

Stroke in Young Adults: A Multifactorial Case-Control Analysis of the Established and
Emerging Risk Factors

by

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This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

This thesis consists of 4 manuscripts that have been submitted for review to peer-reviewed journals. Although I am the primary author of all the manuscripts, the contributions for each of the papers is as follows:

Chapter 2: Stroke in Young Adults: A comprehensive global analysis of the prevalence of established and emerging risk factors

Sanewal Singh contributed to the conceptualization, methodological design, formal analysis, investigation, data collection, writing of original drafts, as well as review and editing of manuscript.

Samantha Meyer contributed to the conceptualization, methodological design and analysis, review and editing of manuscript, project administration, and supervision.

Joel Dubin contributed to the conceptualization, methodological design, formal analysis, as well as review and editing of manuscript.

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Chapter 4: Caffeine Consumption and Stroke Risk in Young Adults: A Global Case Control Study

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Chapter 5: Leveraging Reddit and Facebook for sampling rare and uncommon populations: A modern approach to overcoming recruitment challenges in young adults with stroke

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Mike Sharma contributed to the conceptualization, methodological design, formal analysis, as well as review and editing of manuscript.

Diane Williams contributed to the conceptualization and the methodological design.

Abstract

While the incidence of stroke continues to decline among older adults in most parts of the world, stroke rates in younger adults have shown a concerning rise. Despite growing awareness and research, the etiology and risk profiles of stroke in young adults remains poorly understood and often explained using studies focused on older populations. However, applying findings from older adults to younger populations may be limited, due to given substantial differences in lifestyle and health risk factors. To better understand the rise of stroke in young adults, this thesis utilizes a case-control study design with primary data to investigate the sociodemographic, behavioural, and clinical characteristics of stroke in young adults.

This thesis includes a four-paper approach. The first study provides a comprehensive descriptive analysis of young adult stroke survivors, with a comparison to healthy adults within the same age range. The purpose of this study is to identify the sociodemographic attributes (e.g., race, education level, income), lifestyle factors (e.g., exercise, diet), health conditions (e.g., hypertension, heart conditions), and unique risk factors to young adults (e.g., caffeine consumption, mental health). Additionally, this study examines the temporal patterns of comorbidities in relation to stroke occurrence. Thereby, this study distinguishes between pre-existing and post-stroke diagnoses, and thus provides temporal insight into identifying prevalent risk factors and those that may go undiagnosed.

The second study uses a multiple conditional logistic regression analysis to explore the associations between a broad range of established and emerging risk factors and stroke risk in young adults. This paper expands on previous research by considering risk factors that may be unique to young adults, such as mental health conditions, substance use, and certain lifestyle factors. This paper challenges the direct application of risk factor analyses developed among older adults, underscoring the importance of age-specific research.

The third study examines the relationship between caffeine intake and stroke risk in young adults. Specifically, this paper examines the overall association between daily caffeine consumption and stroke risk, as well as the dose-and source-specific impact (e.g., coffee, tea, energy drinks, soda). Notably, this study approaches the intake of caffeine and various sources as a non-linear association, which is often overlooked in the progression of cardiovascular disease. Given that caffeine is widely consumed in young adults, this study offers new perspectives into how it may influence cerebrovascular health amongst this population.

Study four highlights the challenges of recruiting participants from rare or uncommon populations and presents a key methodological contribution of this thesis. Specifically, it examines the challenges of using traditional methods of recruitment, such as polling firms or clinical settings, which are often costly, time consuming, and limited in their reach. This paper demonstrates the use of social media as a cost-effective solution to the aforementioned recruitment challenges, using young adults who have experienced a stroke as an example. Nonetheless, study four highlights the key considerations for researchers planning on using social media for recruitment of rare or uncommon populations, while also acknowledging its limitations.

Together, this thesis seeks to provide a novel, multifactorial analysis of stroke risk in young adults by incorporating both established and emerging variables, as well as focusing on age-specific risk factors. In addition, this thesis offers a key methodological contribution to the field of stroke research by demonstrating the effective use of social media for recruiting uncommon populations and by capturing temporal patterns of health conditions related to stroke onset. Overall, this thesis aims to advance the current understanding of stroke risk in young adults and highlights the need for prevention and clinical strategies specific to their unique risk profiles.

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List of Abbreviations

HIV – Human immunodeficiency virus

PFO – Patent foramen ovale

RCVS – Reversible cerebral vasoconstriction syndrome

SDOH – Social determinants of health

TIA – Transient ischemic attack

Chapter 1

Introduction

1.1 Thesis Structure and Format

This dissertation follows an integrated thesis format, also commonly referred to as a “sandwich” thesis. The thesis consists of three main research articles and a commentary, all of which are currently under review for publication in peer-reviewed journals. Each article is a standalone study, making significant and novel contributions to the field of stroke research. Although these studies could not have been possible without the expertise and assistance of each co-author, my individual contribution to each article warrants primary author recognition.

This dissertation is organized in accordance with the University of Waterloo’s thesis formatting guidelines and consists of six chapters. The first chapter of this thesis is an introduction, that provides an overview of the overall scope of stroke research. This chapter highlights the current state of the literature, identifies research gaps, and explains the relevance of the topic within the broader field of Public Health Sciences and Epidemiology. Chapter One also outlines the thesis objectives and the methodological approaches used throughout the research. Chapters Two, Three, and Four present the three primary research articles. Specifically, Chapter Two identifies the prevalence of characteristics of young adults who experienced a stroke. Chapter Three applies an exploratory approach to examine the associations between established and emerging risk factors and stroke in this population. Chapter Four examines the impact of caffeine, particularly the dose-response and source-specific association with stroke risk in young adults. Chapter Five consists of a commentary that highlights the methodological contributions of this thesis. Specifically, this chapter underscores the use of social media platforms for recruiting rare and uncommon populations for research. Chapter Six consists of the conclusion. The final chapter summarizes the main findings, highlights the studies contributions, addresses the limitations, and discusses future directions and broader public health implications.

1.2 The History of Stroke, Stroke Research, and Medical Classification

1.2.1 The History of Stroke and Stroke Research

Human knowledge of stroke can be divided largely into two major time periods, the evolution of stroke prior to 1812 and the period following it up until present day. Pre-1812, stroke was defined as “apoplexy”, a definition created by philosophers Hippocrates and Galen to describe the sudden onset and loss of consciousness (Bukhari et al., 2023; Rutten-Jacobs et al., 2013; Sič et al., 2025). Early depictions of stroke consisted of sudden pain in the head of a healthy individual, followed by speechlessness, and then gaping of the mouth (Karenberg, 2020). Philosophers believed that the accumulation of noxious mucus and phlegm was responsible for disrupting the flow of the “animal spirit” leading to loss of consciousness, sensory dysfunctions, and even death (Karenberg, 2020). To alleviate the imbalances between phlegm and blood in the body, the treatment of stroke was often bloodletting, which is when an individual is purposefully cut open to allow for the removal of blood (Roushdy, 2024).

Post 1812, can be described as the modern era of stroke research and understanding, marked by a shift towards recognizing the importance of vascular abnormalities (Karenberg, 2020). The recognition of vascular lesions introduced the discipline of neurology. Specifically, famous physicians such as Jean-Andre Rochoux and Rudolf Virchow were instrumental in discovering the role of blood flow and arteries, particularly, the recognition of vascular occlusions in infarction (Karenberg, 2020). Over time, neurology gained more interest and in the late 19th century became its own medical specialty with various clinics and schools dedicated to its research and teachings (Karenberg, 2020). Similarly, post-1975 stroke research gained increasing focus with research on risk factors, clinical trials, and treatments and ultimately became a subspecialty of neurology (Karenberg, 2020). These advancements in stroke research have amplified our understanding on prevention and treatment: however, irrespective of this progress, research has not sufficiently kept up to date

on the rising incidence of stroke in young adults. Specifically, age-standardized rates of stroke indicate that among young adults, stroke cases have risen by 36-41% since the 1990s, with the largest increase occurring after 2015 (M. Zhang et al., 2025). While the broader topic of stroke has gained attention, the specific issue of stroke in young adults remains largely overlooked, despite being a growing global concern.

1.2.2 Medical Definition of Stroke

Building on the evolving knowledge of stroke and the present focus of stroke in young adults, it is essential to define what this condition is in modern medical terms. A stroke can be defined as a set of neurological symptoms caused by acute, focal impairment of blood flow to the brain, resulting in the reduction of oxygen and essential nutrients, such as glucose (Murphy & Werring, 2020). Stroke can be classified into two broad processes of vascular dysfunction: ischemic stroke, which is most commonly caused by vessel occlusion, or hemorrhagic stroke, which is most commonly caused by vessel rupture. Both forms of stroke result in compromised blood perfusion, and consequently reduced oxygen and nutrients essential for brain functioning. Together, this lack of blood perfusion results in the manifestation of neurological symptoms, such as face drooping, arm weakness, speech difficulty, as well as severe headaches, trouble walking, dizziness, and loss of balance (Andersson et al., 2024). Vessel occlusion can often occur as a result of atherosclerosis, which is a progressive disease, resulting in the rupture of fatty plaques, causing thrombosis (blood clot) within the arterial system (Pahwa & Jialal, 2023; Singh et al., 2002).

Atherosclerosis (buildup of plaques in the arteries resulting in narrowing and hardening) commonly affects arteries with higher rates of blood flow, leading to subsequent plaque formation (Björkegren & Lusis, 2022). Common arteries affected by atherosclerosis include coronary, carotid, peripheral, aorta, renal, mesenteric, iliac, cerebral, vertebral, and basilar arteries (Singh et al., 2002). If left unmanaged, the subsequent thrombosis from the plaque rupture causes occlusion, which may lead to impaired organ perfusion, skin necrosis, and/or tissue death (King et al., 2020). In contrast, a hemorrhagic stroke is often caused by the

rupture of a blood vessel in the brain, resulting in impaired perfusion, but also blood loss and increased intracranial pressure (Unnithan et al., 2025). Both concepts will be further examined throughout the duration of this thesis.

The term “young adult” in the context of stroke tends to vary from everyday use. In terms of stroke, researchers and clinicians often describe young adults as individuals aged between 18 to 55 years old (Murphy & Werring, 2020). Although 55 years old would not generally be considered young to the general public, this age range is considered young compared to the typical stroke patient population, who are often over 65 years of age (Kelly-Hayes, 2010). For the purpose of this thesis, young adults will be defined as individuals who experienced their first stroke between the ages of 18 to 50, consistent with definitions used in various studies (Bukhari et al., 2023a; Rutten-Jacobs et al., 2013; Sič et al., 2025).

1.3 Clinical Perspective of Stroke

1.3.1 Stroke Subtypes and Physiological Symptoms

The brain is perfused via a network of arteries, including the carotid, cerebral, vertebral, and basilar arteries, which in the context of an ischemic stroke can become occluded due to a plaque rupture and subsequent thrombosis (Banerjee & Chimowitz, 2017). See Figure 1 for a comparison between a vessel rupture and thrombus. The obstruction of the proximal cerebral arteries is common (Nicholls et al., 2022; Yahya et al., 2020a), and accounts for nearly half of ischemic stroke cases (Nicholls et al., 2022). A thrombus (blood clot) can form in the arteries of the brain (ischemic stroke) obstructing blood flow and resulting in anoxia (complete lack of oxygen in the tissues) (Ashorobi et al., 2025; Lacerte et al., 2025). Approximately 80% of all stroke occurrences are diagnosed as ischemic strokes (Saini et al., 2021). Common signs of an ischemic stroke include sudden numbness in the face or limbs, confusion or difficulty with communication, sudden vision impairments, abrupt dizziness,

difficulty walking and maintaining balance, and severe headaches (Randolph, 2016). Collectively, these stroke symptoms are described to the general public as F.A.S.T. (F- face droop, A- arm weakness, S- speech impairment, T- time to call 911). In some individuals these symptoms may be brief, typically associated with transient ischemic attacks (TIA), or commonly referred as “mini strokes”, which are clinically less severe than an ischemic stroke (Randolph, 2016).

