study and Implications for Prevention. *Front Public Health,* 9**,** 559751.

LI, Z.-Y., TAVIANI, V. & GILLARD, J. H. The impact of wall shear stress and pressure drop on the stability of the atherosclerotic plaque. 2008 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2008. IEEE, 1373-1376.

LIBBY, P., RIDKER, P. M. & MASERI, A. 2002. Inflammation and atherosclerosis. *Circulation,* 105**,** 1135-1143.

LIN, H.-F., HUANG, L.-C., CHEN, C.-K., JUO, S.-H. H. & CHEN, C.-S. 2020. Carotid atherosclerosis among middle-aged individuals predicts cognition: A 10-year follow-up study. *Atherosclerosis,* 314**,** 27-32.

LIN, M. P. & LIEBESKIND, D. S. 2016. Imaging of Ischemic Stroke. *Continuum (Minneap Minn),* 22**,** 1399-1423.

LINTON, M. F., YANCEY, P. G., DAVIES, S. S., JEROME, W. G., LINTON, E. F., SONG, W. L., DORAN, A. C. & VICKERS, K. C. 2019. The role of lipids and lipoproteins in atherosclerosis. *Endotext [Internet]*.

LIU, X., GAO, Z., XIONG, H., GHISTA, D., REN, L., ZHANG, H., WU, W., HUANG, W. & HAU, W. K. 2016a. Three-dimensional hemodynamics analysis of the circle of Willis in the patient-specific nonintegral arterial structures. *Biomechanics and Modeling in Mechanobiology,* 15**,** 1439-1456.

LIU, X.-J., CHE, P., XING, M., TIAN, X.-B., GAO, C., LI, X. & ZHANG, N. 2021. Cerebral Hemodynamics and Carotid Atherosclerosis in Patients With Subcortical Ischemic Vascular Dementia. *Frontiers in aging neuroscience,* 13.

LIU, Z., ZHAO, Y., WANG, X., ZHANG, H., CUI, Y., DIAO, Y., XIU, J., SUN, X. & JIANG, G. 2016b. Low carotid artery wall shear stress is independently associated with brain white-matter hyperintensities and cognitive impairment in older patients. *Atherosclerosis,* 247**,** 78-86.

LIVINGSTON, G., SOMMERLAD, A., ORGETA, V., COSTAFREDA, S. G., HUNTLEY, J., AMES, D., BALLARD, C., BANERJEE, S., BURNS, A., COHEN-MANSFIELD, J., COOPER, C., FOX, N., GITLIN, L. N., HOWARD, R., KALES, H. C., LARSON, E. B., RITCHIE, K., ROCKWOOD, K., SAMPSON, E. L., SAMUS, Q., SCHNEIDER, L. S., SELBAEK, G., TERI, L. & MUKADAM, N. 2017. Dementia prevention, intervention, and care. *Lancet,* 390**,** 2673-2734.

LLINÀS-REGLÀ, J., VILALTA-FRANCH, J., LÓPEZ-POUSA, S., CALVÓ-PERXAS, L., TORRENTS RODAS, D. & GARRE-OLMO, J. 2017. The Trail Making Test. *Assessment,* 24**,** 183-196.

LORENZATTI, A. J. & TOTH, P. P. 2020. New Perspectives on Atherogenic Dyslipidaemia and Cardiovascular Disease. *Eur Cardiol,* 15**,** 1-9.

LOVE, S. & MINERS, J. S. 2016. Cerebrovascular disease in ageing and Alzheimer's disease. *Acta Neuropathol,* 131**,** 645-58.

LUO, X., LV, Y., BAI, X., QI, J., WENG, X., LIU, S., BAO, X., JIA, H. & YU, B. 2021. Plaque Erosion: A Distinctive Pathological Mechanism of Acute Coronary Syndrome. *Front Cardiovasc Med,* 8**,** 711453.

LYNCH, C. 2020. World Alzheimer Report 2019: Attitudes to dementia, a global survey: Public health: Engaging people in ADRD research. *Alzheimer's & Dementia,* 16**,** e038255.

MACKINNON, A. D., JERRARD-DUNNE, P., PORTEOUS, L. & MARKUS, H. S. 2010. Carotid Intima-Media Thickness is Greater but Carotid Plaque Prevalence is Lower in Black Compared with White Subjects. *American Journal of Neuroradiology,* 31**,** 1951-1955.

MACKINNON, A. D., JERRARD-DUNNE, P., SITZER, M., BUEHLER, A., VON KEGLER, S. & MARKUS, H. S. 2004. Rates and determinants of site-specific progression of carotid artery intima-media thickness: the carotid atherosclerosis progression study. *Stroke,* 35**,** 2150-2154.

MASI, S., D'AIUTO, F., MARTIN-RUIZ, C., KAHN, T., WONG, A., GHOSH, A. K., WHINCUP, P., KUH, D., HUGHES, A., VON ZGLINICKI, T., HARDY, R. & DEANFIELD, J. E. 2014. Rate of telomere shortening and cardiovascular damage: a longitudinal study in the 1946 British Birth Cohort. *Eur Heart J,* 35**,** 3296-303.

MASI, S., GEORGIOPOULOS, G., KHAN, T., JOHNSON, W., WONG, A., CHARAKIDA, M., WHINCUP, P., HUGHES, A. D., RICHARDS, M., HARDY, R. & DEANFIELD, J. 2018. Patterns of adiposity, vascular phenotypes and cognitive function in the 1946 British Birth Cohort. *BMC Medicine,* 16**,** 75.

MATSUMOTO, L., SUZUKI, K., MIZUNO, Y., OHIKE, Y., OZEKI, A., ONO, S., TAKANASHI, M., SAWAKI, D., SUZUKI, T., YAMAZAKI, T., TSUJI, S. & IWATA, A. 2018. Association of subclinical carotid atherosclerosis with immediate memory and other cognitive functions. *Geriatrics & gerontology international,* 18**,** 65-71.

MCKEIGUE, P., FERRIE, J., PIERPOINT, T. & MARMOT, M. 1993. Association of early-onset coronary heart disease in South Asian men with glucose intolerance and hyperinsulinemia. *Circulation,* 87**,** 152-161.

MCKEIGUE, P., SHAH, B. & MARMOT, M. 1991. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *The Lancet,* 337**,** 382-386.

MCPHILLIE, R., BARNES, J., TILLIN, T., CHATURVEDI, N., HUGHES, A. D., JÄGER, H. R. & SUDRE, C. H. 2021. Beyond WMH volume: Coalescence score as a new measure of cerebral small-vessel disease pattern. *Alzheimer's & Dementia,* 17**,** e053034.

MEERSHOEK, A., VAN DIJK, R. A., VERHAGE, S., HAMMING, J. F., VAN DEN BOGAERDT, A. J., BOGERS, A. J., SCHAAPHERDER, A. F. & LINDEMAN, J. H. 2016. Histological evaluation disqualifies IMT and calcification scores as surrogates for grading coronary and aortic atherosclerosis. *Int J Cardiol,* 224**,** 328-334.

MEYERS, C. A. & WEFEL, J. S. 2003. The use of the mini-mental state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. *J Clin Oncol,* 21**,** 3557-8.

MILEI, J., OTTAVIANI, G., LAVEZZI, A. M., GRANA, D. R., STELLA, I. & MATTURRI, L. 2008. Perinatal and infant early atherosclerotic coronary lesions. *Can J Cardiol,* 24**,** 137-41.

MITCHELL, A. J. 2009. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *Journal of Psychiatric Research,* 43**,** 411-431.

MOHER, D., LIBERATI, A., TETZLAFF, J., ALTMAN, D. G. & GROUP, P. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS med,* 6**,** e1000097.

MONAHAN, K. & REDLINE, S. 2011. Role of obstructive sleep apnea in cardiovascular disease. *Curr Opin Cardiol,* 26**,** 541-7.

MONTAUBAN VAN SWIJNDREGT, A. D., DE LANGE, E. E., DE GROOT, E. & ACKERSTAFF, R. G. A. 1999. An in vivo evaluation of the reproducibility of intima-media thickness measurements of the carotid artery segments using B-mode ultrasound. *Ultrasound in Medicine & Biology,* 25**,** 323-330.

MORONI, F., AMMIRATI, E., MAGNONI, M., D'ASCENZO, F., ANSELMINO, M., ANZALONE, N., ROCCA, M. A., FALINI, A., FILIPPI, M. & CAMICI, P. G. 2016a. Carotid atherosclerosis, silent ischemic brain damage and brain atrophy: A systematic review and meta-analysis. *International Journal of Cardiology,* 223**,** 681-687.

MORONI, F., AMMIRATI, E., MAGNONI, M., D'ASCENZO, F., ANSELMINO, M., ANZALONE, N., ROCCA, M. A., FALINI, A., FILIPPI, M. & CAMICI, P. G. 2016b. Carotid atherosclerosis, silent ischemic brain damage and brain atrophy: A systematic review and meta-analysis. *Int J Cardiol,* 223**,** 681-687.

MUELA, H. C. S., COSTA-HONG, V. A., YASSUDA, M. S., MORAES, N. C., MEMORIA, C. M., MACHADO, M. F., BOR-SENG-SHU, E., NOGUEIRA, R. C., MANSUR, A. J., MASSARO, A. R., NITRINI, R., MACEDO, T. A. & BORTOLOTTO, L. A. 2018. Higher arterial stiffness is associated with lower cognitive performance in patients with hypertension. *Journal of Clinical Hypertension,* 20**,** 22-30.

MULLER, J. E., TOFLER, G. & STONE, P. 1989. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation,* 79**,** 733-743.

MULLER, M., GROBBEE, D. E., ALEMAN, A., BOTS, M. & VAN DER SCHOUW, Y. T. 2007. Cardiovascular disease and cognitive performance in middle-aged and elderly men. *Atherosclerosis,* 190**,** 143-149.

MULLER, M., VAN DER GRAAF, Y., ALGRA, A., HENDRIKSE, J., MALI, W. P. & GEERLINGS, M. I. 2011. Carotid atherosclerosis and progression of brain atrophy: The SMART-MR Study. *Annals of Neurology,* 70**,** 237-244.

MUNRO, J. & COTRAN, R. 1988. The pathogenesis of atherosclerosis: atherogenesis and inflammation. *Laboratory investigation; a journal of technical methods and pathology,* 58**,** 249-261.

MÜNZEL, T., HAHAD, O., SØRENSEN, M., LELIEVELD, J., DUERR, G. D., NIEUWENHUIJSEN, M. & DAIBER, A. 2021. Environmental risk factors and cardiovascular diseases: a comprehensive expert review. *Cardiovascular Research,* 118**,** 2880-2902.

MURRAY, C. S., NAHAR, T., KALASHYAN, H., BECHER, H. & NANDA, N. C. 2018. Ultrasound assessment of carotid arteries: Current concepts, methodologies, diagnostic criteria, and technological advancements. *Echocardiography,* 35**,** 2079-2091.

MUSUNURU, K. 2010. Atherogenic Dyslipidemia: Cardiovascular Risk and Dietary Intervention. *Lipids,* 45**,** 907-914.

MWOROZI, K., AMEDA, F., BYANYIMA, R. K. & NAKASUJJA, N. 2019a. Carotid artery plaque detected on ultrasound is associated with impaired cognitive state in the elderly: A population-based study in Wakiso district, Uganda. *J Clin Neurosci,* 68**,** 194-200.

MWOROZI, K., AMEDA, F., BYANYIMA, R. K. & NAKASUJJA, N. 2019b. Carotid artery plaque detected on ultrasound is associated with impaired cognitive state in the elderly: A population-based study in Wakiso district, Uganda. *Journal of Clinical Neuroscience,* 68**,** 194-200.

NABEL, E. G. 2003. Cardiovascular disease. *New England Journal of Medicine,* 349**,** 60-72.

NAGAI, M., HOSHIDE, S., NISHIKAWA, M., MASAHISA, S. & KARIO, K. 2014. Visit-to-visit blood pressure variability in the elderly: associations with cognitive impairment and carotid artery remodeling. *Atherosclerosis,* 233**,** 19-26.

NAGHAVI, M., ABAJOBIR, A. A., ABBAFATI, C., ABBAS, K. M., ABD-ALLAH, F., ABERA, S. F., ABOYANS, V., ADETOKUNBOH, O., ARNLOV, J., AFSHIN, A., AGRAWAL, A., KIADALIRI, A. A., AHMADI, A., AHMED, M. B., AICHOUR, A. N., AICHOUR, I., AICHOUR, M. T. E., AIYAR, S., AL-EYADHY, A., ALAHDAB, F., AL-ALY, Z., ALAM, K., ALAM, N., ALAM, T., ALENE, K. A., ALI, S. D., ALIZADEH-NAVAEI, R., ALKAABI, J. M., ALKERWI, A., ALLA, F., ALLEBECK, P., ALLEN, C., AL-RADDADI, R., ALSHARIF, U., ALTIRKAWI, K. A., ALVIS-GUZMAN, N., AMARE, A. T., AMINI, E., AMMAR, W., AMOAKO, Y. A., ANBER, N., ANDERSEN, H. H., ANDREI, C. L., ANDROUDI, S., ANSARI, H., ANTONIO, C. A. T., ANWARI, P., ARORA, M., ARTAMAN, A., ARYAL, K. K., ASAYESH, H., ASGEDOM, S. W., ATEY, T. M., AVILA-BURGOS, L., AVOKPAHO, E. F. G. A., AWASTHI, A., PAULINA, B., QUINTANILLA, A., BEJOT, Y., BABALOLA, T. K., BACHA, U., BALAKRISHNAN, K., BARAC, A., BARBOZA, M. A., BARKER-COLLO, S. L., BARQUERA, S., BARREGARD, L., BARRERO, L. H., BAUNE, B. T., BEDI, N., BEGHI, E., BEKELE, B. B., BELL, M. L., BENNETT, J. R., BENSENOR, I. M., BERHANE, A., BERNABE, E., BETSU, B. D., BEURAN, M., BHATT, S., BIADGILIGN, S., BIENHOFF, K., BIKBOV, B., BISANZIO, D., BOURNE, R. R. A., BREITBORDE, N. J. K., NEGESA, L., BULTO, B., BUMGARNER, B. R., BUTT, Z. A., CARDENAS, R., CAHUANA-HURTADO, L., CAMERON, E., CAMPUZANO, J. C., CAR, J., CARRERO, J. J., CARTER, A., CASEY, D. C., CASTANEDA-ORJUELA, C. A., CATALA-LOPEZ, F., et al. 2017. Global, regional, and national age-sex specific mortality for

264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet,* 390**,** 1151-1210.

NAMBI, V., CHAMBLESS, L., FOLSOM, A. R., HE, M., HU, Y., MOSLEY, T., VOLCIK, K., BOERWINKLE, E. & BALLANTYNE, C. M. 2010. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol,* 55**,** 1600-7.

NAZROO, J. Y., FALASCHETTI, E., PIERCE, M. & PRIMATESTA, P. 2009. Ethnic inequalities in access to and outcomes of healthcare: analysis of the Health Survey for England. *J Epidemiol Community Health,* 63**,** 1022-7.

NESTO, R. W. 2004. Correlation between cardiovascular disease and diabetes mellitus: current concepts. *The American Journal of Medicine,* 116**,** 11-22.

NEZU, T. & HOSOMI, N. 2020. Usefulness of Carotid Ultrasonography for Risk Stratification of Cerebral and Cardiovascular Disease. *J Atheroscler Thromb,* 27**,** 1023-1035.

NHS 13 September 2022. Stroke.

NONTERAH, E. A., CROWTHER, N. J., KLIPSTEIN-GROBUSCH, K., ODURO, A. R., KAVOUSI, M., AGONGO, G., ANDERSON, T. J., ASIKI, G., BOUA, P. R., CHOMA, S. S. R., COUPER, D. J., ENGSTRÖM, G., DE GRAAF, J., KAUHANEN, J., LONN, E. M., MATHIESEN, E. B., MICKLESFIELD, L. K., OKAZAKI, S., POLAK, J. F., RUNDEK, T., SALONEN, J. T., TOLLMAN, S. M., TUOMAINEN, T. P., GROBBEE, D. E., RAMSAY, M. & BOTS, M. L. 2022. Racial and Ethnic Differences in the Association Between Classical Cardiovascular Risk Factors and Common Carotid Intima-Media Thickness: An Individual Participant Data Meta-Analysis. *J Am Heart Assoc,* 11**,** e023704.

NORDESTGAARD, L. T., CHRISTOFFERSEN, M. & FRIKKE-SCHMIDT, R. 2022. Shared Risk Factors between Dementia and Atherosclerotic Cardiovascular Disease. *Int J Mol Sci,* 23.

NORTH AMERICAN SYMPTOMATIC CAROTID ENDARTERECTOMY TRIAL (NASCET) STEERING COMMITTEE 1991. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke,* 22**,** 711-20.

NOVELLA, R. & OLIVERA, J. 2019. Gender Differences in Cognitive Abilities Among the Elderly Poor of Peru. *Economía , 42 (83) pp. 95-109. (2019)*.

O'BRIEN, E., ASMAR, R., BEILIN, L., IMAI, Y., MANCIA, G., MENGDEN, T., MYERS, M., PADFIELD, P., PALATINI, P., PARATI, G., PICKERING, T., REDON, J., STAESSEN, J., STERGIOU, G., VERDECCHIA, P. & EUROPEAN SOCIETY OF HYPERTENSION WORKING GROUP ON BLOOD PRESSURE, M. 2005. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens,* 23**,** 697-701.

O'LEARY, D. H. & BOTS, M. L. 2010. Imaging of atherosclerosis: carotid intima–media thickness. *European Heart Journal,* 31**,** 1682-1689.

OATES, C. P., NAYLOR, A. R., HARTSHORNE, T., CHARLES, S. M., FAIL, T., HUMPHRIES, K., ASLAM, M. & KHODABAKHSH, P. 2009. Joint Recommendations for Reporting Carotid Ultrasound Investigations in the United Kingdom. *European Journal of Vascular and Endovascular Surgery,* 37**,** 251-261.

OFFICE FOR NATIONAL STATISTICS 2015. Harmonised Concepts and Questions for Social Data Sources. Primary Principles. Ethnic Group.

OKRAINEC, K., BANERJEE, D. K. & EISENBERG, M. J. 2004. Coronary artery disease in the developing world. *American heart journal,* 148**,** 7-15.

OLIN, J. W. & SEALOVE, B. A. Peripheral artery disease: current insight into the disease and its diagnosis and management. Mayo Clinic Proceedings, 2010. Elsevier, 678-692.

ON SMOKING, O., CONTROL, C. F. D. & PREVENTION 2010. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the surgeon general.

OSTLING, G., HEDBLAD, B., BERGLUND, G. & GONÇALVES, I. 2007. Increased echolucency of carotid plaques in patients with type 2 diabetes. *Stroke,* 38**,** 2074-8.

OTA, H., YU, W., UNDERHILL, H. R., OIKAWA, M., DONG, L., ZHAO, X., POLISSAR, N. L., NERADILEK, B., GAO, T., ZHANG, Z., YAN, Z., GUO, M., ZHANG, Z., HATSUKAMI, T. S. & YUAN, C. 2009. Hemorrhage and large lipid-rich necrotic cores are independently associated with thin or ruptured fibrous caps: an in vivo 3T MRI study. *Arterioscler Thromb Vasc Biol,* 29**,** 1696-701.

PACIARONI, M. & BOGOUSSLAVSKY, J. 2013. Connecting Cardiovascular Disease and Dementia: Further Evidence. *Journal of the American Heart Association,* 2**,** e000656.

PANTONI, L. 2010. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet Neurology,* 9**,** 689-701.

PANZA, G. A., PUHL, R. M., TAYLOR, B. A., ZALESKI, A. L., LIVINGSTON, J. & PESCATELLO, L. S. 2019. Links between discrimination and cardiovascular health among socially stigmatized groups: A systematic review. *PLoS One,* 14**,** e0217623.

PARK, C. M., WILLIAMS, E. D., CHATURVEDI, N., TILLIN, T., STEWART, R. J., RICHARDS, M., SHIBATA, D., MAYET, J. & HUGHES, A. D. 2017. Associations Between Left Ventricular Dysfunction and Brain Structure and Function: Findings From the SABRE (Southall and Brent Revisited) Study. *J Am Heart Assoc,* 6.

PATEL, J. V., VYAS, A., CRUICKSHANK, J. K., PRABHAKARAN, D., HUGHES, E., REDDY, K. S., MACKNESS, M. I., BHATNAGAR, D. & DURRINGTON, P. N. 2006. Impact of migration on coronary heart disease risk factors: Comparison of Gujaratis in Britain and their contemporaries in villages of origin in India. *Atherosclerosis,* 185**,** 297-306.

PATNODE, C. D., PERDUE, L. A., ROSSOM, R. C., RUSHKIN, M. C., REDMOND, N., THOMAS, R. G. & LIN, J. S. 2020. *Screening for Cognitive Impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task Force,* Rockville (MD), Agency for Healthcare Research and Quality.

PENHA, P. D., ZAK, F. G., LIN, J. C. & LIN, C.-S. 1988. Morphodynamic interpretation of acute coronary thrombosis, with special reference to volcano-like eruption of atheromatous plaque caused by coronary artery spasm. *Angiology,* 39**,** 535-547.

PERWAIZ KHAN, S., GUL, P., KHEMANI, S. & YAQUB, Z. 2013. Determination of site-specific carotid-intima media thickness: common -carotid artery and carotid bifurcation in hypercholesterolemia patients. *Pak J Med Sci,* 29**,** 1249-52.

PETERS, S. A. & BOTS, M. L. 2013. Carotid intima-media thickness studies: study design and data analysis. *J Stroke,* 15**,** 38-48.

PETERS, S. A. E., DEN RUIJTER, H. M., PALMER, M. K., GROBBEE, D. E., CROUSE, J. R., O'LEARY, D. H., EVANS, G. W., RAICHLEN, J. S. & BOTS, M. L. 2012. Extensive or Restricted Ultrasound Protocols to Measure Carotid Intima-Media Thickness: Analysis of Completeness Rates and Impact on Observed Rates of Change Over Time. *Journal of the American Society of Echocardiography,* 25**,** 91-100.

PETTIGREW, C. & SOLDAN, A. 2019. Defining Cognitive Reserve and Implications for Cognitive Aging. *Curr Neurol Neurosci Rep,* 19**,** 1.

PIEGZA, M., JAWORSKA, I., PIEGZA, J., BUJAK, K., DĘBSKI, P., LEKSOWSKA, A., GORCZYCA, P., GĄSIOR, M. & PUDLO, R. 2022. Cognitive Functions after Carotid Artery Stenting—1-Year Follow-Up Study. *Journal of Clinical Medicine,* 11**,** 3019.

PIGNOLI, P., TREMOLI, E., POLI, A., ORESTE, P. & PAOLETTI, R. 1986. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation,* 74**,** 1399-1406.

PINTO, T. C. C., MACHADO, L., BULGACOV, T. M., RODRIGUES-JÚNIOR, A. L., COSTA, M. L. G., XIMENES, R. C. C. & SOUGEY, E. B. 2019. Is the Montreal Cognitive Assessment (MoCA) screening superior to the Mini-Mental State Examination (MMSE) in the detection of mild cognitive impairment (MCI) and Alzheimer's Disease (AD) in the elderly? *Int Psychogeriatr,* 31**,** 491-504.

PIRI, R., GERKE, O. & HOILUND-CARLSEN, P. F. 2020. Molecular imaging of carotid artery atherosclerosis with PET: a systematic review. *Eur J Nucl Med Mol Imaging,* 47**,** 2016-2025.

POTIER, L., ABI KHALIL, C., MOHAMMEDI, K. & ROUSSEL, R. 2011. Use and utility of ankle brachial index in patients with diabetes. *European Journal of Vascular and Endovascular Surgery,* 41**,** 110-116.

PRATI, P., TOSETTO, A., VANUZZO, D., BADER, G., CASAROLI, M., CANCIANI, L., CASTELLANI, S. & TOUBOUL, P.-J. 2008. Carotid intima media thickness and plaques can predict the occurrence of ischemic cerebrovascular events. *Stroke,* 39**,** 2470-2476.

PRINCE, M., ACOSTA, D., FERRI, C. P., GUERRA, M., HUANG, Y., JACOB, K., LLIBRE RODRÍGUEZ, J. J., SALAS, A., SOSA, A. L. & WILLIAMS, J. D. 2011. A brief dementia screener suitable for use by non-specialists in resource poor settings—the cross-cultural derivation and validation of the brief Community Screening Instrument for Dementia. *International journal of geriatric psychiatry,* 26**,** 899-907.