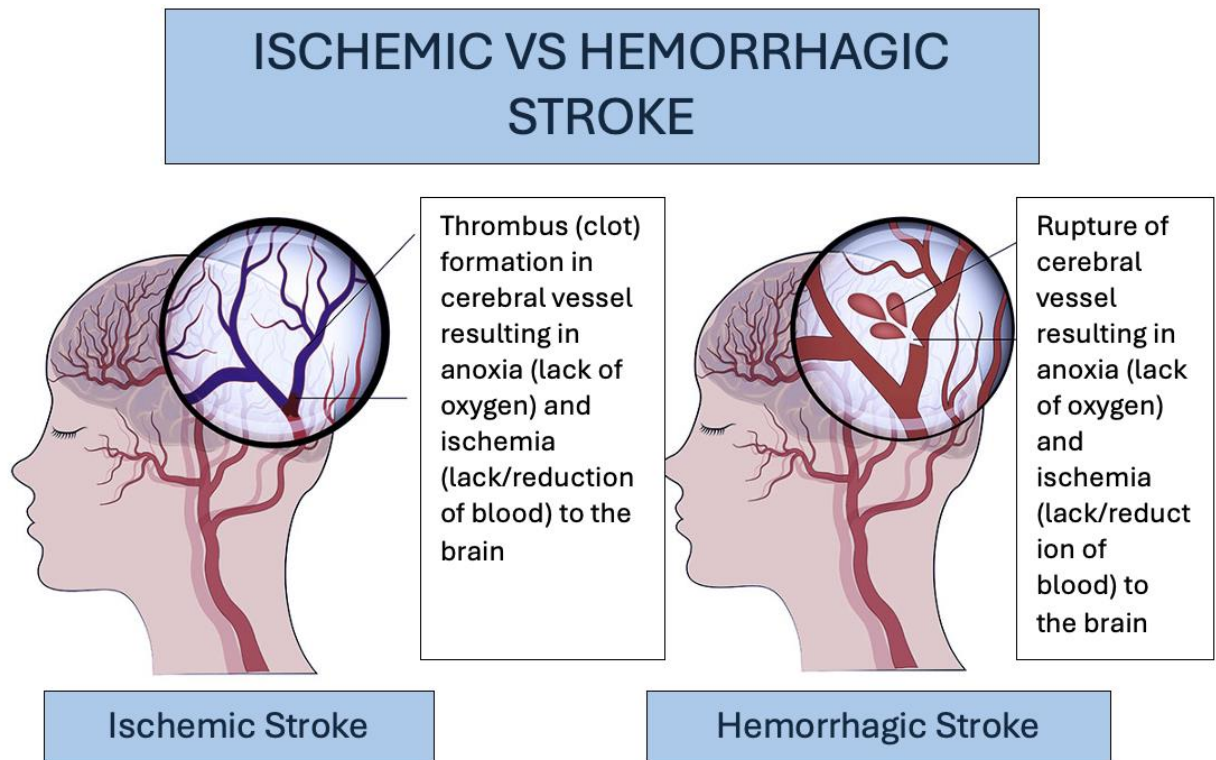
Another form of stroke is hemorrhagic stroke, which still causes impaired perfusion to the brain; however, mechanistically hemorrhagic stroke is commonly caused by the rupture of an artery. Vessel rupture often occurs in the vessels where the shear forces are the greatest, such as the aorta, coronary arteries, or cerebral arteries (Norman & Powell, 2010; Tada et al., 2014). High shear forces coupled with a dysfunction of the endothelium, weakens the integrity of the blood vessel (Norman & Powell, 2010; Tada et al., 2014). The subsequent hemorrhage from the ruptured blood vessel leads to increased intracranial pressure (Unnithan et al., 2023). The accumulation of blood exerts pressure on the brain, further mechanically occluding surrounding blood vessels and impairing perfusion to the brain (Unnithan et al., 2023). In addition, the toxic effects of blood products on surrounding regions of the brain following a hemorrhage induce inflammation and oxidative stress pathways, resulting in secondary brain damage (Madangarli et al., 2019).

Prolonged hypertension, vascular aneurysms and malformations, as well as severe head trauma can increase the risk for hemorrhagic stroke (Magid-Bernstein et al., 2022; Qu et al., 2022). Hemorrhagic stroke is further classified into two main types: intracerebral hemorrhage and subarachnoid hemorrhage. These two forms of hemorrhage stroke affect different parts of the brain. Intracerebral hemorrhage is described as bleeding from the parenchyma region of the brain (Naidech, 2011). The likelihood of an intracerebral hemorrhage increases with age and hypertension is often a risk factor (Josephson et al., 2010; Yahya et al., 2020a). Intracerebral hemorrhage caused by hypertension commonly occurs at

the small arteries coming from the basilar arteries or the anterior, middle, or the posterior positions of the cerebral arteries (Unnithan et al., 2023). Subarachnoid hemorrhage is characterized by the hemorrhage from the space between the pia and the arachnoid membranes of the brain (Naidech, 2011; Ziu et al., 2023). Moreover, subarachnoid hemorrhages are commonly caused by the rupturing of intracranial aneurysm due to weakening of blood vessels (Ziu et al., 2023). Factors such as hypertension, tobacco and illicit drug use, as well as genetic predispositions have shown to increase the risk factors of subarachnoid hemorrhage (Ziu et al., 2023).

While there is some overlap of symptoms between ischemic and hemorrhagic stroke, hemorrhagic strokes more commonly depict severe headaches, vomiting, stiffness in the neck region, seizures or aphasia, and an increased heart rate (An et al., 2017). Depending on the location of the stroke, some may result in paralysis or paresis (Price & Campbell, 2023), as well as cause motor sensory impairment due to cell death and damage to the motor cortex (Bolognini et al., 2016). Regardless, whether a stroke is classified as ischemic or hemorrhagic, any disruption in blood perfusion to the brain is a life-threatening condition. Even when blood flow is briefly impaired, cell death begins, which may lead to permanent neurological damage or death if treatment is delayed (Maaijwee et al., 2014).

Figure 1 Ischemic vs Hemorrhagic Stroke



Mechanistic comparison between ischemic and hemorrhagic strokes. Ischemic strokes can be characterized as the clot formation in the cerebral vessels, while hemorrhagic strokes are characterized as vessel ruptures. Adapted from: (Covenant Health, n.d.)

1.3.2 Behavioural Symptoms

In addition to physiological symptoms, a stroke can also be associated with behavioural symptoms, such as changes in empathy, mood and emotional regulation (Carota et al., 2002; Nijssen et al., 2019). Damage to regions of the brain responsible for cognition and behaviour can lead to irreversible changes to an individual's behaviour, impulse control, as well as psychological changes including depression and anxiety (Khedr et al., 2020; Srivastava et al., 2010; Turkeltaub, 2019). These stroke-induced psychological implications can also impede recovery outcomes and negatively affect the quality of life (Wijeratne & Sales, 2021). Further, neurological damage can also occur, affecting neurotransmitters, such as dopamine

and serotonin, thereby increasing the risk of depression (Khedr et al., 2020). Ultimately, a stroke can have detrimental physiological, as well as behavioural consequences resulting in poorer patient outcomes. Therefore, it is important to understand the etiology of strokes in order to develop better preventative measures and treatments to improve patient outcomes.

1.3.3 Etiology of Stroke in Young Adults

The diagnostic evaluation and treatment protocols for older adults cannot be applied directly to young adults (Smajlović, 2015). Researchers have highlighted that the nature and etiology of strokes vary based on age group, and findings from studies on older stroke patients may not be relevant to young adults (Smajlović, 2015), emphasizing the need for research dedicated to this population. For example, arterial dissection is a leading cause of ischemic strokes in young adults (Arning et al., 2022). Arterial dissection can be characterized as a tear and separation of the inner lining of an artery, which can result in the narrowing, complete blockage, and/or formation of a clot (thrombus) leading to disruption of blood flow and oxygen to the brain (Goodfriend et al., 2022). Minor trauma such as sports injuries, chiropractic manipulation, and sudden forceful neck movements are common causes of arterial dissections in young adults (J. Jones et al., 2015). Research indicates that arterial dissections are much more common in individuals under 50 years old, accounting for approximately 15 to 25% of ischemic strokes (Metso et al., 2012), compared to only 7% in adults older than 60 years old (Traenka et al., 2017).

Patent foramen ovale (PFO) have also been commonly associated with the etiology of ischemic strokes in young adults. PFO is a congenital cardiac lesion that remains present in about 27% of adults (Hara et al., 2005). The foramen ovale is essential in the fetus, as it allows oxygen rich blood from the mother to pass between the right and left atria, bypassing the fetal lungs during development (Moore & Persaud, 1998). However, lack of natural PFO closure results in the increased risk of various conditions, including but not limited to

myocardial infarction, decompression sickness, complications of pulmonary embolism, and ischemic strokes (Hara et al., 2005). It is believed that PFO can allow small clots in the venous system to pass into brain causing a stroke (Kavinsky et al., 2022). Research on young adults who have experienced a stroke have found that in those patients under 55 years old, upwards of 40% had a PFO, compared to only 10% in the control group (Lechat et al., 1988a). Another study that examined adults 45 years and younger found that 50% of the patients had a PFO (Besson et al., 1994). Though some studies have reported lower prevalence rates, the relatively high occurrence of PFO demonstrated in the aforementioned studies suggests that it may play a significant role in stroke, particularly in young adults.

In young adults, infections and inflammatory causes have been identified as potential stroke triggers, highlighting their relevance in this population. Factors such as human immunodeficiency virus (HIV) and syphilis have been shown to impact stroke through various mechanisms, including inflammation, endothelial dysfunction, hypercoagulability, and direction embolization (Bahouth & Venkatesan, 2021). HIV has been shown to impact stroke risk as a result of chronic damage to blood vessels, increased hypercoagulability, and increased risk of vasculitis caused by related infections (e.g. tuberculosis) (Ahn et al., 2020; L. A. Benjamin et al., 2012). Other chronic conditions, such as syphilis, can impact the central nervous system (known as neurosyphilis) to cause long-term inflammation and damage to blood vessels in the brain, ultimately increasing the risk of stroke (Fugate et al., 2014).

Hemorrhagic strokes have distinct etiologies that are particularly important in young adults. For instance, the prevalence of intracranial aneurysms, drug-induced-hemorrhages, and Reversible Cerebral Vasoconstriction Syndrome (RCVS) occur more commonly in young adults. While intracranial aneurysms are more common in older adults, certain genetic conditions such Ehlers Danlos syndrome and Polycystic Kidney Disease significantly increase to risk of hemorrhagic strokes in young adults (Shabani et al., 2023; Yoo et al.,

2014). These genetic conditions are associated with the weakening of blood vessel walls, increasing the risk of aneurysm and rupture, often seen at a younger age (Shabani et al., 2023; Yoo et al., 2014).