RAO, R. 2001. The role of carotid stenosis in vascular cognitive impairment. *European neurology,* 46**,** 63-69.

REDWOOD, S. & GILL, P. S. 2013. Under-representation of minority ethnic groups in research — call for action. *British Journal of General Practice,* 63**,** 342.

REN, L., CAI, J., LIANG, J., LI, W. & SUN, Z. 2015. Impact of Cardiovascular Risk Factors on Carotid Intima-Media Thickness and Degree of Severity: A Cross-Sectional Study. *PLoS One,* 10**,** e0144182.

RODGERS, J. L., JONES, J., BOLLEDDU, S. I., VANTHENAPALLI, S., RODGERS, L. E., SHAH, K., KARIA, K. & PANGULURI, S. K. 2019. Cardiovascular Risks Associated with Gender and Aging. *J Cardiovasc Dev Dis,* 6.

ROGNE, S. O., SOLBU, M. D., ARNTZEN, K. A., HERDER, M., MATHIESEN, E. B. & SCHIRMER, H. 2013. Albuminuria and carotid atherosclerosis as predictors of cognitive function in a general population. *European Neurology,* 70**,** 340-8.

ROMERO, J. R., BEISER, A., SESHADRI, S., BENJAMIN, E. J., POLAK, J. F., VASAN, R. S., AU, R., DECARLI, C. & WOLF, P. A. 2009a. Carotid Artery Atherosclerosis, MRI Indices of Brain Ischemia, Aging, and Cognitive Impairment. *Stroke,* 40**,** 1590-1596.

ROMERO, J. R., BEISER, A., SESHADRI, S., BENJAMIN, E. J., POLAK, J. F., VASAN, R. S., AU, R., DECARLI, C. & WOLF, P. A. 2009b. Carotid artery atherosclerosis, MRI indices of brain ischemia, aging, and cognitive impairment: the Framingham study. *Stroke,* 40**,** 1590-1596.

ROMERO, J. R., BEISER, A., SESHADRI, S., BENJAMIN, E. J., POLAK, J. F., VASAN, R. S., AU, R., DECARLI, C. & WOLF, P. A. 2009c. Carotid artery atherosclerosis, MRI indices of brain ischemia, aging, and cognitive impairment: the Framingham study. *Stroke,* 40**,** 1590-6.

ROSE, G. 2001. Sick individuals and sick populations. *International Journal of Epidemiology,* 30**,** 427-432.

ROSENGREN, A., SMYTH, A., RANGARAJAN, S., RAMASUNDARAHETTIGE, C., BANGDIWALA, S. I., ALHABIB, K. F., AVEZUM, A., BENGTSSON BOSTRÖM, K., CHIFAMBA, J., GULEC, S., GUPTA, R., IGUMBOR, E. U., IQBAL, R., ISMAIL, N., JOSEPH, P., KAUR, M., KHATIB, R., KRUGER, I. M., LAMELAS, P., LANAS, F., LEAR, S. A., LI, W., WANG, C., QUIANG, D., WANG, Y., LOPEZ-JARAMILLO, P., MOHAMMADIFARD, N., MOHAN, V., MONY, P. K., POIRIER, P., SRILATHA, S., SZUBA, A., TEO, K., WIELGOSZ, A., YEATES, K. E., YUSOFF, K., YUSUF, R., YUSUFALI, A. H., ATTAEI, M. W., MCKEE, M. & YUSUF, S. 2019. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. *The Lancet Global Health,* 7**,** e748-e760.

ROSS, R. 1986. The pathogenesis of atherosclerosis—an update. *New England journal of medicine,* 314**,** 488-500.

ROSS, R. 1993. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature,* 362**,** 801-809.

ROTHWELL, P. M., ELIASZIW, M., GUTNIKOV, S. A., FOX, A. J., TAYLOR, D. W., MAYBERG, M. R., WARLOW, C. P. & BARNETT, H. J. 2003. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet,* 361**,** 107-16.

ROUCH, L., CESTAC, P., SALLERIN, B., ANDRIEU, S., BAILLY, H., BEUNARDEAU, M., COHEN, A., DUBAIL, D., HERNANDORENA, I., SEUX, M. L., VIDAL, J. S. & HANON, O. 2018. Pulse wave velocity is associated with greater risk of dementia in mild cognitive impairment patients. *Journal of Hypertension,* 36 (Supplement 3)**,** e340.

ROY, E. 2013. Cognitive Function. *In:* GELLMAN, M. D. & TURNER, J. R. (eds.) *Encyclopedia of Behavioral Medicine.* New York, NY: Springer New York.

ROYSTON, P. & ALTMAN, D. G. 1994. Regression Using Fractional Polynomials of Continuous Covariates: Parsimonious Parametric Modelling. *Journal of the Royal Statistical Society. Series C (Applied Statistics),* 43**,** 429-467.

SABAYAN, B., VAN BUCHEM, M. A., SIGURDSSON, S., ZHANG, Q., HARRIS, T. B., GUDNASON, V., ARAI, A. E. & LAUNER, L. J. 2015. Cardiac hemodynamics are linked with structural and functional features of brain aging: the age, gene/environment susceptibility (AGES)-Reykjavik Study. *Journal of the American Heart Association,* 4**,** e001294.

SACCO, R. L., KASNER, S. E., BRODERICK, J. P., CAPLAN, L. R., CONNORS, J., CULEBRAS, A., ELKIND, M. S., GEORGE, M. G., HAMDAN, A. D. & HIGASHIDA, R. T. 2013. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke,* 44**,** 2064-2089.

SACCO, R. L., ROBERTS, J. K., BODEN-ALBALA, B., GU, Q., LIN, I. F., KARGMAN, D. E., BERGLUND, L., HAUSER, W. A., SHEA, S. & PAIK, M. C. 1997. Race-ethnicity and determinants of carotid atherosclerosis in a multiethnic population. The Northern Manhattan Stroke Study. *Stroke,* 28**,** 929-35.

SAMIERI, C., PERIER, M.-C., GAYE, B., PROUST-LIMA, C., HELMER, C., DARTIGUES, J.-F., BERR, C., TZOURIO, C. & EMPANA, J.-P. 2018. Association of cardiovascular health level in older age with cognitive decline and incident dementia. *Jama,* 320**,** 657-664.

SARKAR, S., GHOSH, S., GHOSH, S. K. & COLLIER, A. 2007. Role of transcranial Doppler ultrasonography in stroke. *Postgrad Med J,* 83**,** 683-9.

SAXENA, A., NG, E. Y. K. & LIM, S. T. 2019a. Imaging modalities to diagnose carotid artery stenosis: progress and prospect. *Biomed Eng Online,* 18**,** 66.

SAXENA, A., NG, E. Y. K. & LIM, S. T. 2019b. Imaging modalities to diagnose carotid artery stenosis: progress and prospect. *BioMedical Engineering OnLine,* 18**,** 66.

SAXENA, Y., SAXENA, V., MITTAL, M., SRIVASTAVA, M. & RAGHUVANSHI, S. 2017. Age-Wise Association of Carotid Intima Media Thickness in Ischemic Stroke. *Ann Neurosci,* 24**,** 5-11.

SCHAICH, C. L., YEBOAH, J., ESPELAND, M. A., BAKER, L. D., DING, J., HAYDEN, K. M., SACHS, B. C., CRAFT, S., RAPP, S. R., LUCHSINGER, J. A., FITZPATRICK, A. L., HECKBERT, S. R., POST, W. S., BURKE, G. L., ALLEN, N. B. & HUGHES, T. M. 2022. Association of Vascular Risk Scores and Cognitive Performance in a Diverse Cohort: The Multi-Ethnic Study of Atherosclerosis. *J Gerontol A Biol Sci Med Sci,* 77**,** 1208-1215.

SCHULTZ, W. M., KELLI, H. M., LISKO, J. C., VARGHESE, T., SHEN, J., SANDESARA, P., QUYYUMI, A. A., TAYLOR, H. A., GULATI, M., HAROLD, J. G., MIERES, J. H., FERDINAND, K. C., MENSAH, G. A. & SPERLING, L. S. 2018. Socioeconomic Status and Cardiovascular Outcomes. *Circulation,* 137**,** 2166-2178.

SCHWARTZ, C., VALENTE, A., SPRAGUE, E. A., KELLEY, J. & NEREM, R. 1991. The pathogenesis of atherosclerosis: an overview. *Clinical cardiology,* 14**,** 1-16.

SEEKIRCHER, L., TSCHIDERER, L., LIND, L., SAFAROVA, M. S., KAVOUSI, M., IKRAM, M. A., LONN, E., YUSUF, S., GROBBEE, D. E., KASTELEIN, J. J. P., VISSEREN, F. L. J., WALTERS, M., DAWSON, J., HIGGINS, P., AGEWALL, S., CATAPANO, A., DE GROOT, E., ESPELAND, M. A., KLINGENSCHMID, G., MAGLIANO, D., OLSEN, M. H., PREISS, D., SANDER, D., SKILTON, M., ZOZULINSKA-ZIOLKIEWICZ, D. A., GROOTEMAN, M. P. C., BLANKESTIJN, P. J., KITAGAWA, K., OKAZAKI, S., MANZI, M. V., MANCUSI, C., IZZO, R., DESVARIEUX, M., RUNDEK, T., GERSTEIN, H. C., BOTS, M. L., SWEETING, M. J., LORENZ, M. W. & WILLEIT, P. 2023. Intima-media thickness at the near or far wall of the common carotid artery in cardiovascular risk assessment. *Eur Heart J Open,* 3**,** oead089.

SETHI, D., GOFUR, E. M. & MUNAKOMI, S. 2019. Anatomy, head and neck, carotid arteries.

SHARMA, M., HART, R. G., CONNOLLY, S. J., BOSCH, J., SHESTAKOVSKA, O., NG, K. K. H., CATANESE, L., KELTAI, K., ABOYANS, V., ALINGS, M., HA, J.-W., VARIGOS, J., TONKIN, A., O'DONNELL, M., BHATT, D. L., FOX, K., MAGGIONI, A., BERKOWITZ, S. D., BRUNS, N. C., YUSUF, S. & EIKELBOOM, J. W. 2019. Stroke Outcomes in the COMPASS Trial. *Circulation,* 139**,** 1134-1145.

SILVESTRINI, M., GOBBI, B., PASQUALETTI, P., BARTOLINI, M., BARUFFALDI, R., LANCIOTTI, C., CERQUA, R., ALTAMURA, C., PROVINCIALI, L. & VERNIERI, F. 2009. Carotid atherosclerosis and cognitive decline in patients with Alzheimer's disease. *Neurobiology of Aging,* 30**,** 1177-1183.

SIMMONS, J. P., NELSON, L. D. & SIMONSOHN, U. 2011. False-positive psychology: undisclosed flexibility in data collection and analysis allows presenting anything as significant. *Psychol Sci,* 22**,** 1359-66.

SINGH-MANOUX, A., BRITTON, A., KIVIMAKI, M., GUEGUEN, A., HALCOX, J. & MARMOT, M. 2008a. Socioeconomic status moderates the association between carotid intima-media thickness and cognition in midlife: Evidence from the Whitehall II study. *Atherosclerosis,* 197**,** 541-548.

SINGH-MANOUX, A., BRITTON, A., KIVIMAKI, M., GUÉGUEN, A., HALCOX, J. & MARMOT, M. 2008b. Socioeconomic status moderates the association between carotid intima-media thickness and cognition in midlife: Evidence from the Whitehall II study. *Atherosclerosis,* 197**,** 541-548.

SIRICO, G., SPADERA, L., DE LAURENTIS, M. & BREVETTI, G. 2009. Carotid artery disease and stroke in patients with peripheral arterial disease. The role of inflammation. *Monaldi Arch Chest Dis,* 72**,** 10-7.

SKOOG, I. 1998. Status of Risk Factors for Vascular Dementia. *Neuroepidemiology,* 17**,** 2-9.

SKROBOT, O. A., BLACK, S. E., CHEN, C., DECARLI, C., ERKINJUNTTI, T., FORD, G. A., KALARIA, R. N., O'BRIEN, J., PANTONI, L. & PASQUIER, F. 2018. Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the Vascular Impairment of Cognition Classification Consensus Study. *Alzheimer's & Dementia,* 14**,** 280-292.

SOBIESZCZYK, P. & BECKMAN, J. 2006. Carotid artery disease. *Circulation,* 114**,** e244-e247.

SOL, A. I. D., MOONS, K. G. M., HOLLANDER, M., HOFMAN, A., KOUDSTAAL, P. J., GROBBEE, D. E., BRETELER, M. M. B., WITTEMAN, J. C. M. & BOTS, M. L. 2001. Is Carotid Intima-Media Thickness Useful in Cardiovascular Disease Risk Assessment? *Stroke,* 32**,** 1532-1538.

SONG, P., FANG, Z., WANG, H., CAI, Y., RAHIMI, K., ZHU, Y., FOWKES, F. G. R., FOWKES, F. J. I. & RUDAN, I. 2020a. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *Lancet Glob Health,* 8**,** e721-e729.

SONG, P., FANG, Z., WANG, H., CAI, Y., RAHIMI, K., ZHU, Y., FOWKES, F. G. R., FOWKES, F. J. I. & RUDAN, I. 2020b. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *Lancet Global Health,* 8**,** e721-e729.

SOSA, A. L., ALBANESE, E., PRINCE, M., ACOSTA, D., FERRI, C. P., GUERRA, M., HUANG, Y., JACOB, K., DE RODRIGUEZ, J. L. & SALAS, A. 2009. Population normative data for the 10/66 Dementia Research Group cognitive test battery from Latin America, India and China: a cross-sectional survey. *BMC neurology,* 9**,** 1-11.

STAFFORD, M., BLACK, S., SHAH, I., HARDY, R., PIERCE, M., RICHARDS, M., WONG, A. & KUH, D. 2013. Using a birth cohort to study ageing: representativeness and response rates in the National Survey of Health and Development. *Eur J Ageing,* 10**,** 145-157.

STANEK, K. M., GUNSTAD, J., SPITZNAGEL, M. B., WAECHTER, D., HUGHES, J. W., LUYSTER, F., JOSEPHSON, R. & ROSNECK, J. 2011. Improvements in Cognitive Function Following Cardiac Rehabilitation for Older Adults With Cardiovascular Disease. *International Journal of Neuroscience,* 121**,** 86-93.

STEFANOVA, E., PAVLOVIC, A., JOVANOVIC, Z., VESELINOVIC, N., DESPOTOVIC, I., STOJKOVIC, T., STERNIC, N. & KOSTIC, V. 2012. Vascular risk factors in Alzheimer's disease - preliminary report. *J Neurol Sci,* 322**,** 166-9.

STEIN, J. H., KORCARZ, C. E., HURST, R. T., LONN, E., KENDALL, C. B., MOHLER, E. R., NAJJAR, S. S., REMBOLD, C. M. & POST, W. S. 2008a. Use of Carotid Ultrasound to Identify Subclinical Vascular

Disease and Evaluate Cardiovascular Disease Risk: A Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force Endorsed by the Society for Vascular Medicine. *Journal of the American Society of Echocardiography,* 21**,** 93-111.

STEIN, J. H., KORCARZ, C. E., HURST, R. T., LONN, E., KENDALL, C. B., MOHLER, E. R., NAJJAR, S. S., REMBOLD, C. M. & POST, W. S. 2008b. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr,* 21**,** 93-111; quiz 189-90.

STEIN, J. H., KORCARZ, C. E., HURST, R. T., LONN, E., KENDALL, C. B., MOHLER, E. R., NAJJAR, S. S., REMBOLD, C. M. & POST, W. S. 2008c. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr,* 21**,** 93-111.

STEINL, D. C. & KAUFMANN, B. A. 2015. Ultrasound imaging for risk assessment in atherosclerosis. *Int J Mol Sci,* 16**,** 9749-69.

STERN, Y. 2002. What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society,* 8**,** 448-460.

STERN, Y. 2009. Cognitive reserve. *Neuropsychologia,* 47**,** 2015-28.

STERN, Y. 2012. Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology,* 11**,** 1006-1012.

STOLL, G. & BENDSZUS, M. 2006. Inflammation and atherosclerosis: novel insights into plaque formation and destabilization. *Stroke,* 37**,** 1923-1932.

STRONG, J. P., MALCOM, G. T., OALMANN, M. C. & WISSLER, R. W. 1997. The PDAY Study: natural history, risk factors, and pathobiology. Pathobiological Determinants of Atherosclerosis in Youth. *Ann N Y Acad Sci,* 811**,** 226-35; discussion 235-7.

SUDRE, C. H., SMITH, L., ATKINSON, D., CHATURVEDI, N., OURSELIN, S., BARKHOF, F., HUGHES, A. D., JAGER, H. R. & CARDOSO, M. J. 2018. Cardiovascular Risk Factors and White Matter Hyperintensities: Difference in Susceptibility in South Asians Compared With Europeans. *J Am Heart Assoc,* 7**,** e010533.

TAN, B. K., WONG, C. H. & CHEN, H. C. 2010. Anatomic variations in head and neck reconstruction. *Semin Plast Surg,* 24**,** 155-70.

TATTERSALL, M. C., GASSETT, A., KORCARZ, C. E., GEPNER, A. D., KAUFMAN, J. D., LIU, K. J., ASTOR, B. C., SHEPPARD, L., KRONMAL, R. A. & STEIN, J. H. 2014. Predictors of Carotid Thickness and Plaque Progression During a Decade. *Stroke,* 45**,** 3257-3262.

TAYLOR, C., TILLIN, T., CHATURVEDI, N., DEWEY, M., FERRI, C., HUGHES, A., PRINCE, M., RICHARDS, M., SHAH, A. & STEWART, R. 2013. Midlife Hypertensive Status and Cognitive Function 20 Years Later: The Southall and Brent Revisited Study. *Journal of the American Geriatrics Society,* 61**,** 1489-98.

TENDERA, M., ABOYANS, V., BARTELINK, M.-L., BAUMGARTNER, I., CLÉMENT, D., COLLET, J.-P., CREMONESI, A., DE CARLO, M., ERBEL, R., FOWKES, F. G. R., HERAS, M., KOWNATOR, S., MINAR, E., OSTERGREN, J., POLDERMANS, D., RIAMBAU, V., ROFFI, M., RÖTHER, J., SIEVERT, H., VAN SAMBEEK, M., ZELLER, T., BAX, J., AURICCHIO, A., BAUMGARTNER, H., CECONI, C., DEAN, V., DEATON, C., FAGARD, R., FUNCK-BRENTANO, C., HASDAI, D., HOES, A., KNUUTI, J., KOLH, P., MCDONAGH, T., MOULIN, C., POPESCU, B., REINER, Z., SECHTEM, U., SIRNES, P. A., TORBICKI, A., VAHANIAN, A., WINDECKER, S., KOLH, P., TORBICKI, A., AGEWALL, S., BLINC, A., BULVAS, M., COSENTINO, F., DE BACKER, T., GOTTSÄTER, A., GULBA, D., GUZIK, T. J., JÖNSSON, B., KÉSMÁRKY, G., KITSIOU, A., KUCZMIK, W., LARSEN, M. L., MADARIC, J., MAS, J.-L., MCMURRAY, J. J. V., MICARI, A., MOSSERI, M., MÜLLER, C., NAYLOR, R., NORRVING, B., OTO, O., PASIERSKI, T., PLOUIN, P.-F., RIBICHINI, F., RICCO, J.-B., RUILOPE, L., SCHMID, J.-P., SCHWEHR, U., SOL, B.

G. M., SPRYNGER, M., TIEFENBACHER, C., TSIOUFIS, C. & VAN DAMME, H. 2011. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases. *European heart journal,* 32**,** 2851-2906.

THURSTON, R. C., WU, M., BARINAS-MITCHELL, E., CHANG, Y., AIZENSTEIN, H., DERBY, C. A. & MAKI, P. M. 2023. Carotid intima media thickness and white matter hyperintensity volume among midlife women. *Alzheimer's & Dementia,* 19**,** 3129-3137.

TILLIN, T., FOROUHI, N. G., MCKEIGUE, P. M. & CHATURVEDI, N. 2012a. Southall And Brent REvisited: Cohort profile of SABRE, a UK population-based comparison of cardiovascular disease and diabetes in people of European, Indian Asian and African Caribbean origins. *International journal of epidemiology,* 41**,** 33-42.

TILLIN, T., FOROUHI, N. G., MCKEIGUE, P. M. & CHATURVEDI, N. 2012b. Southall And Brent REvisited: Cohort profile of SABRE, a UK population-based comparison of cardiovascular disease and diabetes in people of European, Indian Asian and African Caribbean origins. *Int J Epidemiol,* 41**,** 33-42.

TILLIN, T., HUGHES, A. D., GODSLAND, I. F., WHINCUP, P., FOROUHI, N. G., WELSH, P., SATTAR, N., MCKEIGUE, P. M. & CHATURVEDI, N. 2013a. Insulin resistance and truncal obesity as important determinants of the greater incidence of diabetes in Indian Asians and African Caribbeans compared with Europeans: the Southall And Brent REvisited (SABRE) cohort. *Diabetes Care,* 36**,** 383-93.

TILLIN, T., HUGHES, A. D., MAYET, J., WHINCUP, P., SATTAR, N., FOROUHI, N. G., MCKEIGUE, P. M. & CHATURVEDI, N. 2013b. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited) -- a prospective population-based study. *J Am Coll Cardiol,* 61**,** 1777-86.

TILLIN, T., HUGHES, A. D., MAYET, J., WHINCUP, P., SATTAR, N., FOROUHI, N. G., MCKEIGUE, P. M. & CHATURVEDI, N. 2013c. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited)—a prospective population-based study. *Journal of the American College of Cardiology,* 61**,** 1777-1786.

TINDALL, G. T., ODOM, G. L., CUPP, H. B. & DILLON, M. L. 1962. Studies on carotid artery flow and pressure. Observations in 18 patients during graded occlusion of proximal carotid artery. *J Neurosurg,* 19**,** 917-23.

TOORN, J. E. V. D., BOS, D., IKRAM, M. K., VERWOERT, G. C., LUGT, A. V. D., IKRAM, M. A., VERNOOIJ, M. W. & KAVOUSI, M. 2022. Carotid Plaque Composition and Prediction of Incident Atherosclerotic Cardiovascular Disease. *Circulation: Cardiovascular Imaging,* 15**,** e013602.

TOUBOUL, P.-J., HENNERICI, M., MEAIRS, S., ADAMS, H., AMARENCO, P., BORNSTEIN, N., CSIBA, L., DESVARIEUX, M., EBRAHIM, S. & HERNANDEZ, R. H. 2012a. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). *Cerebrovascular diseases,* 34**,** 290-296.

TOUBOUL, P. J., HENNERICI, M. G., MEAIRS, S., ADAMS, H., AMARENCO, P., BORNSTEIN, N., CSIBA, L., DESVARIEUX, M., EBRAHIM, S., FATAR, M., HERNANDEZ HERNANDEZ, R., JAFF, M., KOWNATOR, S., PRATI, P., RUNDEK, T., SITZER, M., SCHMINKE, U., TARDIF, J. C., TAYLOR, A., VICAUT, E., WOO, K. S., ZANNAD, F. & ZUREIK, M. 2007. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis,* 23**,** 75-80.

TOUBOUL, P. J., HENNERICI, M. G., MEAIRS, S., ADAMS, H., AMARENCO, P., BORNSTEIN, N., CSIBA, L., DESVARIEUX, M., EBRAHIM, S., HERNANDEZ HERNANDEZ, R., JAFF, M., KOWNATOR, S., NAQVI, T., PRATI, P., RUNDEK, T., SITZER, M., SCHMINKE, U., TARDIF, J. C., TAYLOR, A., VICAUT, E. & WOO, K. S. 2012b. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany,

2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovascular diseases (Basel, Switzerland),* 34**,** 290-296.

TOUBOUL, P. J., HENNERICI, M. G., MEAIRS, S., ADAMS, H., AMARENCO, P., BORNSTEIN, N., CSIBA, L., DESVARIEUX, M., EBRAHIM, S., HERNANDEZ HERNANDEZ, R., JAFF, M., KOWNATOR, S., NAQVI, T., PRATI, P., RUNDEK, T., SITZER, M., SCHMINKE, U., TARDIF, J. C., TAYLOR, A., VICAUT, E. & WOO, K. S. 2012c. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis,* 34**,** 290-6.