Drug-induced hemorrhages have increased over time, particularly in young adults due to the rise in the availability of drugs, such as amphetamines, cocaine, and ecstasy (McEvoy et al., 2000). These substances can lead to hemorrhagic strokes through various mechanisms. Specifically, acute increases in blood pressure, damage to vessels by constriction, and vasospasms can result in hemorrhage. The acute rise in blood pressure caused by methamphetamines and cocaine overtime can make small blood vessels in the brain more susceptible to rupture and intracerebral hemorrhage (Banimostafavi et al., 2024). Researchers highlight that ongoing drug use can lead to acute intoxication, perpetuating the formation of clots and vascular damage, ultimately resulting in rupture of vessels (Davis & Swalwell, 1996). These effects are primarily the result of drug induced hypertension and tachycardia (increased heartbeat and increased blood pressure) (Davis & Swalwell, 1996). Additionally, the use of cocaine and methamphetamine has been associated with increased risk of cerebral vasospasm, as repeated constriction of blood vessels can weaken vessels' walls and lead to rupture (Nussbaum et al., 1997; Wang et al., 1990). Research indicates that individuals are more likely to start using hard drugs, such as cocaine and methamphetamines under the age of 50 (Lipari et al., 2012). These examples highlight the conditions that tend to emerge or become more prominent in younger populations and increases in stroke risk by affecting individuals blood vessels, immune responses, or clotting factors.

1.4 Epidemiological Trends

1.4.1 Stroke in the General Population

Stroke in the general population varies significantly from that in young adults. While some risk factors are shared, differences exist in common causes, stroke type, recovery outcomes,

and long-term impact. For instance, in older adults, stroke is more often associated with chronic conditions, such as hypertension or diabetes, while younger adults the various risk factors identified throughout this chapter. Similarly, differences in stroke mortality and disability exist between older and younger survivors. In comparison to younger stroke survivors, older patients have higher rates of disability and increased mortality for strokes of similar severity and pathology (Furlan et al., 2021; Sharma et al., 1999). Research examining the acute and three month mortality of stroke patients found that older adults experienced significantly higher disability and mortality at both stages (Sharma et al., 1999). Findings of the study suggest that the poorer stroke outcomes experienced by older adults may be associated with worse pre-stroke health, often as a result of chronic diseases, and reduced capacity for neuroplasticity (Alawieh et al., 2018; Furlan et al., 2021). While research shows that young adults may have lower mortality and better functional recovery, the long-term impact of stroke is worse compared to older adults (Furlan et al., 2021; Sharma et al., 1999). The long-term impact of stroke in young adults is often marked by psychosocial and economic impacts that occur during important developmental stages, whereas in older adults they have already typically been established (Morris, 2011a). Although stroke in the general population has historically been more common in older adults, recent trends suggest an increasing incidence in younger populations (L. Li et al., 2022).

1.4.2 Global Burden of Stroke in Young Adults

Stroke has long been considered a disease that primarily impacts older adults; however, recent data indicates a growing burden among younger adults. Globally, studies indicate that 10 to 15% of all strokes occur in adults younger than 50 years old (Ji et al., 2013; Maaijwee et al., 2014; Singhal et al., 2013). Research has depicted global increases in stroke incidence in young adults, while rates of strokes in older adults have remained stable or decreased (Bukhari et al., 2023a). In Canada, the crude weighted incidence rate of stroke for 2003-2004 for those 50 years and older was 1,508 per 100,000, and for those 20-49 years old it was 62 per 100,000 (Canada, 2024). In 2022-2023, for individuals 50 years and older it was 929 per

100,000, and for those 20 to 49 years old it was 66 per 100,000 (Canada, 2024). Notably, rates declined over the 19-year period in all ages over 50, while there was an increase for those aged 20 to 49. Among Canadian young adults, a study found that the incidence of ischemic strokes in young adults aged 18 to 54 in Ontario had increased over the 15-year study period ranging from 2003 to 2017 (Joundi et al., 2021). Specifically, stroke rates among adults aged 35 to 39 increased from 9.5 per 100,000 in 2003 to 23.6 per 100,000 in 2017 (Joundi et al., 2021). For those aged 40 to 44, rates rose from 22.9 to 46.0 per 100,000 during the same period (Joundi et al., 2021). In the United States, the incidence of stroke in young adults aged 20 to 44 increased from 17 per 100,000 in 1993 to 28 per 100,000 in 2015 (Yahya et al., 2020a). A study examining the incidence of ischemic strokes in New Jersey from 1995 to 2014, found that rates of strokes in those aged 35 to 54 increased, whereas they decreased in all age groups over 55 years old (Swerdel et al., 2016). Over the 20-year study period, stroke incidence among adults aged 35 to 39 increased from 9.5 per 100,000 person-years to 23.6 per 100,000 person years (Swerdel et al., 2016). Similarly, rates increased from 22.9 to 46.0 per 100,000 person-years in adults aged 40 to 44, from 45.5 to 76.5 in those adults aged 45 to 49, from 103.0 to 126.9 per 100,000 person-years in individuals aged 50 to 54 (Swerdel et al., 2016).

Stroke trends among young adults outside of North America are similar. In Europe, rates of stroke have increased among young adults aged 18 to 55 over time. Specifically, ischemic stroke incidence increased from 10.7 per 100,000 between 1992 to 2002 to 18.1 per 100,000 between 2003 to 2011 (Béjot et al., 2014). Comparably, countries in Asia also indicate increases in stroke rates among young adults. In China, a study examining the trends in incidence over 24-years found that stroke rates significantly increased over time among adults 35 to 64 years old (Ning et al., 2017). Specifically, stroke rates increased from 122 per 100,000 person years between 1992 to 1999 to 471.8 per 100,000 person-years between 2008 to 2015 (Ning et al., 2017). While stroke rates in young adults typically vary between 10 to 15%, the proportion of strokes occurring in adults under 50 years old in India has

increased to 20 to 30% (Behera et al., 2024). Overall, research indicates a growing global burden of stroke in young adults. Although incidence rates may vary by country, the overarching trend points to an increase of stroke in young adults, calling for increased attention and research.

1.5 Risk Factors of Stroke

From an epidemiological perspective, there are various risk factors that may influence the risk of an ischemic or hemorrhagic stroke. These factors can be further classified as modifiable or non-modifiable risk factors. Modifiable risk factors for stroke are factors that can be changed or controlled to decrease the risk of the outcome (Moskowitz et al., 2010). Studies show that multiple modifiable risk factors coexist, and are responsible for 60 to 80% of the risk associated with stroke occurrence in the general population (Moskowitz et al., 2010). Some examples of modifiable risk factors of stroke include hypertension, diabetes, smoking/tobacco use, illicit drug use, oral contraceptive use, lack of exercise, and poor diet (Moskowitz et al., 2010). From the aforementioned examples of modifiable risk factors, some have been studied more extensively regarding their association with stroke incidence.

1.5.1 Modifiable Risk Factors

Hypertension is a modifiable risk factor that has been linked to increased stroke susceptibility by causing increased stress on the endothelium, ultimately leading to narrowing, rupturing, or leaking of the affected blood vessels (Johansson, 1999a; Shekhar et al., 2019). Although hypertension may not be reversible, the contributing factors such as poor diet and lack of exercise can be managed through lifestyle modifications to reduce stroke risk. Diabetes mellitus, specifically, type 2 diabetes, is another modifiable risk factor that can increase the risk of stroke (R. Chen et al., 2016; Virani et al., 2020). Type 2 diabetes is largely influenced by factors such as diet, exercise, and obesity (Sami et al., 2017). Diabetes has been shown to cause systematic inflammation, arterial stiffness, and endothelial dysfunction leading to an

increase in stroke susceptibility (R. Chen et al., 2016). Furthermore, studies have shown strong associations between smoking, tobacco use, and recreational drug use with onset of a stroke (Giroto, 2009; Pan et al., 2019; Shah & Cole, 2010; Virani et al., 2020).

Smoking/tobacco use has been shown to have adverse vascular effects caused by the exposure of toxins, which contain a number of reactive oxygen species that cause long-term damage to the cells, resulting in inflammation while increasing the risk of thrombosis (Mazzone et al., 2010). Moreover, smoking has shown to contribute to other risk factors, such as hypertension, thereby increasing the overall risk of stroke (Virani et al., 2020).

1.5.2 Non-modifiable Risk Factors

In contrast, non-modifiable risk factors cannot be changed or altered to decrease the risk of the outcome from occurring (Moskowitz et al., 2010). Examples of non-modifiable risk factors that can increase one's overall risk of having a stroke include family history and genetic factors (Virani et al., 2020). For instance, genome-wide association studies have genetic predisposition as a risk factor for stroke (Pourasgari & Mohamadkhani, 2020). Specifically, genome-wide studies have shown multiple genetic variants in loci that are shared with vascular traits (Pourasgari & Mohamadkhani, 2020). As a result of genetic predispositions, it is important to consider family history when assessing individual's risk for stroke (Pourasgari & Mohamadkhani, 2020). To add, genetic conditions, such as sickle cell anemia can also affect the risk of stroke as this condition affects red blood cells and has shown to increase the risk of vessel occlusion (Runge et al., 2022).

Another non-modifiable risk factor is biological sex, as it has been shown to contribute to stroke risk (Virani et al., 2020). In the United States, the incidence of stroke in adults 85 years and older is higher in females and account for the majority (60%) of deaths associated with stroke (Persky et al., 2010). However, under 85 years old, males have a greater risk and incidence of stroke (Persky et al., 2010). Studies controlling for confounders

have shown that the quality of life after stroke occurrence and functional outcomes are consistently lower in females (Reeves et al., 2008). While rates of stroke incidence declined for males since 1993, they have not for females (Virani et al., 2020). Sex-related differences in stroke have been largely attributed to the biological difference of sex steroid hormones, particularly, estrogen (Abdu & Seyoum, 2022). Estrogen may contribute to stroke risk by affecting female's blood pressure, coagulation, and the endothelium (Henderson & and Lobo, 2012).

In addition to genetic predispositions and sex, another non-modifiable risk factor for stroke is age, which increases risk for stroke as individuals get older (E. J. Benjamin et al., 2018; Kelly-Hayes, 2010; Yousufuddin & Young, 2019). The incidence of stroke doubles every 10 years after an individual exceeds 55 years-old (Yousufuddin & Young, 2019). A study examining the impact of the rapidly growing aging population in Dijon, France found that increases in age were associated with increases in stroke incidence (Béjot et al., 2019). Studies controlling for health-related factors, such as stroke type, vascular risk, and blood composition have shown that age is an important predictor of stroke mortality (Soriano-Tárraga et al., 2018; Yousufuddin & Young, 2019). Despite these studies, the average age of stroke onset has unprecedentedly decreased as the number of young adults suffering from stroke have increased (Maaijwee et al., 2014).

1.6 Age-associated Risk

Various aforementioned research illustrates the impact of age on stroke. Research findings indicate that as age increases, so does an individual's risk of stroke, primarily due to the accumulation of fatty deposits in the cardiovascular system (Mazza et al., 2001; Rothwell et al., 1997; The Stroke Risk in Atrial Fibrillation Working Group, 2007). In addition, studies suggest that age plays a role in the severity of stroke (Khaw et al., 1984), recovery (Kwakkel et al., 1996; Patel et al., 2000), and rehabilitation (Bagg et al., 2002; Benjo et al., 2007). For

instance, studies on age and stroke severity largely found that there is an increase in fatality as individuals age (Andersen et al., 2009; Khaw et al., 1984; Sohrabji et al., 2013). The prevalence of stroke has commonly been associated with older adults. As mentioned previously, while incidence rates of stroke have decreased in developed countries in recent years due to the advancements in treatments for thrombosis and atherosclerosis, there has been a rise in the incidence of stroke in young adults (Sultan & Elkind, 2013). Figures 2 and 3 illustrate that Canadian young adults between the age groups of 20 to 34 and 35 to 49 have an increase in stroke incidence rates per 100,000 between 2003-2004 and 2021-2022, whereas the 50+ age group showed a decrease. Given that the increase in stroke occurrence among young adults is rather recent, a large subset of literature on stroke is focused on the correlates and risk factors among the elderly population. Thus, there is limited research focusing on the risk factors of stroke among young adults. The risk factors that contribute to stroke risk in young adult may be different from those of older adults; however, this is unclear and requires further investigation.

Figure 2 Stroke Incidence Rate Per 100,000, from 2003-2004 and 2021-2022

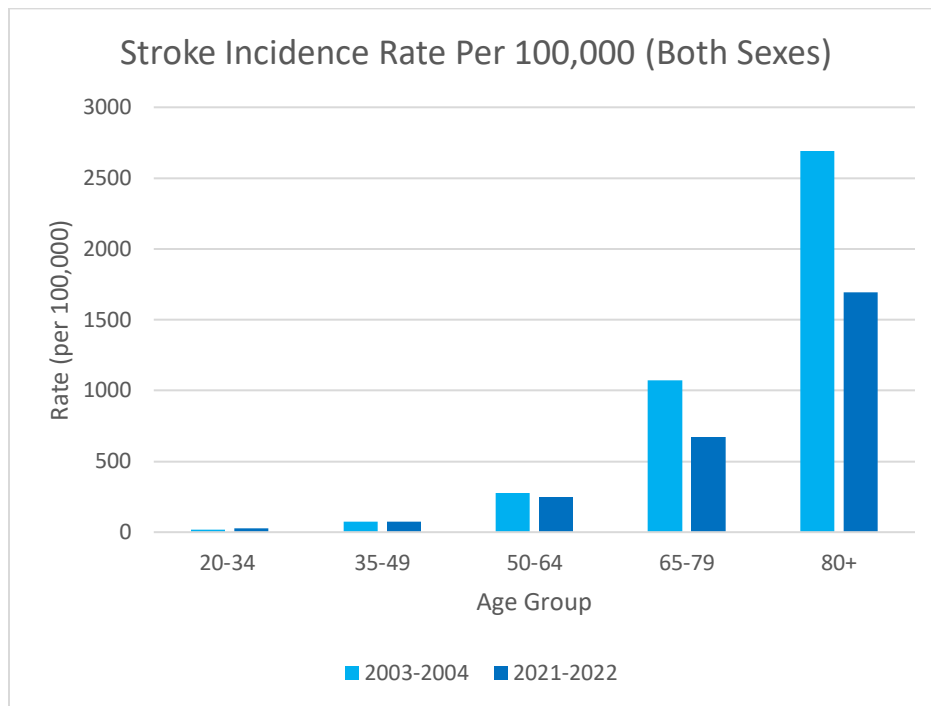


Figure 2 Presents the Canadian stroke incidence rate per 100,000 in both sexes between 2003-2004 and 2021-2022 among all age groups. The graph illustrates decreases in per 100,000 incidence rate in all age ranges greater than 50 years old. Data from (Canada, 2024)

Figure 3 Young Adult Stroke Incidence Rate Per 100,000, from 2003-2004 and 2021-2022

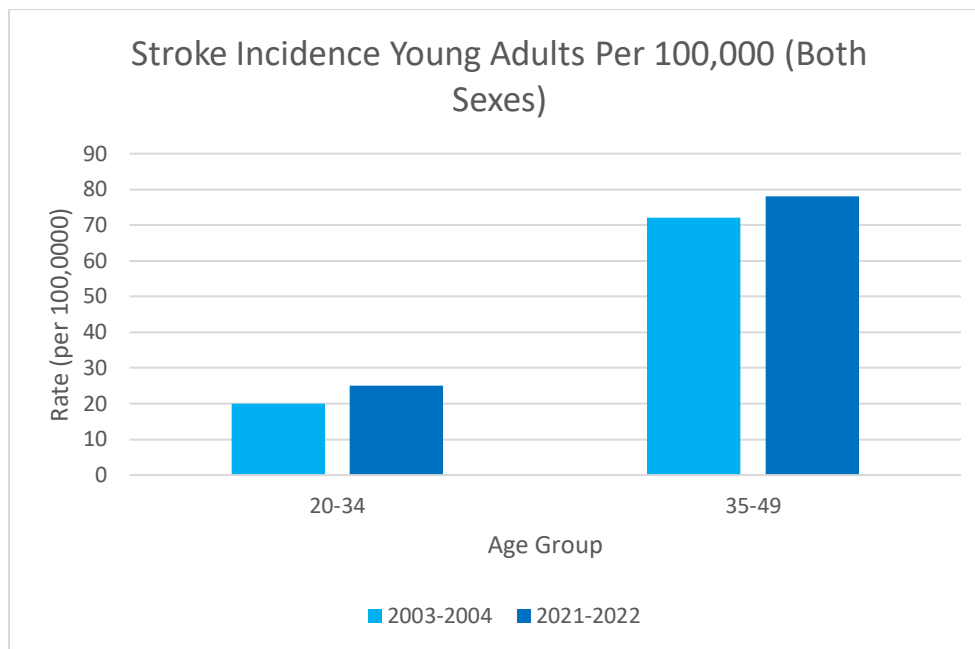


Figure 3 Presents the Canadian stroke incidence rate per 100,000 in both sexes between 2003-2004 and 2021-2022 among young adults 20 to 49 years old. The graph illustrates the increase in per 100,000 incidence rate among those less than 50 years old. Data from (Canada, 2024)

1.7 Social Determinants of Health and Stroke

The impact and prevention of modifiable risk factors can be better understood and addressed by acknowledging social determinants of health (SDOH). The term “social determinants of health” is a concept that acknowledges that various mechanisms impact the health of individuals when they belong to different socioeconomic groups (Raphael, 2006). More specifically, the term was defined 1996 to describe how the differences in the quality of housing, education, workplace conditions, and social capital, in addition to income relate to differences in health outcomes (Raphael, 2006). Today, the WHO defines SDOH as the influence of factors such as conditions in which people are born, grow, live, work, and age, as well as their access to power, money, and resources on an individual’s health outcomes

(Braveman & Gottlieb, 2014a). Therefore, SDOH can be classified as non-medical factors, such as lifestyle choices and environment that collectively contribute to an individual's overall health. In the last two decades, compelling research has provided evidence that social factors significantly influence the overall well-being (physical and emotional) of individuals and is no longer thought to be limited to the influence of medical care alone (Braveman & Gottlieb, 2014b). Nonetheless, studies have shown that in addition to access to high quality medical care, SDOH have been shown to impact the likelihood of illness and injury in the first place (Braveman & Gottlieb, 2014b).

The role of SDOH is not as straightforward as one might assume, rather, there are many complex pathways that involve biopsychosocial processes (Braveman & Gottlieb, 2014b). SDOH contributes to the wellbeing of an individual in a combination of biological, social, psychological, and economic pathways. From a biological perspective, SDOH can impact the health of an individual through changes in genetic expression, latent effects, and allostatic load (Braveman & Gottlieb, 2014b; Raphael, 2006). Changes to an individual's genetic expression can be influenced by social factors that regulate whether a gene is expressed or suppressed, which is known as epigenetics (Braveman & Gottlieb, 2014b). Factors of SDOH such as nutrition have been shown to play an important role in epigenetics as nutritional deficiencies have been linked to the availability of methyl donors (changes in DNA methylation), which regulates gene expression (O. S. Anderson et al., 2012). Moreover, studies suggest that SDOH factors, such as diet, exercise, education, and occupational class can impact an individual's telomere length (Cherkas et al., 2006; Steptoe et al., 2011). Telomeres are protective caps at the end of chromosomes, and their length is an important predictor of cell aging and disease risk, such as cardiovascular disease (Ordovás & Smith, 2010; Rizvi et al., 2014).

SDOH can also have latent effects, in which early life experiences can accumulate and manifest later in life through biological pathways (Raphael, 2006). For instance, babies

with low birth weights and inadequate fetal nutrition are at higher risk of developing diabetes or cardiovascular diseases later in life (Ordovás & Smith, 2010; Raphael, 2006). This phenomenon is better known as the fetal origin's hypothesis, which reiterates that biological pathways are impacted by SDOH and have a profound effect on one's future health outcomes and manifestation of disease later in life (Calkins & Devaskar, 2011). Allostatic load is another biological factor that is impacted by the SDOH to impact the health of an individual. Allostatic load refers to the physiological changes that occur across various biological systems as a response to ongoing social and environmental stressors (Braveman & Gottlieb, 2014b). For instance, unmanaged chronic stress from daily life can cause physiological consequences, such as lack of sleep and exercise, which in turn may alter the neuroendocrine system and increase the overall risk of illnesses and adverse health outcomes (Guidi et al., 2021).

From a psychological perspective, negative SDOH can have adverse effects on an individual's health. These negative SDOH include, poverty, racial discrimination, family conflict, and neighbourhood violence, which can all cause psychological stress and subsequently deteriorate mental and physical health (Braveman & Gottlieb, 2014b; Raphael, 2006; Rootman et al., 2017). Studies indicate that chronic exposure to social and psychological stressors from the environment can result in physiological changes (Ershler, 1993; Morey et al., 2015). For example, chronic psychological stress can result in dysregulated cortisol release, resulting in abnormal immune system activation, thereby increasing the risk of cardiovascular disease (e.g., stroke) and other illnesses (Dimsdale, 2008; Ershler, 1993; Morey et al., 2015).

In addition, certain populations experience a disproportionate burden of stroke risk due to the impact of complex social and structural inequities. For example, Indigenous populations in Canada often face systemic barriers to healthcare and socioeconomic disadvantages that contribute to the higher rates of cardiovascular disease and stroke (Schultz

et al., 2021). Similarly, LGBTQ+ individuals may encounter chronic unmanaged stress, family conflict, and discrimination which can also increase prevalence of mental health challenges and behavioral risk factors associated with increased stroke risk (Gmelin et al., 2022; Hu et al., 2024). People facing homelessness face unique vulnerabilities, including housing and food insecurities, and barriers to preventative and acute care (Padgett, 2016), all of which can increase an individual's risk of stroke. Together, these inequalities highlight the intersection between SDOH and biological pathways, emphasizing the need for population-specific approaches to stroke prevention.

In addition to higher income individuals having greater access to resources for coping strategies to psychological stressors, income and socioeconomic/employment status also significantly impacts an individual's access to health care and medications. Health inequalities, even in Canada, a country which provides citizens with free universal healthcare, has various health inequalities because of differences in income (Rootman et al., 2017). Although health care may be “free”, income is associated with an individual's health as it mediates one's access to protective factors, such as medication, quality food, improved housing, sanitation, and transportation to health services (Braveman & Gottlieb, 2014b; French et al., 2019). An example of the impact of income on health can be demonstrated in neighbourhoods from lower social classes, which can have fewer grocery stores and health care facilities, but an increased number of fast-food restaurants (Ellen & Glied, 2015). Inequalities in injury can also vary based on income. For instance, children that belong to the poorest neighbourhoods in Ontario, Canada had 67% higher rate of injury in comparison to children from the wealthiest neighbourhoods (Rootman et al., 2017). Similarly, Canadian mortality rates also vary based on income, as findings estimate that approximately 110 Canadians die each day as result of income inequalities (Rootman et al., 2017). Economic factors also impact education levels to consequently impact health. Education level not only impacts health education and knowledge (Johnston et al., 2015), but also an individual's income and ultimately their health (Cutler & Lleras-Muney, 2006).

1.8 The Burden of Stroke and Importance of Age-specific Research

The rise in stroke incidence among young adults is cause for additional research given the social, economic, and health implications. Although stroke has traditionally been considered a disease primarily affecting the elderly, the increasing prevalence of stroke in individuals under the age of 55 challenges this notion (L. Li et al., 2022). The risk factors such as hypertension, obesity, and diabetes, once primarily associated with older age, are now increasingly seen in younger populations due to poor lifestyle choices (Yahya et al., 2020a; Yousufuddin & Young, 2019). As stroke rates continue to increase in younger age groups, it is imperative that researchers investigate the unique factors driving these trends and understand their broader implications. Stroke is the second leading cause of death globally, and its impact on humanity is widespread, particularly where health care coverage, access, and health literacy are limited (Katan & Luft, 2018). Although these disparities influence the incidence and mortality rates, the burden of stroke is universal. Ultimately, stroke is no longer a consequence of primarily aging, as cases continue to rise in young adults at an unprecedented rate. In young adults, the impact of stroke adults is unique and often more severe in terms of long-term disability and often marked by economic and psychosocial decline.