TOUSOULIS, D., OIKONOMOU, E., VOGIATZI, G. & VARDAS, P. 2020. Cardiovascular disease and socioeconomic status: It is mainly education that counts and not wealth ! *European Heart Journal,* 41**,** 3213-3214.

TSAO, C. W., ADAY, A. W., ALMARZOOQ, Z. I., ANDERSON, C. A. M., ARORA, P., AVERY, C. L., BAKER-SMITH, C. M., BEATON, A. Z., BOEHME, A. K., BUXTON, A. E., COMMODORE-MENSAH, Y., ELKIND, M. S. V., EVENSON, K. R., EZE-NLIAM, C., FUGAR, S., GENEROSO, G., HEARD, D. G., HIREMATH, S., HO, J. E., KALANI, R., KAZI, D. S., KO, D., LEVINE, D. A., LIU, J., MA, J., MAGNANI, J. W., MICHOS, E. D., MUSSOLINO, M. E., NAVANEETHAN, S. D., PARIKH, N. I., POUDEL, R., REZK-HANNA, M., ROTH, G. A., SHAH, N. S., ST-ONGE, M. P., THACKER, E. L., VIRANI, S. S., VOEKS, J. H., WANG, N. Y., WONG, N. D., WONG, S. S., YAFFE, K. & MARTIN, S. S. 2023. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation,* 147**,** e93-e621.

TSCHIDERER, L., KLINGENSCHMID, G., SEEKIRCHER, L. & WILLEIT, P. 2020. Carotid intima-media thickness predicts carotid plaque development: Meta-analysis of seven studies involving 9341 participants. *Eur J Clin Invest,* 50**,** e13217.

TSOI, K. K. F., CHAN, J. Y. C., HIRAI, H. W., WONG, S. Y. S. & KWOK, T. C. Y. 2015. Cognitive Tests to Detect Dementia: A Systematic Review and Meta-analysis. *JAMA Internal Medicine,* 175**,** 1450-1458.

TURK, A. S., CHAUDRY, I., HAUGHTON, V. M., HERMANN, B. P., ROWLEY, H. A., PULFER, K., AAGAARD-KIENITZ, B., NIEMANN, D. B., TURSKI, P. A., LEVINE, R. L. & STROTHER, C. M. 2008. Effect of carotid artery stenting on cognitive function in patients with carotid artery stenosis: preliminary results. *AJNR Am J Neuroradiol,* 29**,** 265-8.

UNNITHAN, A. K. A. & MEHTA, P. 2020. Hemorrhagic stroke.

URBINA, E. M., WILLIAMS, R. V., ALPERT, B. S., COLLINS, R. T., DANIELS, S. R., HAYMAN, L., JACOBSON, M., MAHONEY, L., MIETUS-SNYDER, M., ROCCHINI, A., STEINBERGER, J. & MCCRINDLE, B. 2009. Noninvasive Assessment of Subclinical Atherosclerosis in Children and Adolescents. *Hypertension,* 54**,** 919-950.

VAN DEN BERG, J. F., DOGGE, B., KIST, N., KOK, R. M. & VAN DER HIELE, K. 2017. Gender Differences in Cognitive Functioning in Older Alcohol-Dependent Patients. *SUBST USE MISUSE,* 52**,** 574-580.

VAN DEN OORD, S. C. H., SIJBRANDS, E. J. G., TEN KATE, G. L., VAN KLAVEREN, D., VAN DOMBURG, R. T., VAN DER STEEN, A. F. W. & SCHINKEL, A. F. L. 2013. Carotid intima-media thickness for cardiovascular risk assessment: Systematic review and meta-analysis. *Atherosclerosis,* 228**,** 1-11.

VAN OIJEN, M., JAN DE JONG, F., WITTEMAN, J. C., HOFMAN, A., KOUDSTAAL, P. J. & BRETELER, M. M. 2007. Atherosclerosis and risk for dementia. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society,* 61**,** 403-410.

VANDERWEELE, T. J. & VANSTEELANDT, S. 2009. Conceptual issues concerning mediation, interventions and composition. *Statistics and Its Interface,* 2**,** 457-468.

VENKETASUBRAMANIAN, N. 2024. A Comparative Study of Three Dementia Screening Instruments (CSI-D, CMMSE, and ECAQ) in a Multi-Ethnic Asian Population. *Healthcare (Basel),* 12.

VILLADSEN, P. R., PETERSEN, S. E., DEY, D., ZOU, L., PATEL, S., NADERI, H., GRUSZCZYNSKA, K., BARON, J., DAVIES, L. C., WRAGG, A., BOTKER, H. E. & PUGLIESE, F. 2017. Coronary atherosclerotic

plaque burden and composition by CT angiography in Caucasian and South Asian patients with stable chest pain. *Eur Heart J Cardiovasc Imaging,* 18**,** 556-567.

VITICCHI, G., FALSETTI, L., VERNIERI, F., ALTAMURA, C., BARTOLINI, M., LUZZI, S., PROVINCIALI, L. & SILVESTRINI, M. 2012. Vascular predictors of cognitive decline in patients with mild cognitive impairment. *Neurobiology of Aging,* 33**,** 1127e1-1127e9.

VLACHOPOULOS, C., XAPLANTERIS, P., ABOYANS, V., BRODMANN, M., CIFKOVA, R., COSENTINO, F., DE CARLO, M., GALLINO, A., LANDMESSER, U., LAURENT, S., LEKAKIS, J., MIKHAILIDIS, D. P., NAKA, K. K., PROTOGEROU, A. D., RIZZONI, D., SCHMIDT-TRUCKSASS, A., VAN BORTEL, L., WEBER, T., YAMASHINA, A., ZIMLICHMAN, R., BOUTOUYRIE, P., COCKCROFT, J., O'ROURKE, M., PARK, J. B., SCHILLACI, G., SILLESEN, H. & TOWNSEND, R. R. 2015. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis,* 241**,** 507-32.

VON REUTERN, G.-M., GOERTLER, M.-W., BORNSTEIN, N. M., SETTE, M. D., EVANS, D. H., GOERTLER, M.-W., HETZEL, A., KAPS, M., PERREN, F. & RAZUMOVKY, A. 2012. Grading carotid stenosis using ultrasonic methods. *Stroke,* 43**,** 916-921.

WADSWORTH, M., KUH, D., RICHARDS, M. & HARDY, R. 2006. Cohort profile: the 1946 national birth cohort (MRC National Survey of Health and Development). *International journal of epidemiology,* 35**,** 49-54.

WATANABE, T., KOBA, S., KAWAMURA, M., ITOKAWA, M., IDEI, T., NAKAGAWA, Y., IGUCHI, T. & KATAGIRI, T. 2004. Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. *Metabolism, clinical and experimental,* 53**,** 476-482.

WECHSLER, D. 1955. Wechsler adult intelligence scale. *Archives of Clinical Neuropsychology*.

WELLS, G., SHEA, B., O'CONNELL, D., PETERSON, J., WELCH, V., LOSOS, M. & TUGWELL, P. 2000. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. .

WENDELHAG, I., LIANG, Q., GUSTAVSSON, T. & WIKSTRAND, J. 1997. A new automated computerized analyzing system simplifies readings and reduces the variability in ultrasound measurement of intima-media thickness. *Stroke,* 28**,** 2195-200.

WENDELL, C. R., WALDSTEIN, S. R., EVANS, M. K. & ZONDERMAN, A. B. 2016. Subclinical carotid atherosclerosis and neurocognitive function in an urban population. *Atherosclerosis,* 249**,** 125-31.

WENDELL, C. R., WALDSTEIN, S. R., FERRUCCI, L., O'BRIEN, R. J., STRAIT, J. B. & ZONDERMAN, A. B. 2012. Carotid atherosclerosis and prospective risk of dementia. *Stroke,* 43**,** 3319-24.

WENDELL, C. R., ZONDERMAN, A. B., METTER, E. J., NAJJAR, S. S. & WALDSTEIN, S. R. 2009a. Carotid Intimal Medial Thickness Predicts Cognitive Decline Among Adults Without Clinical Vascular Disease. *Stroke,* 40**,** 3180-3185.

WENDELL, C. R., ZONDERMAN, A. B., METTER, E. J., NAJJAR, S. S. & WALDSTEIN, S. R. 2009b. Carotid intimal medial thickness predicts cognitive decline among adults without clinical vascular disease. *Stroke,* 40**,** 3180-5.

WIKSTRAND, J. 2007. Methodological considerations of ultrasound measurement of carotid artery intima–media thickness and lumen diameter. *Clinical Physiology and Functional Imaging,* 27**,** 341-345.

WILLEIT, P., TSCHIDERER, L., ALLARA, E., REUBER, K., SEEKIRCHER, L., GAO, L., LIAO, X., LONN, E., GERSTEIN, H. C., YUSUF, S., BROUWERS, F. P., ASSELBERGS, F. W., VAN GILST, W., ANDERSSEN, S. A., GROBBEE, D. E., KASTELEIN, J. J. P., VISSEREN, F. L. J., NTAIOS, G., HATZITOLIOS, A. I., SAVOPOULOS, C., NIEUWKERK, P. T., STROES, E., WALTERS, M., HIGGINS, P., DAWSON, J., GRESELE, P., GUGLIELMINI, G., MIGLIACCI, R., EZHOV, M., SAFAROVA, M., BALAKHONOVA, T., SATO, E., AMAHA, M., NAKAMURA, T., KAPELLAS, K., JAMIESON, L. M., SKILTON, M., BLUMENTHAL, J. A., HINDERLITER, A., SHERWOOD, A., SMITH, P. J., VAN AGTMAEL, M. A., REISS,

P., VAN VONDEREN, M. G. A., KIECHL, S., KLINGENSCHMID, G., SITZER, M., STEHOUWER, C. D. A., UTHOFF, H., ZOU, Z. Y., CUNHA, A. R., NEVES, M. F., WITHAM, M. D., PARK, H. W., LEE, M. S., BAE, J. H., BERNAL, E., WACHTELL, K., KJELDSEN, S. E., OLSEN, M. H., PREISS, D., SATTAR, N., BEISHUIZEN, E., HUISMAN, M. V., ESPELAND, M. A., SCHMIDT, C., AGEWALL, S., OK, E., AŞÇI, G., DE GROOT, E., GROOTEMAN, M. P. C., BLANKESTIJN, P. J., BOTS, M. L., SWEETING, M. J., THOMPSON, S. G. & LORENZ, M. W. 2020. Carotid Intima-Media Thickness Progression as Surrogate Marker for Cardiovascular Risk: Meta-Analysis of 119 Clinical Trials Involving 100 667 Patients. *Circulation,* 142**,** 621-642.

WILLETT, W. C., KOPLAN, J. P., NUGENT, R., DUSENBURY, C., PUSKA, P. & GAZIANO, T. A. 2006. Prevention of chronic disease by means of diet and lifestyle changes. *Disease Control Priorities in Developing Countries. 2nd edition*.

WILLIAMS, D. R., MOHAMMED, S. A., LEAVELL, J. & COLLINS, C. 2010. Race, socioeconomic status, and health: complexities, ongoing challenges, and research opportunities. *Annals of the new York Academy of Sciences,* 1186**,** 69-101.

WILLIAMS, D. R. & RUCKER, T. D. 2000. Understanding and addressing racial disparities in health care. *Health Care Financ Rev,* 21**,** 75-90.

WILLIAMS, R. 2006. Generalized Ordered Logit/Partial Proportional Odds Models for Ordinal Dependent Variables. *Stata Journal,* 6**,** 58-82.

WILLIAMS, S., GLASER, K. & RAY, B. 2023. Strokes and Predictors of Outcomes. *Critical Care Nursing Clinics of North America,* 35**,** 1-15.

WOLF, P. A. 2012. Contributions of the Framingham Heart Study to stroke and dementia epidemiologic research at 60 years. *Arch Neurol,* 69**,** 567-71.

WOO, S. Y., JOH, J. H., HAN, S. A. & PARK, H. C. 2017. Prevalence and risk factors for atherosclerotic carotid stenosis and plaque: A population-based screening study. *Medicine (Baltimore),* 96**,** e5999.

WORLD HEALTH ORGANIZATION 1999. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Geneva, Switzerland: World Health Organization.