Young stroke survivors often face a longer period of living with the effects of a stroke, which can include motor deficits, cognitive impairments, and speech difficulties. Although research indicates that a smaller proportion of young stroke survivors have poor functional outcomes on the Rankin Scale (Braveman & Gottlieb, 2014; Raphael, 2006; Rootman et al., 2017), young adults may suffer from these effects for a longer period of time due to their age. Specifically, 6-20% of young stroke survivors had poor functional outcomes after their stroke, compared to 40% of older survivors (Maaijwee et al., 2014). However, conditions such as poststroke epilepsy (with or without reoccurring seizures), further complicates recovery and are more common in young survivors (Maaijwee et al., 2014). These neurological challenges suggest that cognitive impairments may have a greater

prolonged impact on young adults. In comparison to older stroke survivors, young-onset patients displayed impairments to multiple cognitive domains (Schaapsmeeders et al., 2013), whereas older patients typically exhibit impairments to the frontal region (Sachdev et al., 2004). Unfortunately, these impairments result in significant disruptions in daily life.

Research suggests that in young stroke patients, quality of life is reported to be impacted to a greater degree by factors such as motor impairments, aphasia, difficulties in language, and physical impairments, compared to older patients (J. S. Kim et al., 2005). These impairments can have a profound impact on younger stroke survivors, particularly due to the long-term economic and psychosocial consequences. For example, the psychological and cognitive impairments caused by a stroke can lead to unemployment and reduced social relationships (Daniel et al., 2009), contributing to overall decline in quality of life. Stroke survivors also often experience chronic post-stroke pain and fatigue, however, young adults tend to experience these symptoms for longer given their increased demands from their social environments and financial responsibilities (Maaijwee et al., 2015). Although the impact of a stroke impacts both young and old adults, research indicates that stroke survivors under 50 years old were impacted to a greater extent by family conflict and loss of home, loss of employment, and spousal issues, commonly resulting in the development of post-stroke depression and anxiety (Morris, 2011b). Moreover, compared to older stroke survivors, young survivors reported experiencing more limitations in activities of daily living, ultimately leading to higher levels of frustration and difficulty adjusting to post-stroke life (Gil-Salcedo et al., 2022).

The mental impact of a stroke is detrimental, regardless of age. However, given that stroke is not common in young adults, and it has life-long effects, it uniquely and significantly impacts the mental health of young stroke survivors and their families. The prevalence of post-stroke anxiety and depression is higher in young stroke survivors compared to older survivors (Kapoor et al., 2019). A study examining age-specific post-

stroke depression and anxiety found that anxiety was prevalent in 42% of young patients, compared to 17% in older adults, while depression was prevalent in 40% of young patients compared to 22% in older adults after a 2-year period (Kapoor et al., 2019). In addition to prevalence, young stroke survivors tend to face greater challenges in social reintegration and relationships. Specifically, in comparison to older adults, young survivors often lack established social roles and relationships, coupled with limited time for rehabilitation, they face challenges of reintegration into society and challenges with self-management (Zhou et al., 2024). Moreover, many young stroke survivors face unemployment as a result of their physical and/or cognitive disabilities, further perpetuating the decline of their mental health (Zhou et al., 2024). Given the young age of the stroke occurrence, young survivors often struggle with a loss of independence as a result of their disabilities and new restrictions, thus causing conflicts of self-identity and isolation from friends, family, and peers (Morris, 2011b).

Despite the serious outcomes of a stroke, young survivors exhibit lower rates of lifestyle modifications post-stroke. For instance, a study examining smoking cessation in the United States found that young stroke survivors were less likely to stop smoking after their stroke in comparison to older adults (Parikh et al., 2022). These results may further explain the psychological trauma of a stroke, invulnerability and risk awareness, or overall less compliance with medical advice among younger stroke survivors. Post-stroke care and rehabilitation also tends to vary age based on needs. Researchers state that based on the differences between older and younger adult stroke survivors, the rehabilitation needs are different due to the nature and etiology of their stroke differences (Purvis et al., 2021). However, given that prevalence of young stroke patients is low in comparison to older adults, there are no age-related model of care or specific guidelines, ultimately leading to more unmet needs and poorer long-term outcomes (Purvis et al., 2021; Ullberg et al., 2016). This gap highlights the importance and need for age-specific guidelines that address the unique medical, psychological, and social needs of young stroke survivors.

Given that young adults have a longer period of recovery due to their young age and the early occurrence of the stroke, they are often imposed with long lasting medical care costs, which further impose a considerable burden on the society and families' of survivors (Zhou et al., 2024). At the familial and individual level, hospitalization, rehabilitation, medication, and follow-up care have substantial costs (Godwin et al., 2011; Van Meijeren-Pont et al., 2021), especially for young adults as they have higher rates of more severe stroke subtypes and may require more intensive treatments (Smajlović, 2015). Additionally, as mentioned previously, the young age of stroke onset results in a longer period of dealing with stroke related disabilities, thereby increasing the burdens of care-related costs. At the societal level, a study examining the economic burden of stroke in the United States found that the cumulative total inflation-adjusted cost of ischemic strokes between 2002-2017 was \$12.3 billion USD and \$10.3 billion USD for hemorrhagic strokes (Khan et al., 2021a). While the inflation-adjusted mean cost of stay increased for all ages over this period, young stroke patients had the highest increase, with a 47% increase in cost over 15 years (Khan et al., 2021a). Similar results can be seen in Canada, where younger patients tend to have higher average 1-year attributable costs of care, compared to older patients (Vyas et al., 2023).

Together, the unique, multifaceted burdens that are faced by young stroke survivors emphasize the need for additional research to better understand this populations risk profiles and age-specific interventions. As mentioned, these individuals face prolonged mental and physical disabilities, unmet healthcare needs, and significant financial and emotional strains. However, despite all these challenges, research on young adults is largely limited in comparison to older adults. Thus, given the substantial gaps that exist in the literature, understanding the predictors, mechanisms, and outcomes specific to young adults is imperative. Targeted research is needed to develop age-specific prevention strategies, targeted interventions, and age-specific rehabilitation programs. As a result, this research can help inform policy and age-specific rehabilitation recommendations to improve long-term

well-being and reduce the broader personal and societal burdens associated with stroke in young adults.

1.9 Thesis Aims and Objectives

To date, research on stroke in young adults is still limited, with most studies focusing on specific risk factors. For instance, studies have examined the impact of sex on stroke (Gardener et al., 2020; Rexrode et al., 2022; Vyas et al., 2023), alcohol and drug consumption and stroke (Dutta et al., 2021; Gill et al., 1986; J. Jones et al., 2015; Klonoff et al., 1989; Reynolds et al., 2003; Treadwell & Robinson, 2007), or the impact of genetics and stroke (Guo et al., 2010; Jousilahti et al., 1997; Rosengren et al., 2004); however, research has yet to examine the role of multiple variables on stroke, particularly in young adults.

Traditional risk factors, such as hypertension, cholesterol, and drug use have been recognized to be influential in the onset of stroke in young adults. However, the role of emerging risk factors that may uniquely be impacting young adults have not been thoroughly examined. For instance, factors such as mental health and caffeine consumption have been largely overlooked, despite their high prevalence in young adults. This study aims to bridge these gaps by examining both established and emerging risk factors to broaden the scope of stroke research, particularly in young adults. Specifically, regression analyses will be used to explore the impact of mental health and caffeine consumption, while also controlling for traditional risk factors. Expanding the scope of the research beyond traditional risk factors is essential to understanding the risk profiles of young adults, as well as developing targeted prevention, intervention, and treatment strategies.

The current state of stroke literature is predominantly focused on older populations, likely due to the condition's typical association with later-life onset. However, the increasing rates of stroke in young adults now demands urgent investigation. As mentioned previously,

stroke in young adults is unique as it leaves these individuals with unexpected physical and cognitive impairments, and psychosocial challenges caused by disruptions to individuals' lifestyles. Ultimately, young adults face unique burdens furthering the need for additional research to inform appropriate prevention and rehabilitation programs that are tailored for their needs.

Therefore, the aim of this thesis is three-fold.

1. Determine the risk profiles of young adults who experience a stroke.
2. Conduct an exploratory analysis examining the multiple correlates (including emerging risk factors, such as mental health) of stroke in young adults 18 to 50 years old, using a conditional logistic regression analysis.
3. Examine the role of emerging risk factors, such as caffeine, given its widespread use among young adults. Specifically, examine the linear and non-linear association between dose and source-specific caffeine consumption and stroke risk in young adults.

1.9.1 Study One Research Objectives

Study one seeks to identify and analyze the frequencies of stroke risk factors in young adults. Specifically, this study aims to uncover the risk profiles of young adults who experience a stroke between 18 to 50 years old. By using descriptive statistics, including summary and crosstabulation tables, this study will demonstrate the occurrence of risk factors of stroke, such as race, income, and comorbidities. The objective of this study is to characterize at risk individuals/groups within the sample and identify those who are disproportionately impacted.

The current state of stroke research is focused on understanding the risk and prevalence of single traditional risk factors of stroke, such as hypertension, diabetes, high cholesterol, and smoking (Schaapsmeeders et al., 2013). Other research examines only stroke pathophysiological (Smajlović, 2015; van Alebeek et al., 2018), or long-term cognitive, physical, and emotional outcomes (Fei et al., 2016; Yahya et al., 2020a), with little

focus on pre-stroke data. Thus, there is a significant gap in the current literature on stroke. Specifically, a comprehensive, epidemiological study that quantifies stroke risk from a pre-and-post stroke perspective in young adults is missing.

This study addresses these gaps by examining stroke risk in young adults by incorporating a multifactorial approach that integrates established and emerging risk factors, such as mental health conditions, lifestyle factors, etiology-related factors, chronic infections, geographic variations, and demographic variables. Moreover, this study will be the first to analyze the prevalence of stroke risk factors both before and after stroke onset; thus, providing a novel perspective on stroke data in young adults. This study's integrated approach expands our current understanding of stroke in young adults, identifies important risk factors, and highlights potential issues with risk factor screening/diagnosis. Thus, the purpose of this study is to better understand this population by examining the prevalence of both established and emerging risk factors, as well as health behaviours and conditions, among young adults who experienced a stroke. Gaining insight into these patterns is essential for improving targeted prevention efforts and guiding future research.

1.9.2 Study Two Research Objectives

Study two takes an exploratory approach to understanding the predictors of stroke in young adults. The case-control study design will match participants based on biological sex with a 1:2 ratio of one case matched to two controls. Given the complex nature of stroke, the objective of this research is to explore the multiple risk factors of stroke in young adults. The regression models will include both established risk factors (e.g., hypertension, diabetes, diet, exercise) and emerging risk factors that may uniquely impact young adults (e.g., mental health). Despite the increasing recognition of stroke among young adults, research is still largely focused on older adults and traditional risk factors. Currently, research on young adults is largely descriptive and focused on prevalence, often without addressing temporality,

causality, or broader risk factor profiles. Herein, the purpose of this study is to address this gap by identifying a broader and more age-specific set of risk factors of stroke in young adults.

Justification for this study is based on the lack of research taking a multifactorial approach to understanding the complex nature of stroke, particularly in young adults. As stated earlier, much of the existing literature is limited as it either focused on specific geographical locations or on certain clinical subpopulations (Greenlund et al., 2004; Yi et al., 2020). Moreover, most studies contain small samples and lack robust analyses (González-Gómez et al., 2016; D. Jones et al., 2017; Leys et al., 2002). Furthermore, there is absence of temporal insight for most research, making it challenging to determine whether the observed risk factors occur prior to stroke onset or develop as a result of the stroke.

Although the current literature provides valuable insight, it generally overlooks the emerging or age-specific risk factors that may help explain the rising rates of stroke in young adults. For instance, research has yet to examine the impact of pre-existing mental health conditions, such as depression, anxiety, and stress disorders. Mental health conditions can uniquely affect young adults due to developmental and social transitions that are common in this age group (Halaris, 2016; Sable et al., 2011). These emerging risk factors could affect stroke risk as a result of biological and psychosocial mechanisms, that existing models have yet to include. Moreover, a broader, multinational lens is also lacking, despite geographical and population-level differences in stroke incidence and etiology offering important insights into environmental and sociocultural differences. This study responds to the need for a more comprehensive analysis of stroke risk in young adults by addressing these critical research gaps. Specifically, it examines geographic variation, incorporates both established and emerging risk factors, and utilizes both pre-and-post stroke data to better assess risk factor association and possible temporal implications.

1.9.3 Study Three Research Objectives

The objective of study three is to examine the impact of caffeine consumption and stroke risk in young adults. Specifically, the study aims to examine the dose and source-specific association with stroke risk. Similar to study two, this study will use a conditional logistic regression model matched on biological sex in a 1:2 ratio. The regression model will adjust for a broad range of potential confounders, including substance use, family history of stroke, mental health, health comorbidities, and lifestyle factors.

Prior research on caffeine and stroke has largely focused on specific caffeine sources, such as coffee (Shao et al., 2021), tea (Tian et al., 2020), and energy drinks (Sinha et al., 2024). Study three will examine caffeine intake from all sources. Although some research has examined the impact of caffeine from combined caffeine sources, such as tea and coffee (Y. Zhang et al., 2021), they are missing increasingly popular beverages, such as energy drinks. Energy drinks often contain additional ingredients, such as taurine, l-carnitine, guarana, and ginseng, which may have adverse effects on stroke risk (Seifert et al., 2011). There is a notable gap in the literature regarding the combined effects of various caffeine sources, despite the growing popularity of high-dose caffeine beverages, such as energy drinks or pre-workout supplements, particularly in young adults. Additionally, the current literature on the effect of caffeine on stroke in young adults remains limited, given that majority of research is representative of older adults (Greenberg et al., 2008; Larsson et al., 2008; Silletta et al., 2007; Y. Zhang et al., 2021). To add, much of the present research assumes a linear association between caffeine intake and stroke risk, however, we believe that there may be non-linear pattern. Therein, study three attempts to address the aforementioned gaps by examining the linear and non-linear associations of various caffeine doses and sources among young adults. Given the widespread use of caffeine among young adults, this study offers valuable insight for public health officials to develop targeted intervention and prevention strategies.

1.10 Overview of Thesis Methodology

1.10.1 Study Design

This thesis will use a case-control study design. Given that stroke occurrence in young adults is uncommon, a case-control study design can allow for efficient statistical power. Specifically, the number of participants can be increased by incorporating controls in addition to cases (Tenny et al., 2023). Using a 1:2 matched design on biological sex, we can increase statistical power, control for the confounding effect of sex, and improve the accuracy of our inferences.

1.10.2 Questionnaire and Recruitment

This thesis will utilize primary quantitative data. Particularly, using cross sectional data collected from a questionnaire, we hope to better understand the predictors of stroke. Descriptive statistics of demographic variables, crude and adjusted conditional logistic regression analysis, and restricted cubic splines will be conducted to understand the correlates of stroke risk in young adults. The questionnaire will be generated using a variation of validated measures, such as the American College of Health Association-National College Health Assessment (NCHA-ACHA) 2019 survey or the Canadian Community Health Survey (CCHS). The questionnaire will be administered using the online software Qualtrics. To ensure that the self-reported survey responses are reliable and accurate, participants who have had cognitive impairments that may impact their ability to report consistent information, such as severe aphasia, will not be included in the study. Moreover, responses that are completed outside the allocated time ranges (maximum and minimum time for completion), responses with all repeated answers, and failed attention check questions, will also not be included. Recruitment of participants will come through various avenues, such as hospitals, rehabilitation centres, stroke survivor groups, and social media.

1.10.3 Statistical Analyses

The primary statistical analyses techniques in this thesis will consist of descriptive statistics and conditional logistic regression analyses. Descriptive statistics will be used to summarize and describe the characteristics of the sample. Whereas, the conditional logistic regression analyses will be used as the main analytical tool to examine the associations between various risk factors and stroke. Although various specific logistic regression techniques will be used in this thesis, they will be specified in detail in each corresponding study.

A logistic regression is a useful method for modelling binary outcomes, such as the onset of a stroke. Similarly, it serves as a useful method in epidemiological research, where many predictors (e.g., hypertension, age, sex, or income) can influence the outcome. In comparison to other models, such as a linear regression, a logistic regression is suitable for binary outcomes. A logistic regression models the log-odds of the outcome, resulting in predicted probabilities that fall between 0 and 1. Whereas, predictions for a binary outcome in a linear regression may fall outside of 0 and 1. Thus, outputs from a logistic regression for an outcome variable like stroke (yes or no) tend to be more easily interpretable and more accurate. Nonetheless, a logistic regression has its limitations as well, such as its assumptions of linearity and the risk of overfitting. These limitations, as well as others, will be considered in the analyses of these studies. Irrespective of these limitations, logistic regression remains a useful method for examining stroke risk in young adults.

1.11 Conclusion

Stroke is no longer a condition exclusive to older adults, as rising incidence rates among young adults urges the need for further research. Understanding the multifactorial nature of stroke through clinical, epidemiological, and social lenses will aid in developing effective interventions. Moreover, exclusively analyzing established risk factors is not sufficient in capturing the complexity of stroke in young adults, who differ significantly from older adults

in terms of lifestyle, comorbidities, and overall health profiles. Thus, applying research findings from the vast existing literature on older adults does not fully explain the rising rates of stroke in young adults. This research aims to address these knowledge gaps and contribute to improved prevention and management strategies for young stroke survivors.

Chapter 2

Stroke in Young Adults: A Global Analysis of the Prevalence of Established and Emerging Risk Factors

Abstract

Background:

While stroke is considered a cardiovascular disease that commonly occurs in older adults, the increasing incidence in young adults is becoming a growing global concern. The purpose of this study is to examine the global prevalence of established and emerging stroke risk factors in young patients to better guide age-specific prevention and intervention.

Methods:

This study uses primary cross-sectional questionnaire data collected from an international case-control study, including 1,277 participants (435 stroke-positive participants). The questionnaire included questions regarding participants' demographics, health history, stroke etiology, chronic infections, mental health questions, and lifestyle factors. Data were analyzed using descriptive statistics to identify the prevalence of established and emerging risk factors before and after stroke.

Results:

We found a high pre-stroke prevalence of established risk factors among, such as high blood pressure (22.69% compared to 13.76% in controls), obesity (24.78% vs. 7.09%), and an unbalanced diet (42.48% vs. 33.73%). Notably, pre-stroke sleep disorders (33.82%) and regularly occurring migraines (28.78%) were both highly common prior to stroke onset, suggesting that they may play a potential role as stroke risk factors. Moreover, etiological factors, arterial dissections were commonly diagnosed post-stroke onset, indicating that these

conditions may go underdiagnosed. Emerging risk factors such as mental health conditions were highly prevalent pre-stroke onset. Specifically, 39.60% reported having anxiety, 34.23% reported having depression, and 20.13% had seriously considered suicide prior to having their stroke. Lastly, cases reported an average daily caffeine consumption of 343 mg pre-stroke (~ 3 cups of standard coffee plus 1 cup of tea), compared to 223mg/day in controls.

Discussion:

The present study highlights the complex, multifactorial nature of stroke in young adults. It underscores the importance of early screening and the potential impact of emerging risk factors, such as mental health and caffeine consumption. The high prevalence of established risk factors, such as hypertension, poor diet, and obesity demonstrates the on-going issue inadequately identified and treated risk factors. Nonetheless, the findings of this research highlight the unique risk profiles of young adults and urge the need for age-specific research, intervention, and prevention.

2.1 Introduction

A stroke is a medical condition that occurs when blood flow to the brain is disrupted, most commonly caused by a blockage (ischemic stroke) or a bleed (hemorrhagic stroke) of an artery. Although strokes often occur in older adults, young adults account for 10-15% of all cases (Smajlović, 2015). Moreover, while rates of strokes in older adults have remained stable or decreased, stroke incidence among young adults has steadily increased globally (Bukhari et al., 2023a). For example, in the United States, the incidence of stroke in young adults aged 20 to 44 increased from 17 per 100,000 in 1993 to 28 per 100,000 in 2015, with similar trends occurring globally (Yahya et al., 2020a).

2.1.1 Etiology of Stroke in Young Adults

The diagnostic evaluation and treatment protocols for older adults cannot always be applied to young adults as there are many differences in stroke etiology (Smajlović, 2015). For example, arterial dissection is a leading cause of ischemic strokes in young adults (Arning et al., 2022). Minor trauma such as sports injuries, chiropractic manipulation, and dangerous sudden neck movements are often the cause of arterial dissections in young adults (J. Jones et al., 2015). These account for 15-25% of ischemic strokes in those under 50, compared to only 2-7% in adults over 60 (Metso et al., 2012; Traenka et al., 2017; Yaghi et al., 2024).

Patent foramen ovale (PFO), a congenital cardiac lesion present in approximately 27% of adults (Hara et al., 2005), has been associated with ischemic strokes in young adults. In individuals who had a stroke under 55 years old, upwards of 40% had a PFO, compared to 10% in controls (Lechat et al., 1988b). The prevalence of PFO is disproportionately higher in young adults with a cryptogenic stroke compared to older adults (Handke et al., 2007), further highlighting age-related differences in stroke etiology. Infections such as HIV and syphilis can also contribute uniquely to stroke risk in young adults by triggering chronic inflammatory responses. The inflammation contributes to endothelial dysfunction, hypercoagulability, and facilitate embolic strokes (Bonett et al., 2022; Epstein et al., 2014). Although these effects occur in people of all ages, infections are a significant concern for young adults, as they experience a higher prevalence due to factors such as increased sexual activity and risky behaviours (Bonett et al., 2022; Epstein et al., 2014). Moreover, sleep disorders such as insomnia and sleep apnea have also become increasingly more common in young adults and can be associated with higher stroke risk, potentially due to their impact on hypertension, reduced physical activity, and cardiac abnormalities (Calhoun, 2017; Chennaoui et al., 2015; McArdle et al., 2020)

Hemorrhagic strokes also have distinct etiologies in young adults. For instance, the prevalence of drug-induced-hemorrhages and reversible cerebral vasoconstriction syndrome (RCVS) occur more often in young adults (Ribas et al., 2023). While intracranial aneurysms are more common in older adults, genetic conditions such Ehlers Danlos syndrome and polycystic kidney disease increase hemorrhagic stroke risk in young adults (Shabani et al., 2023; Yoo et al., 2014). These conditions weaken blood vessel walls, increasing the risk of aneurysm and rupture, often seen at a younger age (Shabani et al., 2023; Yoo et al., 2014). Drug-induced hemorrhage is increasing in young adults, linked to the rise in the availability of drugs, such as amphetamines, cocaine, and ecstasy (McEvoy et al., 2000). These substances can lead to hemorrhagic strokes as a result of acute blood pressure increases, blood vessel constriction, and vasospasm (Banimostafavi et al., 2024).

2.1.2 Risk Factors of Stroke in Young Adults

Risk factors differ from etiology and are often categorized as modifiable and non-modifiable. Non-modifiable risk factors of stroke include sex, family history, race, and age (Aigbogun et al., 2021). Whereas, modifiable risk factors of stroke include exercise, cigarette and alcohol consumption, high fat-diets, hypertension, dyslipidemia, and drug use (Boden-Albala & Sacco, 2000; Sabih et al., 2023). Risk factors can also vary by age, with young adults facing additional risks, such as stress, mental health conditions, caffeine consumption, drug use, and sleep disorders.