XIANG, J., ZHANG, T., YANG, Q. W., LIU, J., CHEN, Y., CUI, M., YIN, Z. G., LI, L., WANG, Y. J., LI, J. & ZHOU, H. D. 2013. Carotid artery atherosclerosis is correlated with cognitive impairment in an elderly urban Chinese non-stroke population. *Journal of Clinical Neuroscience,* 20**,** 1571-1575.

XU, D., LI, J., ZOU, L., XU, Y., HU, D., PAGOTO, S. L. & MA, Y. 2010. Sensitivity and specificity of the ankle—brachial index to diagnose peripheral artery disease: a structured review. *Vascular medicine,* 15**,** 361-369.

XUE, G., CHEN, C., LU, Z. L. & DONG, Q. 2010. Brain Imaging Techniques and Their Applications in Decision-Making Research. *Xin Li Xue Bao,* 42**,** 120-137.

YANO, Y., BAKRIS, G. L., INOKUCHI, T., OHBA, Y., TAMAKI, N., NAGATA, M., KUWABARA, M., YOKOTA, N., ETO, T., KUROKI, M., SHIMADA, K. & KARIO, K. 2014. Association of cognitive dysfunction with cardiovascular disease events in elderly hypertensive patients. *J Hypertens,* 32**,** 423-31.

YAO, B. C., MENG, L. B., HAO, M. L., ZHANG, Y. M., GONG, T. & GUO, Z. G. 2019. Chronic stress: a critical risk factor for atherosclerosis. *J Int Med Res,* 47**,** 1429-1440.

YAQUB, B. A., SHAMENA, A. R., KOLAWOLE, T. M. & PATEL, P. J. 1991. Cerebrovascular disease in Saudi Arabia. *Stroke,* 22**,** 1173-1176.

YUSUF, S., JOSEPH, P., RANGARAJAN, S., ISLAM, S., MENTE, A., HYSTAD, P., BRAUER, M., KUTTY, V. R., GUPTA, R., WIELGOSZ, A., ALHABIB, K. F., DANS, A., LOPEZ-JARAMILLO, P., AVEZUM, A., LANAS, F., OGUZ, A., KRUGER, I. M., DIAZ, R., YUSOFF, K., MONY, P., CHIFAMBA, J., YEATES, K., KELISHADI, R., YUSUFALI, A., KHATIB, R., RAHMAN, O., ZATONSKA, K., IQBAL, R., WEI, L., BO, H., ROSENGREN, A., KAUR, M., MOHAN, V., LEAR, S. A., TEO, K. K., LEONG, D., O'DONNELL, M., MCKEE, M. & DAGENAIS, G. 2020. Modifiable risk factors, cardiovascular disease, and mortality

in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet,* 395**,** 795-808.

ZHENG, K., QIAN, Y., LIN, T., HAN, F., YOU, H., TAO, X., HOU, B., YUAN, J., WANG, H., ZHANG, D., LV, K., FENG, F., ZHU, Y. & LI, X. 2020. Carotid intima–media thickness relative to cognitive impairment in dialysis patients, and their relationship with brain volume and cerebral small vessel disease. *Therapeutic Advances in Chronic Disease,* 11**,** 2040622320953352.

ZHONG, W., CRUICKSHANKS, K. J., HUANG, G.-H., KLEIN, B. E., KLEIN, R., NIETO, F. J., PANKOW, J. S. & SCHUBERT, C. R. 2011a. Carotid atherosclerosis and cognitive function in midlife: the Beaver Dam Offspring Study. *Atherosclerosis,* 219**,** 330-333.

ZHONG, W., CRUICKSHANKS, K. J., HUANG, G. H., KLEIN, B. E., KLEIN, R., NIETO, F. J., PANKOW, J. S. & SCHUBERT, C. R. 2011b. Carotid atherosclerosis and cognitive function in midlife: the Beaver Dam Offspring Study. *Atherosclerosis,* 219**,** 330-3.

ZHONG, W., CRUICKSHANKS, K. J., SCHUBERT, C. R., ACHER, C. W., CARLSSON, C. M., KLEIN, B. E., KLEIN, R. & CHAPPELL, R. J. 2012a. Carotid atherosclerosis and 10-year changes in cognitive function. *Atherosclerosis,* 224**,** 506-10.

ZHONG, W., CRUICKSHANKS, K. J., SCHUBERT, C. R., ACHER, C. W., CARLSSON, C. M., KLEIN, B. E. K., KLEIN, R. & CHAPPELL, R. J. 2012b. Carotid atherosclerosis and 10-year changes in cognitive function. *Atherosclerosis,* 224**,** 506-510.

ZUREIK, M., BUREAU, J.-M., TEMMAR, M., ADAMOPOULOS, C., COURBON, D., BEAN, K., TOUBOUL, P.-J., BENETOS, A. & DUCIMETIÈRE, P. 2003. Echogenic Carotid Plaques Are Associated With Aortic Arterial Stiffness in Subjects With Subclinical Carotid Atherosclerosis. *Hypertension,* 41**,** 519-527.

Appendix 1

Eligibility Form: IS ASYMPTOMATIC ATHEROSCLEROSIS IN CAROTID ARTERIES ASSOCIATED WITH COGNITIVE FUNCTION? A SYSTEMATIC REVIEW AND META-ANALYSIS

1. Reference details			
Reference citation			
First author			
Year of publication			
Title of the paper			
Assessor's identifier	1 ☐	2 ☐	
2. Study eligibility			
Inclusion of the study	Yes ☐ √	No ☐ √	Unclear r ☐
Eligibility criteria	**Reason for exclusion (if excluded)**	Yes	No
ALL studies except : review articles, conference abstract, letters to the editor, case reports; pilot study,	☐ no MMSE cognitive test	☐	☐
cIMT measured by ultrasound	☐ No IMT Assessment	√	☐
	☐ Other imaging modality not ultrasound	☐	☐
	☐ review articles, conference abstract, letters to the editor, case reports	☐	☐
Notes:	☐ Duplicate	☐	☐
Additional information			
Notes:			

DO NOT PROCEED IF PAPER EXCLUDED FROM REVIEW

Data Extraction Form

3. Study details		
Study (cohort) name	The EVA Study	
Study design	longitudinal study	
Region/country	Nantes (western France).	
Sample size	1279	
Mean (range) age	Mean ± SD : mean age, 65.0+/-3.0 years	Range (IQR):
Sex	Male, n (%): 526 men	Female, n (%): 753 women
Follow-up duration		
Clinical variables (n, %)		
☐ Hypertension	n./a	
☐ Diabetes mellitus	n/a	
4. Exposure details		
Hardware: Ultrasound Machine	an Aloka SSD-650 with a 7.5-MHz transducer.	
Method and site	The ultrasound examination involved scanning the common carotid arteries, the carotid bifurcations, and the first 2 cm of the internal carotid arteries. The IMT (distance between the media-adventitia interface and the lumen-intima interface) was automatically measured twice on longitudinal B-mode images of the far wall of each common carotid artery at plaque-free sites. The common carotid IMT was defined as the mean of four measurements. All segments of the carotid arteries were scanned longitudinally and transversely to assess the presence of plaques, and a localized echo-structure protruding into the lumen was considered to be a plaque if the distance between the media-adventitia interface and the internal side of the lesion was >or=to1 mm. The total number of plaques was recorded. For each, maximum thickness was measured perpendicular to the vessel wall. When several plaques were present in the same carotid segment (ie, common carotid artery or bifureation/origin of the internal carotid artery), plaque thickness measurement was made only for that with the greatest protrusion into the lumen. On the basis of transverse views, the degree of carotid stenosis was defined as (1-residual area/vessel area) times 100%.	

Notes:

5. Outcomes' details	
Type has of outcomes used in this review	Outcomes reported in this study (n)
Primary outcome(s) Global cognitive function	neuropsychological battery that included seven tests assessing different cognitive functions and a global test (MMSE) of 18 items roughly assessing various cognitive skills with scores ranging from 0 to 30.
Notes:	

6. Available number of participants		
		Number
Baseline sample size	Yes ☐ No ☐	
follow-up	Yes ☐ No ☐	
Total number included in the analysis	Yes ☐ No ☐	
All subjects accounted for	Yes ☐ No ☐	
Notes:		

7. Statistical analysis	
Statistical method used	Nominal polychotomous logistic regressions [13] (BMDP statistical software) were used to analyze the relationships between each cognitive score distribution of the eight neuropsychological tests and carotid characteristics (presence of plaques, IMT), adjusting for age, education, depressive symptomatology, systolic blood pressure, body mass index, smoking, and alcohol consumption.

Appendix 2

A Modified Newcastle-Ottawa Quality Assessment for Observational Studies.The quality of included studies was assessed using a modified seven-point criteria derived from Newcastle-Ottawa scale (Wells et al., 2000). Each of the following criteria (A to G) was assigned 1 point if met.

Title and reference:				
Criteria				
Sample	**Yes**	**No**	**NR**	**Note**
A) Representativeness of the target sample Yes = sampling designed to ensure adequaterepresentativeness No = inappropriately selected sample, or no description of sample selection				
B) Non-response satisfactorily dealt with Yes = comparability between respondent andnon-respondent characteristics established and response rate is satisfactory No = the response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory, or no description of the response rate or the characteristics of the responders and the non-responders.				
Exposure	**Yes**	**No**	**NR**	**Note**
C) Validated measurement tool Yes = high-resolution ultrasound system with linear ultrasound transducers at frequencies >7 MHz and measurement protocol for cIMT and plaque in accord* with American Society Echocardiography/Mannheim Consensus Guidelines. Data analysis performed independently and blinded using validatedanalysis system No = inadequate ultrasound system, protocol, or analysis process, or notdescribed				

* 'In accord' needs to be interpreted reasonably since some studies will precede these guidelines and others, while deviating slightly may not deviate sufficiently to be out of accord with the guidelines.

D) Relevant confounders measured[†] Yes = sex, age, smoking, hypertension/bloodpressure, diabetes, hyperlipidemia/blood lipids/body mass index No = potential confounders not measured ornot reported				
Outcome	**Yes**	**No**	**NR**	**Note**
E) Assessment of outcome Yes = independent blinded assessment of cognitive status using a validated instrumentNo = unvalidated instrument, or not described				
F) Statistical analysis Yes = statistical analysis clearly describedand appropriate: estimate of the central tendency of the outcome with a measure ofprecision is provided (e.g. mean/median (95% confidence interval/standard deviation/range)). No = the statistical analysis is inappropriate,missing or inadequately described				
G) Missing data Yes = extent of missing data reported andthe methods for addressing missing data described No = extent of missing data not reported and/or no description of how missing datawere dealt with				
TOTAL (maximum 7)				

[†] Relevant confounders listed here were selected on the basis of various components of the Framingham Cardiovascular risk score (https://framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/).

Title and reference:				
Criteria				
Sample	**Yes**	**No**	**NR**	**Note**
A) Representativeness of the target sample Yes = sampling designed to ensure adequaterepresentativeness No = inappropriately selected sample, or no description of sample selection				
B) Non-response satisfactorily dealt with Yes = comparability between respondent andnon-respondent characteristics established and response rate is satisfactory No = the response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory, or no description of the response rate or the characteristics of the responders and the non-responders.				
Exposure	**Yes**	**No**	**NR**	**Note**
C) Validated measurement tool Yes = high-resolution ultrasound system with linear ultrasound transducers at frequencies >7 MHz and measurement protocol for cIMT and plaque in accord‡ with American Society Echocardiography/Mannheim Consensus Guidelines. Data analysis performed independently and blinded using validatedanalysis system. No = inadequate ultrasound system, protocol, or analysis process, or notdescribed				

‡ 'In accord' needs to be interpreted reasonably since some studies will precede these guidelines and others, while deviating slightly may not deviate sufficiently to be out of accord with the guidelines.

D) Relevant confounders measured[§] Yes = sex, age, smoking, hypertension/blood pressure, diabetes, hyperlipidemia/blood lipids/body mass index No = potential confounders not measured or not reported				
Outcome	**Yes**	**No**	**NR**	**Note**
E) Assessment of outcome Yes = independent blinded assessment of cognitive status using a validated instrument No = unvalidated instrument, or not described				
F) Statistical analysis Yes = statistical analysis clearly described and appropriate: estimate of the central tendency of the outcome with a measure of precision is provided (e.g. mean/median (95% confidence interval/standard deviation/range)). No = the statistical analysis is inappropriate, missing or inadequately described				
G) Missing data Yes = extent of missing data reported and the methods for addressing missing data described No = extent of missing data not reported and/or no description of how missing data were dealt with				
TOTAL (maximum 7)				

[§] relevant confounders listed here were selected on the basis of various components of the Framingham Cardiovascular risk score (https://framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/).

Appendix Table 2.2 Summary data from cross-sectional studies

Reference	Location	Sampling frame / Health conditions	Sample size	Age (years±SD)	Female (%)	Presence of Plaque (n)	cIMT measurement (mm±SD)	MMSE (score±SD)	Major relevant finding
(Auperin et al., 1996b)	France	Community-based sample	Male: 521 Female: 753	65±3	60	Male: Yes (358) Female: Yes (217)	Male: 0.69±0.14 Female: 0.65±0.11	Male: 28.3±2 Female: 27.9±2.3	No evidence of an association between cIMT and MMSE in either sex. Association between presence of carotid plaques and impaired MMSE in men. No evidence of an association in women
(Watanabe et al., 2004)	Japan	Patients with vascular dementia (VaD) and age-matched controls	Control: 63 VaD: 37 AD: 34	C: 72±11 VaD: 75±8 AD: 76±9	0	Control: Yes (15) VaD: Yes (28) AD: Yes (18)	Control : 0.68±0.11 VaD: 0.94±0.2 AD: 0.85±0.14	Control : 26±3 VaD: 13±6 AD: 10±5	Comparing VaD patients with controls. MMSE was lower, cIMT was greater and carotid plaques more frequent
(Haley et al., 2007)	USA	Cardiology patients	109	69.18±7.43	43	N/A	0.88±0.13	28.55±1.59	cIMT was not independently

		and volunteers							related to performance on measures of global cognitive functioning. Increased cIMT was significantly associated with poorer performance in the attention-executive- psychomotor domain independent of risk factors.
(Muller et al., 2007)	Netherlands	Community-based sample, age-stratified selection and further stratified by cardiovascular disease status	No CVD: 217 Subclinical CVD: 125 Prevalent CVD: 54	No CVD: 54±10.3 Subclinical CVD: 66.8±8.1 Prevalent CVD: 67.7±8.8	0	N/A	No CVD: 0.77±0.01 Subclinical CVD: 0.89±0.01 Prevalent CVD: 0.89±0.02	No CVD: >28 (n=100, 63%) SCVD: >28 (n=49, 31%) PCVD: >28 (n=11, 7%)	No CVD: ≤28 (n=117, 50%) SCVD: ≤28 (n=73, 31%) PCVD: ≤28 (n=43, 18%)	Association of cIMT with MMSE not presented. Thicker cIMT was associated with lower scores on memory functioning.
(Singh-Manoux et al., 2008a)	UK	Occupational sample excluding	High SES,M: 1190	High SES, M: 62.32±5.61	High SES: 17 Intermediate SES: 45	N/A	N/A	High SES, M: 0.8±0.16 High SES, F: 0.76±0.13	High SES, M: 28.9±1.19	An inverse association between cIMT and cognition

		individuals with stroke	High SES, F: 185 Intermediate SES, M: 1477 Intermediate SES, F:490 Low SES, M: 141 Low SES, F: 413	High SES, F: 59.8±5.49 Intermediate SES, M: 60±71 Intermediate SES, F: 60±5.93 Low SES, M: 60.84±6.51 Low SES, F: 62±5.73	Low SES: 38			Intermediate SES, M: 0.79±0.16 Intermediate SES, F: 0.77±0.13 Low SES, M: 0.82±0.18 Low SES, F: 0.79±0.14	High SES, F: 29.16±1.04 Intermediate SES, M: 28.71±1.31 Intermediate SES, F: 28.88±1.24 Low SES, M: 27.86±1.7 Low SES, F: 28.18±1.55	was observed only in the low SES group. Evidence that SES modifies the association between cIMT and cognition.
(Carlsson et al., 2009)	USA	Population-based sample	No CI: 1358 CI: 180	No CI: 74.8±6.6 CI:80±7.1	No CI: 62 CI: 54	N/A	N/A	No CI: 0.95±0.23 CI: 1.00 ± 0.25	No CI: 27.6 ± 1.7 CI: 21.1 ± 2.9	cIMT higher in people with cognitive impairment defined as MMSE <24 or proxy-reported dementia
(El-Kattan et al., 2009)	Egypt	Vascular surgery patients and age-sex-matched healthy controls / PAD (66.6%)	C: 10 PAD wo CVD: 10 PAD w CVD: 10	C: 53.9±9.55 PAD wo CVD: 54.8±8.96 PAD w CVD: 56.1±9.62	C: 20 PAD wo CVD: 10 PAD w CVD: 20	N/A	C: No (0) PAD wo CVD: Yes (1) PAD w CVD: Yes (5)	C: 0.7±0.1 PAD wo CVD: 0.9±0.2 PAD w CVD: 1.07±0.13	C: 30±0 PAD wo CVD: 28±1.4 PAD w CVD: 26±1.5	Patients with peripheral arterial disease had higher cIMT and lower MMSE compared to healthy controls

(Kearney-Schwartz et al., 2009b)	France	Hypertensive patients with subjective memory complaints but excluding individuals with MMSW ≤24	198	69.3±6.2	53	N/A	Yes (50)	0.68±0.09	28.3±1.4	No evidence of an association between cIMT and impaired memory function implied, although data for MMSE or cognition not presented.
(Zhong et al., 2011b)	USA	Population-based sample	2794	49±9.8	54	N/A	Yes (2665)	0.65±0.15	28.7±1.3	Higher Carotid IMT and plaque were associated with lower MMSE score
(Dias et al., 2012)	Brazil	Hypertensive patients and non-hypertensive, non-cognitively impaired controls identified from patients referred for investigation of high blood pressure. People	Controls: 48 Hypertensive without cognitive impairment: 108 Hypertensive with cognitive impairment: 42	Controls: 44.5±7.9 Hypertensive without cognitive impairment: 55.75±8.6 Hypertensive with cognitive impairment: 63.3±9.3	C 62.5 H without 53.7 H with 60.5	N/A		Controls: 0.69±1 Hypertensive without cognitive impairment: 0.89±0.2 Hypertensive with cognitive impairment: 0.99±0.2	Controls: 27.77±4.4 Hypertensive without cognitive impairment: 28.44±1.3 Hypertensive with cognitive impairment: 22.02±2.4	Higher cIMT was associated with higher odds ratio of MMSE score ≤24

		with carotid plaques excluded.								
(Stefanova et al., 2012)	Serbia	Patients with VCD or AD / VCD: HYL (36%) HTN (29%) DM (11%) AD: HYL(62%) HTN (88%) DM (28%)	VCD: 237 AD: 197	VCD: 67.4±8.18 AD: 68.5±9.36	VCD: 52.3 AD: 49	N/A N/A	VCD: Yes (120) AD: Yes (155)	VCD: 1.11±0.2 AD: 1.15±0.18	VCD: 23.81±2.33 AD: 16±5.9	Higher cIMT and plaque type was correlated with poorer MMSE in VCD. No evidence of a correlation between MMSE and cIMT or plaque in AD group.
(Rogne et al., 2013)	Norway	Population-based sample / DM (1%) CHD (5.3%)	1,577	Median (range): 57 (52-61)	48	N/A	N/A	Median (range): 0.78 (0.69–0.89)	N/A	No evidence of association between cIMT and MMSE.
(Xiang et al., 2013)	China	Neurology patients / HTN (55%) DM (35%) CHD (10%)	No cognitive impairment: 1659 Cognitive impairment: 356	No cognitive impairment: 68.1±7.2 Cognitive impairment: 73.2±7.8	No cognitive impairment : 48 Cognitive impairment: 52	N/A N/A	Yes (1377) Yes (299)	No cognitive impairment: 0.76±0.14 Cognitive Impairment: 1.57±0.15	No cognitive impairment: ≥24 Cognitive impairment: <24	cIMT was associated with a higher odds ratio of cognitive impairment (MMSE <24)

(Nagai et al., 2014)	Japan	Patients at high risk of cardiovascular disease / HTN (75.9%) DM (13.9%)	201	79.9±6.4	75	N/A	N/A	1.03±0.3	25.8±4.69	Compared with those with both low blood pressure variability and low IMT, patients with high blood pressure variability and high IMT had lower MMSE score or higher prevalence of cognitive impairment (based on a MMSE score ≤24)
(Yano et al., 2014)	Japan	Hypertensive patients / HTN (100%)	587	73±8.1	59.0	N/A	N/A	NCD, median(range): 0.87(0.75-1.01) CD, median(range): 0.96 (0.82-1.06)	NCD, median(range): 28(27-29) CD, median(range): 24(22-24)	cIMT higher in patients with cognitive impairment (defined as MMSE score ≤ 24)

(Liu et al., 2016b)	China	Community-based sample / HTN (71%) DM (13%)	384	84.65±2.3	67	N/A	N/A	1.45 ± 0.30	Median (range): 24 (22-24)	cIMT inversely related to MMSE score.
(Alhusaini et al., 2018)	Scotland	Population-based cohort HTN (47.3%) DM (10.1%)	518	72.7±0.73	46.6	N/A	Yes (77)	0.84±0.17	28.8±1.3	Data relating cIMT to MMSE not presented. Carotid stenosis was related to lower fluid intelligence.
(Matsumoto et al., 2018)	Japan	Patients undergoing health screening	176	NCI: 64.6 ±9.6 CI: 67.7±12.3	NCI: 59.1 CI: 37	N/A	N/A	NCI :1.7±0.7 CI: 2.0±1	N/A	No evidence of an association between cIMT and MMSE in a model adjusted for sex, age and years of education. cIMT higher in patients with cognitive impairment.

(Muela et al., 2018)	Brazil	Patients. Individuals with cerebrovascular disease excluded / HTN (67%)	Normotensive: 69 Hypertensive stage 1: 83 Hypertensive stage 2: 59	Normotensive: 52.1±13.9 Hypertensive stage 1: 52.1±13 Hypertensive stage 2: 51.3±10.1	Normotensive: 55.1 Hypertensive stage 1: 55.8 Hypertensive stage 2: 53.6	N/A	N/A	Normotensive: 0.7±0.1 Hypertensive stage 1: 0.8±0.1 Hypertensive stage 2: 0.8±0.1	Normotensive: 28.03±1.92 Hypertensive stage 1: 27.43±2.01 Hypertensive stage 2: 26.66±2.07	cIMT showed a weak negative correlation with MMSE consistent with null. Negative correlations of cIMT with other cognitive measures were observed.
(Mworozi et al., 2019b)	Uganda	Community-based study / HTN (25%) DM (5%)	210	69.9±7.76	71.4	N/A	Yes (45)	0.9±0.2	N/A	Presence of carotid artery plaque was associated with abnormal cognitive function defined as MMSE ≤24.

Table 2.3 Cross-sectional plus longitudinal studies

Reference	Location	Sampling frame / Health conditions	Sample size	Age (years±SD)	Female (%)	Follow-up (years)	Presence of Plaque (n)	CIMT measurement (mm±SD)	MMSE (score±SD)	Major relevant finding

(Komulainen et al., 2007b)	Finland	Population-based sample	91 (CS) 47 (LT)	63.5±3.1 (CS) 75±3.2 (LT)	100	12	N/A	1.02±0.26 (Cross-sectional) 1.25±0.33 (Longitudinal)	28.9±1.6 (Cross-sectional) 26.4±2.01 (Longitudinal)	There was no evidence of an association between IMT and MMSE score cross-sectionally or after 12-year follow-up, although confidence intervals of estimates were very wide. Associations between high CIMT and poor memory were seen both cross-sectionally and longitudinally.

(Carcaillon et al., 2015)	France	Population-based sample	5798	73.4±4.8	60.5	7	Yes (3038)	0.71±0.12	N/A	Association between baseline carotid plaques and incident dementia. No association between CIMT and incident dementia

(Kawasaki et al., 2016a)	Japan	Population-based sample	494	Median (range): 87.2 (86.1–88.7)	55	3	Yes (328)	N/A	N/A	Presence of higher carotid artery plaque score was associated with lower MMSE scores. Weak evidence of an association between plaque score and increase rate of decline in MMSE compatible with null.