Young adults face a unique set of significant transitions in life, such as moving out of their family home, pursuing higher education, career development, and relationship challenges, which may lead to depression, anxiety, and stress (Sable et al., 2011). These factors can increase cortisol levels leading to hypertension, increased platelet aggregation and inflammatory responses that negatively impact individuals' vascular health (Halaris, 2016). Also unique to young adults, the average caffeine consumption has risen, as the availability

and options of caffeinated beverages has increased (Branum et al., 2014; Lone et al., 2023). Research on caffeine and stroke risk is inconclusive, as some studies show a protective effect (Mostofsky et al., 2010), while others suggest it is a risk factor (B. Kim et al., 2012), possibly due to differences in dose and source. Caffeine can elevate the heart rate, induce vasoconstriction (Reddy et al., 2024), and is associated with risky behaviours like smoking (Fagan et al., 2020), which may contribute to stroke risk.

2.1.3 Gaps in the Literature

Collectively, these trends highlight an urgent need for additional research to better understand the rise in stroke cases among young adults. Young stroke survivors are an uncommon, yet growing population, whose risk profiles and health behaviours tend to be different from older adults. Despite their growing prevalence, young adults who experience a stroke are largely underrepresented in research. While research on young adults has gained more attention in recent years, most existing research focuses on established risk factors of stroke, such as hypertension, diabetes, high cholesterol, and smoking (Aslam et al., 2022; Bukhari et al., 2023a). Other research examines stroke pathophysiological (Smajlović, 2015; van Alebeek et al., 2018), or long-term cognitive, physical, and emotional outcomes (Fei et al., 2016; Yahya et al., 2020a). Geographical variations in stroke type and incidence provide insight into the regional differences, however, a comprehensive, global analysis is still missing.

This study attempts to address these gaps by examining stroke risk in young adults by incorporating a multifactorial approach that integrates both established and emerging risk factors. Specifically, the present study includes factors such as mental health conditions, lifestyle factors, etiology-related factors, chronic infections, geographic variations, and demographic variables. Moreover, this study is the first to analyze the prevalence of both pre- and post-stroke data; thus, providing a novel perspective on stroke data in young adults. The

purpose of this study is to better understand young adults who have experienced a stroke by examining the prevalence of established and emerging risk factors, health behaviours, and conditions. Gaining insight into these patterns is important for guiding targeted prevention efforts and improving survivor clinical outcomes.

2.2 Methods

The definition of “young adult” in stroke research varies from one study to another, ranging from 18 to between 45 to 55 years old. This study defines young adults as individuals aged 18-50, consistent with previous research (Bukhari et al., 2023a; Ekker et al., 2019; Rutten-Jacobs et al., 2013). The data for this study are drawn from a larger, global project examining stroke risk factors in young adults. This study was conducted between September 2024 to February 2025, enrolling stroke-positive patients and age-matched healthy controls to investigate traditional and novel stroke risk factors in this population. Ethics approval for this research was obtained from the University of Waterloo’s Research Ethics Board in correspondence with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

Individuals self-identified as having experienced a stroke (cases) were recruited from multiple sources to capture a range of stroke severity (excluding fatal cases), including local and international hospitals, stroke patient networks, rehabilitation centres, stroke survivor groups, and social media. Participants self-reported stroke type (ischemic, hemorrhagic, or TIA) within the age range of 18 to 50. Controls, aged 18 to 50 with no stroke history were recruited through Prolific's global database. All data was collected between September 2024 to February 2025.

The questionnaire included questions regarding participants’ demographics (e.g., age, biological sex, income), health history (e.g., high blood pressure, sleep disorders, migraines),

etiology (e.g., PFO, arterial dissection), chronic infections (e.g., HIV), mental health questions (e.g., depression), and lifestyle factors (e.g., substance). To ensure validity, the questionnaire was created using established measures, such as the *National College Health Assessment-American College Health Assessment Survey* (e.g., demographic and mental health variables), *Canadian Community Health Survey* (e.g., demographic variables), and the *Canadian Health Measures Survey* (e.g., health-related variables). When required, novel measures were developed based on the literature. For example, to examine the association between exercise and stroke, participants reported the intensity of weekly exercise sessions, per-literature findings on physical activity and stroke (Prior & Suskin, 2018). To ensure data quality, responses that were not meaningful, such as those that failed the questionnaire's attention checks or those who completed the questionnaire before the minimum completion time were not included.

2.2.1 Data Analysis

For this study, descriptive statistics were analyzed to get a comprehensive understanding of the characteristics and prevalence rates of risk factors in young adult stroke survivors. Variables of interest were summarized using percentages rather than raw counts to provide more meaningful estimates. All statistical analyses were conducted in RStudio (Version 2024.12.0+467) (Posit, 2025) and R (Version 4.5.1) (R Core Team, 2025).

2.3 Results

2.3.1 Descriptive Statistics

Table 1 presents the demographic characteristics of the dataset. A total of 1,277 participant responses were collected, including 435 stroke positive participants and 842 controls. The mean age of stroke-positive participants was 39 years old, while controls had an average age of 31 years old. In terms of biological sex, 57.8% of cases identified as female and 41.8% as

male, and 45.41% female and 53.70% males for controls. For race, the majority of cases identified as White (76%), while controls had a more diverse racial group with majority identifying as either Black (35.20%) or White (47.70%).

Income, Marital Status and Employment status

Information on income, marital status and employment status was post-stroke. For income, most cases had a yearly income of less than \$40,000 USD (25%) or between \$84,000 to \$184,000 USD (26.7%). In terms of employment status, 47.7% of cases were full-time employees, 12.4% part-time, and 36.3% not employed. Lastly, 55.3% of the cases were married/partnered and 37.0% single. Among the controls, most participants had a yearly income of less than \$40,000 USD (38.90%), were full-time employees (56.51%), and married/partnered (48.09%). Although the primary focus of this paper is to examine the characteristics of young adults who experienced a stroke, the demographic characteristics of the controls provide a useful baseline for comparison and helps contextualize the results. A full summary of the demographic characteristics among the cases and controls can be found in Table 1.

Table 1 Demographic Characteristics of the Sample

Variable	Cases (%) (n=435)	Controls (%) (n=842)	Total (%) (n=1,277)
Age	Mean: 39 Years old Min: 18 Max: 75	Mean: 31 Years old Min: 18 Max: 55	
Country of Residence:			
Australia	2.73	0.13	1.02
Belarus	0.42	0	0.14
Belgium	0.63	0.13	0.36

Canada	16.18	3.70	7.94
Denmark	0.21	0.26	0.24
Germany	1.47	0.77	1.03
Greece	0.42	1.79	1.30
India	3.36	0.77	1.73
Ireland	1.05	0.38	0.61
Netherlands	0.84	0.64	0.71
Philippines	1.68	0.26	0.81
South Africa	0.84	16.45	10.81
United Kingdom of Great Britain and Northern Ireland	6.09	18.37	13.95
United States of America	59.45	34.31	42.86
Other	4.62	22.07	14.68
Sex at Birth			
Female	57.77	45.41	49.84
Male	41.81	53.70	49.94
Prefer not to say	0.42	0.51	0.49
Race			
Arab	0.21	0.64	0.47
Black	2.73	35.20	22.02
Chinese	2.10	1.02	1.46
Filipino	1.89	0.51	1.06
Indigenous	1.47	0.13	0.62
Korean	0.21	0.38	0.31
Latin American	3.36	3.70	3.57
Mixed race	3.36	4.34	3.93
South Asian (e.g., East Indian, Pakistani, Sri Lankan)	4.83	3.06	3.75
Southeast Asian (e.g., Vietnamese, Cambodian, Laotian, Thai)	1.68	1.15	1.35

West Asian (e.g., Iranian, Afghan)	0.21	0.00	0.07
White	76.05	47.70	58.76
Other	1.89	1.40	1.56
Relationship Status			
Divorced/separated	5.25	2.55	3.48
Married/partnered	55.25	48.09	50.34
Single	36.97	45.92	42.68
Widowed	0.63	0.38	0.46
Other	1.26	1.66	1.50
Prefer not to say	0.63	1.02	0.84
Income			
Less than \$40,000 USD (Less than \$53,000 CAD, €35,000 EUR, less than \$54,000 AUD)	25.00	38.90	33.49
Between \$41,000 USD to \$67,000 USD (\$54,000 to \$85,000 CAD, €35,000 to €56,000 EUR, \$54,000 to \$85,000 AUD)	15.12	20.79	18.49
Between \$68,000 to \$83,000 USD (\$86,000 to \$105,000 CAD, €56,000 to €68,000 EUR, \$86,000 to \$105,000 AUD)	10.92	13.65	12.90
Between \$84,000 to \$184,000 USD (\$106,000 to \$235,000 CAD, €68,000 to €155,000 EUR, \$106,000 to \$235,000 AUD)	26.68	18.37	21.55
More than \$185,000 USD (more than \$236,000 CAD, €155,000 EUR, more than \$236,000 AUD)	11.13	3.57	6.47
Prefer not to say	11.13	4.33	6.65
Employment Status			
Full-time employee	47.69	56.51	53.09
Part-time employee	12.39	21.81	18.12

Not employed	36.34	19.39	26.04
Prefer not to say	3.57	1.91	2.66

Table 1 presents the demographic characteristics of the sample (n=1,277, Cases=435, Controls=842). The table includes information on the case-control country of residence, biological sex, race, income, and employment status.

2.3.2 Epidemiology of Stroke

Table 2 summarizes stroke occurrence and stroke-related factors. Majority of cases only experienced one stroke (77.3%). The type of stroke was categorized as 61% ischemic stroke, 31% hemorrhagic stroke, and 8% TIA. Among hemorrhagic cases, 42.1% had an intracerebral hemorrhage, 15.8% had a subarachnoid hemorrhage, and 42.1% were not sure which type of hemorrhagic stroke they had. Regarding stroke-related medication, 89.7% of patients who had a stroke were prescribed treatment, with 39% taking it for less than a year and 37% for more than two years. Additionally, 64.5% had no family history of stroke, and the most common age range of stroke occurrence was between 31 to 40 years old (41.9%).

Table 2 Stroke Occurrence, Type, and Associated Factors

Variable	Percentage
Family History of stroke	
No	64.50
Yes	34.67
Number of strokes	
One	77.31
Two	14.23
Three or more	8.08
Age range of stroke occurrence	
18 to 24 years old	10.04
25 to 30 years old	18.16

31 to 35 years old	21.58
36 to 40 years old	20.30
41 to 50 years old	28.63
Type of stroke	
Ischemic	62.26
Hemorrhagic	30.28
Transient Ischemic Attack (T.I.A./mini-stroke)	7.46
Type of hemorrhagic stroke	
Intracerebral	42.11
Subarachnoid	15.79
Not sure	42.11
Prescribed Post-stroke medication	
Prescribed medication	89.77
Not prescribed medication	10.23

Table 2 presents the percentage of stroke related factors including family history of stroke, number of strokes, age of stroke occurrence, type of stroke, type of hemorrhagic stroke (if applicable), and post-stroke medication for the sample of cases (n=435).

Figure 4 presents the stroke type distribution of the five most represented countries in the present study. Across all countries, ischemic strokes were the most common form of stroke. However, India had a higher prevalence of hemorrhagic strokes with 56.25%, followed by 31.25% ischemic strokes, and 12.50% TIA. The high proportion of hemorrhagic stroke in India may reflect a smaller sample size ($n=16$). Nonetheless, the overall distributions of stroke types per-country tend to be similar among countries, with minor regional differences. Detailed distributions of the geographical prevalence of the different stroke types can be found in Figure 4.