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Table 2.4 Longitudinal studies

Reference	Location	Sampling frame / Health conditions	Sample size	Age, year (mean±SD)	Female, %	Mean follow-up (years)	Presence of Plaque (n)	CIMT measurement (mm±SD)	MMSE (score±SD)	Major relevant finding
(Silvestrini et al., 2009)	Italy	Dementia clinic outpatients	66	72.7±6.1	55	1	Yes (52)	1.1±0.3	18.1±3	Higher baseline CIMT was associated with greater decline in MMSE scores
(Viticchi et al., 2012)	Italy	Patients referred to Dementia clinic / HYL (55.6 %) HTN (65%) DM (29.1 %)	IC: 96 DE: 21	IC: 75±6 DE: 77.2±4.28	IC:44.8 DE: 66.7	1	IC: Yes (30) DE: Yes (9)	IC: 0.92±0.15 DE: 1.04±0.16	IC 27.14±1.76 DE: 27±1.56	Patients with abnormal CIMT (>1mm) had higher odds ratio of progressing from mild cognitive

										impairment to AD dementia
(Zhong et al., 2012a)	USA	Population-based sample	1311	66.8	59	5 and 10	Yes (682)	0.86±0.21	N/A	Higher CIMT was associated with higher risk of incident cognitive impairment (MMSE <24). Plaque was not associated with incident cognitive impairment or cognitive test performance.
(Buratti et al., 2014)	Italy	Patients with high vascular risk	159 (NCIMT: 68 PCIMT: 91)	NCIMT:69.7±3.6 PCIMT:70.2±3.8	NCIMT:39.7 PCIMT:37.4	3	NCIMT:Yes (68) PCIMT:Yes (91)	NCIMT: < 1 PCIMT: ≥ 1	NCIMT BL: 26.75±1.05 NCIMT:24.86±1.85 (3 y from BL)	No evidence of an association between CIMT and

									PCIMT BL: 27±1.25 PCIMT FU: 25.27±1.86 (3 y from BL)	change in MMSE score
(Buratti et al., 2015)	Italy	Patients referred to Dementia clinic	MCI: 300 AD: 106	MCI, meadian (range): 72 (67-76) AD, meadian (range): 72 (68-76)	MCI: 37 AD: 43	1	MCI: Yes (114) AD: Yes (53)	N/A	MCI: 27±1 AD: 27±1	CIMT >1mm and plaque associated with increased odds ratio of development of Alzheimer disease over 12-month follow-up
(Wendell et al., 2016)	USA	Community-based sample	1696	46.9±9.3	55	4	N/A	0.69±0.13	N/A	Weak negative association between CIMT and MMSE in fully adjusted models, consistent

										with null.
(Falsetti et al., 2018)	Italy	Patients from neurological clinic with mild to moderate cognitive impairment	310	76.86±7.49	62.9	2	N/A	pNVAF-: 0.97±0.2 pNVAF+: 1.11±0.16	pNVAF-: 18.62±5.22 pNVAF+: 15.8±5.17	CIMT weakly associated with progression to probably Alzheimer Disease but results compatible with null. Patients with non-valvular atrial fibrillation (pNVAF+) had lower MMSE and higher CIMT compared to pNVAF-.
(Rouch et al., 2018)	N/A	Consecutive patients	363	75.2±7	65.6	4.5	NCTD: Yes (50) CTD: Yes (40)	NCTD: 0.85±0.13	NCTD: 28.3±1.6 CTD: 26.6±2.6	Higher CIMT and plaque associated

		attend-ing a memor y clinic						CTD: 0.82±0. 13		with pro-gression from MCI to demen-tia based on MMSE score.

Abbreviations: AD: Alzheimer's disease, CIMT: carotid intima-media thickness, CD: cognitive dysfunction, ICA: internal carotid artery, M: men, MMSE: Mini Mental State Examination, MCI: mild cognitive impairment, pNVAF: permanent non-valvular atrial fibrillation, VaD: vascular dementia, VCD: vascular cognitive decline.

Table 2.5 Exposure measures of the included papers.

Reference	Ultrasound machine / transducer	IMT Measurement sites	Scanning techniques	Intra-observer reproducibility, blinded
(Auperin et al., 1996b)	Aloka SSD-650 7.5-MHz transducer	Bilateral CCA, including the carotid bifurcation, and the first 2 cm of the ICA	Scanned longitudinally and transversely to assess the presence of plaques	Inter-reader agreement regarding the presence of plaques was excellent (κ coefficient=.90).
(Watanabe et al., 2004)	PLE-705S, Toshiba 7.5-MHz linear-array transducer	Bilateral CCA including the carotid bifurcation and from 10 mm below the bifurcation,	Anterolateral and posterolateral angles of CCA with beam focused on the far wall	All measurements were determined by the same examiner, who was blinded to clinical history or risk factor profile.
(Komulainen et al., 2007b)	10-MHz transducer	Bilateral far wall of CCA and bifurcation	N/A	sonographers were blinded to the randomization status of the study participants
(Haley et al., 2007)	Agilent 5500 7.5-MHz transducer	Left, far wall CCA 1 cm proximal to the carotid bulb	N/A	N/A
(Muller et al., 2007)	Acuson Aspen 7.5 MHz linear array transducer	Bilateral distal CCA	N/A	the intra-class correlation coefficient (ICC) for repeated IMT-measurement was 84%
(Singh-Manoux et al., 2008a)	Aloka 5500 7.5-MHz transducer	Bilateral CCA	Longitudinal images triggered on the R-wave of the ECG	N/A

(Silvestrini et al., 2009)	Aspen color-coded duplex sonography	Bilateral CCA	of IMT taken as the thickest plaque-free region on the near and far walls in longitudinal images	N/A
(Carlsson et al., 2009)	AU4 Biosound 7.5MHz transducer	Bilateral, distal CCA, bifurcation, and the proximal portion of ICA	near and far walls scanned in each vessel segment (total of 12 sites)	N/A
(El-Kattan et al., 2009)	Siemens Elegra 7.5 MHz transducer	No details provided	Arteries assessed using longitudinal views and checked for the state of arterial wall and the presence of thrombi	N/A
(Kearney-Schwartz et al., 2009b)	ATL Apogee 800+ 7.5-MHz linear array transducer	Bilateral CCA	Arteries assessed using longitudinal views	N/A
(Zhong et al., 2011b)	Biosound AU4 7.5MHz transducer	Bilateral, near and far walls of CCA, bifurcation and ICA	N/A	The reproducibility of IMT and plaque assessment was good. In a 10% sample (n=280) of participant scans that were re-graded the mean difference in IMT was 0.0019 mm and kappa statistics for plaque assessment ranged from 0.58 (ICA) to 0.71 (bifurcation) with 97.3% agreement within ±1 for the number of sites with plaque.
(Dias et al., 2012)	Philips HD 11 XE	Bilateral CCA	The intima-media thickness was measured in near and far walls over a 1-cm segment of the artery located approximately 0.5 cm	The variability between IMT measurements less than 2%,; analysis performed by a physician blinded to the patient's clinical data

	7–12 MHz linear transducer		below the carotid-artery bulb and considered not to contain any plaque	
(Zhong et al., 2012a)	Biosound AU4 7.5MHz transducer	Bilateral CCA	Near and far walls	The reproducibility of IMT and plaque assessment was good. The mean inter-grader difference in IMT was 0.03 mm; and for plaque, the kappa coefficient was 0.76 and percent agreement was 90%
(Viticchi et al., 2012)	iU22 Philips 7.5MHz transducer	Bilateral, distal segment of CCA	Measurement of near and far wall IMT on longitudinal image of 1.5cm segment of CCA that precedes the carotid bifurcation. Measurement made with an automated system at the thickest point where there were no plaques	N/A
(Stefanova et al., 2012)	Aloka ProSound ALPHA 10 13 MHz linear multifrequency transducer	Far wall of CCA, ICA during diastole	During diastole measurements were done in a supine position with head elevated up to 45°, and tilted to the either side for 30°, depending on the side examined	The inter-rater correlation reliability assessed for 50 randomly selected patients from both groups was excellent (0.932), Physicians that performed ultrasound examinations were blinded to clinical data
(Rogne et al., 2013)	F/U (GE Vivid 7) 12-MHz transducer	Right, far and near wall CCA, bulb	Measurement of IMT was performed in 10-mm segments of the far and near wall of the common carotid artery in the most proximal 10-mm segment of the bulb. The CCA, the bifurcation and the internal carotid artery were examined for plaque presence.	N/A
(Xiang et al., 2013)	Hitachi Aloka SSD-650 7.5 and 10 MHz transducer	Bilateral, far wall CCA	Measurement of far wall CIMT in longitudinal B-mode images of the CCA, the carotid bifurcations, and the first 2 cm of the ICA at plaque-free sites	N/A

(Nagai et al., 2014)	SSA-660A Xario; Toshiba 7.5-MHz transducer with border detection	Bilateral, far wall CCA	CCA scanned bilaterally in longitudinal and transverse projections. The image was focused on the far wall of the artery	N/A
(Yano et al., 2014)	7.5-MHz transducer	Bilaterally at CCA, the bulb, and ICA	CCA, the bulb, and ICA measured from both transverse and longitudinal orientations, Region with the thickest IMT measured.	Coefficient of variation within 10%. Scan performed blind to patient's data
(Buratti et al., 2014)	iU22 Philips	Bilateral CCA	N/A	inter-reader correlation coefficient of 0.88
(Buratti et al., 2015)	iU22 Philips 7.5MHz transducer	Bilateral CCA	A longitudinal image of the distal segment of common carotid arteries was taken, and the measurement was obtained with an automatic system at the thickest point where there were no plaques on the proximal and distal wall	N/A
(Carcaillon et al., 2015)	N/A	Bilateral CCA, bulb, and ICA	scanned longitudinally and transversally to detect plaques.	N/A
(Kawasaki et al., 2016a)	Hitachi EUB-525 10-MHz linear transducer	Bilateral CCA, ICA	N/A	All examinations were performed by a single physician blinded to the subject's clinical information
(Liu et al., 2016b)	Vivid i, GE Medical Systems 7.5-MHz linear array transducer	Bilateral CCA	Three B-mode images were obtained using anterior, lateral, and medial angles. Maximum IMT in the right or left CCA used.	Scanning done by certified ultrasonographer who was unaware of the subjects' clinical details
(Wendell et al., 2016)	Acuson CV 70, Siemens	Left CCA	Far wall IMT measured over a region 1.5 cm proximal to the carotid bifurcation	Intraobserver correlation between repeated carotid IMT measurements on 10 participants was 0.96 ($p < 0.001$).

	standard transducer 5.OL45			
(Rouch et al., 2018)	Sigma 110 Kontron device 7.5 MHz transducer	Bilateral CCA	Near and far wall IMT measured in longitudinal images. Longitudinal and transverse images examined for plaques	N/A
(Alhusaini et al., 2018)	Siemens 7.5 MHz transducer	Far walls of CCA, and bulb*	Far wall CIMT measured as the mean of 3 caliper measurements over a 1cm-long segment of the CCA and carotid bulb	N/A
(Matsumoto et al., 2018)	Xario SSA-660A; TOSHIBA	Bilateral, far wall CCA, ICA	Far wall maximum CIMT of the bilateral CCA, ICA measured at end-diastole in longitudinal images	Certified sonographers who were blinded with cognitive test results carried out the carotid ultrasonography
(Muela et al., 2018)	Sigma 44 Kontrom 7.5- MHz transducer	Left CCA	Near and far wall CIMT was measured at the thickest point of the distal CCA, not including plaques using a computer program	an experienced observer who were blinded with Clinical condition carried out the carotid ultrasonography
(Falsetti et al., 2018)	iU22 Philips	Bilateral CCA	CIMT measurements made on 1.5 cm segment of CCA artery preceding carotid bifurcation in a longitudinal image using a semi-automatic system	N/A
(Mworozi et al., 2019b)	Shantou Institute of ultrasonic instrument 5300 5–12 MHz frequency linear transducer	CCA, ICA*	Participants scanned in both supine and semi recumbent positions, with the head slightly hyperextended and rotated 45 degrees away from the side being examined	N/A

Abbreviations: (ICA) internal carotid artery, (ECA) the external carotid artery, (CCA) common carotid artery , (CIMT) carotid intima-media thickness , (N/A) not applicable. *not clear whether measured bilaterally.