Figure 4 Geographical Variation in Stroke Type

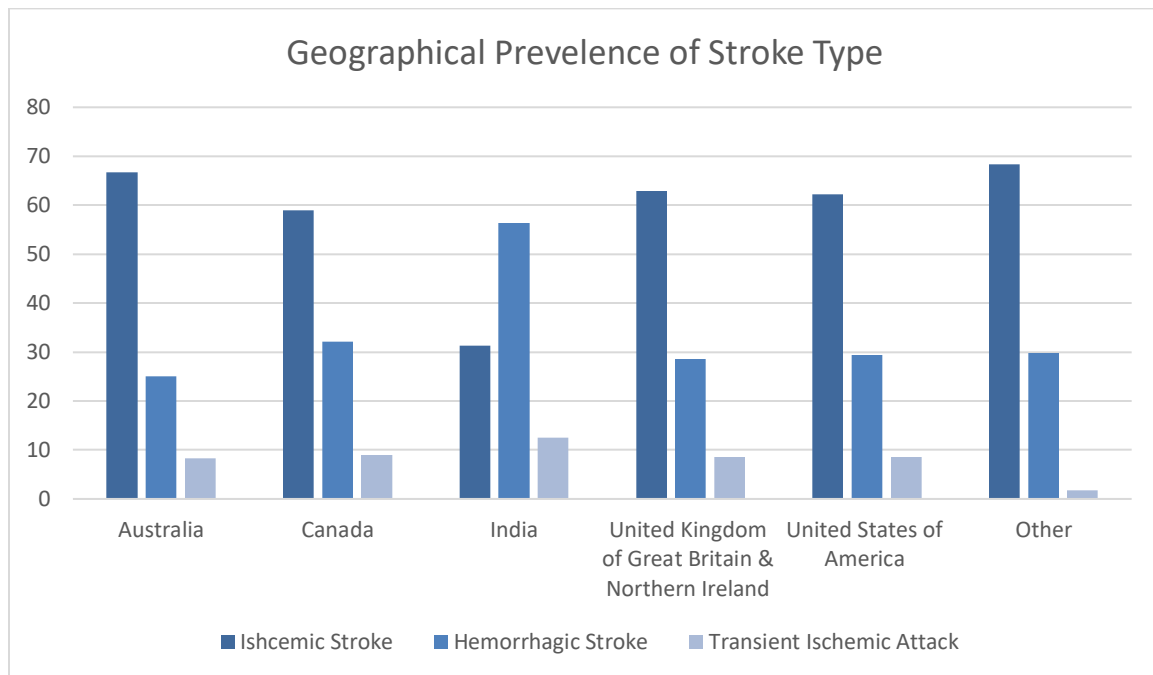


Figure 4 illustrates the prevalence of the different forms of stroke among the cases in the sample (n=435). The table presents the differences in the geographical prevalence of ischemic, hemorrhagic, and transient ischemic attack strokes in the top 5 countries with the largest sample in the dataset.

2.3.3 Etiology of Stroke

Table 3 presents the etiological factors associated with stroke among the study population. Variables were categorized as “No” indicating absence of the condition, “Yes, diagnosed AFTER having a stroke”, referring to conditions diagnosed post-stroke, and “Yes, diagnosed BEFORE having a stroke”, indicating that the condition was diagnosed prior to stroke occurrence. Notably, conditions such as arterial dissection, PFO, and traumatic brain injury were commonly diagnosed after an individual had a stroke. Of the sample, 0.84% was diagnosed with an arterial dissection before having a stroke, 16.18% were diagnosed after having a stroke, and 81.93% had no diagnosis. Similarly, 1.89% were diagnosed with a PFO before having a stroke, 16.98% were diagnosed after having a stroke, and 80.75% had no diagnosis. For traumatic brain injury, 5.88% were diagnosed before having a stroke, 17.23%

were diagnosed after having a stroke, and 76.47% had no diagnosis. Moreover, 33.82% had a sleep disorder before having a stroke, 18.07% after having a stroke, and 48.11% having no diagnosis. Detailed distributions regarding the timing of etiological factors associated with stroke can be found in Table 3.

Table 3 Etiological Factors Associated with Stroke and Timing of Diagnosis

Variable	Percentage
Arterial Dissection	
No	81.93
Yes, diagnosed AFTER having a stroke	16.18
Yes, diagnosed BEFORE having a stroke	0.84
Patent Foramen Ovale -PFO	
No	80.75
Yes, diagnosed AFTER having a stroke	16.98
Yes, diagnosed BEFORE having a stroke	1.89
Traumatic Brain Injury	
No	76.47
Yes, diagnosed AFTER having a stroke	17.23
Yes, diagnosed BEFORE having a stroke	5.88
Respiratory Disease	
No	88.66
Yes, diagnosed AFTER having a stroke	0.21
Yes, diagnosed BEFORE having a stroke	10.71
Sleeping disorder/deprivation	
No	48.11
Yes, diagnosed AFTER having a stroke	18.07
Yes, diagnosed BEFORE having a stroke	33.82
Syphilis	

No	99.24
Yes, diagnosed AFTER having a stroke	0.00
Yes, diagnosed BEFORE having a stroke	0.75
Hepatitis	
No	99.16
Yes, diagnosed AFTER having a stroke	0.00
Yes, diagnosed BEFORE having a stroke	0.63

Table 3 illustrates the prevalence etiological factors of stroke based on the timing of their diagnosis categorized as “No (absence of the condition)”, “Yes, diagnosed AFTER having a stroke”, and “Yes, diagnosed BEFORE having a stroke” among the cases (n=435).

2.3.4 Risk Factors of Stroke

Table 4 presents the prevalence of stroke risk factors with the timing of diagnosis when applicable. Notably, the most common risk factor among the cases was hypertension. Specifically, 22.69% being diagnosed before having a stroke and 17.23% being diagnosed after having a stroke, compared to 13.76% of controls. Regularly occurring migraines were also frequently reported prior to stroke onset (28.78%). On the other hand, diabetes and heart disease were relatively uncommon in the sample, with 5.88% being diagnosed with diabetes and 2.94% with heart disease before stroke onset.

Modifiable risk factors such as weight, diet, substance use, and exercise are also important risk factors of stroke, and their prevalence in the current study is presented in Table 4. For stroke cases, body weight was assessed prior to the stroke. Of the cases, 38.05% was about the right weight (compared to 51.04% of controls), 28.32% slightly overweight, and 24.78% very overweight. Nearly half the participants (48.23%) reported having a balanced diet with limited processed foods, compared to 56.80% of controls. Exercise habits were measured by asking participants to report average moderate to vigorous exercise per-week prior to having a stroke. Of the cases, while most participants reported moderate to

vigorous exercise three to four times a week (29.65%), a similar proportion reported no weekly exercise (28.76%). Additionally, 72.24% of the cases had never smoked and 12.55% were ex-smokers.

Caffeine consumption was measured by taking the average serving mg dose in each caffeine source prior to having a stroke. Each source of caffeine was assigned an average mg based on the typical serving. For example, the average amount of caffeine in a cup of tea is approximately 40 mg (Bunker & McWilliams, 1979). The overall daily consumption was then calculated by averaging daily caffeine consumption in mg. Outliers of caffeine consumption were addressed using Winsorization, in which values outside the 1st and 99th percentiles were replaced. Specifically, daily consumption values below the 1st percentile were set to the 1st percentile value, and values above the 99th percentile were set to the 99th percentile value. Using this capping technique, we were able to preserve all data. After the Winsorization, the overall average caffeine consumption was 343 mg per day for cases and 223 mg per day for controls (Table 5).

Table 4 Prevalence of Stroke Risk Factors and Timing of Diagnosis

Variable	Percentage Cases (n=435)	Percentage Controls (842)
Diabetes		
No	91.39	90.10
Yes, diagnosed AFTER having a stroke	2.73	N.A.
Yes, diagnosed BEFORE having a stroke	5.88	N.A.
Yes, diagnosed but NEVER had a stroke	N.A.	9.58
High Blood Pressure		
No	59.24	83.95
Yes, diagnosed AFTER having a stroke	17.23	N.A.

Yes, diagnosed BEFORE having a stroke	22.69	N.A.
Yes, diagnosed but NEVER had a stroke	N.A.	13.76
Regular Migraines		
No	58.61	71.97
Yes, AFTER having a stroke	12.39	N.A.
Yes, BEFORE having a stroke	28.78	N.A.
Yes, diagnosed but NEVER had a stroke	N.A.	26.39
Heart Disease		
No	92.02	94.86
Yes, diagnosed AFTER having a stroke	4.62	N.A.
Yes, diagnosed BEFORE having a stroke	2.94	N.A.
Yes, diagnosed but NEVER had a stroke	N.A.	4.70
Bodyweight Pre-Stroke		
Very underweight	1.77	0.65
Slightly underweight	7.08	8.62
About the right weight	38.05	51.04
Slightly overweight	28.32	32.61
Very overweight	24.78	7.09
Diet Pre-Stroke		
Vegetarian or vegan diet (limited processed foods)	5.31	7.13
Vegetarian or vegan diet (LOTS OF processed foods)	3.98	2.02
Balanced Diet (limited processed foods)	48.23	56.80
Unbalanced diet (LOTS of processed foods)	31.86	29.10
Unbalanced diet (MOSTLY of processed foods)	10.62	4.63
Average Cigarette consumption (Pre-stroke)		
Never	72.24	67.29
Ex-smoker (used to smoke but not anymore)	12.55	17.72
1 to 10 cigarettes per-day	9.51	12.80

Greater than 10 cigarettes per-day	5.70	2.19
Exercise (moderate to vigorous per week)		
None	28.76	18.76
Once or twice a week	24.78	41.22
Three to four times a week	29.65	29.99
More than five times a week	16.37	10.03

Table 4 illustrates the prevalence of various risk factors associated with stroke among cases (n=435) and controls (n=842).

Table 5 Daily Average Caffeine Consumption

Pre-stroke Caffeine Consumption for Cases		
Daily caffeine consumption	Average for Cases	Average for Controls
Cups of tea	1.11	0.72
Cups of coffee	1.26	1.18
Cans of soda/pop/soft drinks (e.g., Coke, Pepsi, Dr Pepper, etc.)	0.99	0.79
Small cans of energy drinks (e.g., Red Bull, Celsius)	0.37	0.14
Large cans of energy drinks (e.g., Large Can of Red Bull, Monster)	0.20	0.08
Shot or pill of concentrated caffeine (e.g., 5-hour energy or caffeine pill)	0.07	0.03
Serving(s) of pre-workout	0.26	0.09
AVERAGE DAILY CAFFEINE AMOUNT	343 mg	223 mg

Table 5 illustrates the average daily consumption in milligrams (mg) among the study population of young adult stroke survivors (n=435) and the controls (n=842). Average caffeine consumption was measured by calculating the average daily mg dose from various caffeine sources, with the standard caffeine amount assigned for each source (e.g., 40 mg of caffeine for a cup of tea).

Figure 5 presents the prevalence and timing of self-reported mental health issues and substance use among the cases. The results indicate that 80.98% had no substance abuse or addiction issues. However, 16.11% reported substance abuse or addiction issues before having a stroke, and 2.24% after having a stroke. Regarding suicide ideation, 20.13% of participants seriously considered suicide before having a stroke, 20.81% after having a stroke, and 54.14% never considered. In terms of depression, 34.23% reported having depression before having a stroke, 32.66% after having a stroke, and 30.65% having no depression. Similarly, 39.60% reported having anxiety before having a stroke, 28.86% after having a stroke, and 30.87 reported no anxiety.

Figure 5 Prevalence and Timing of Mental Health and Substance Use Risk Factors Associated with Stroke

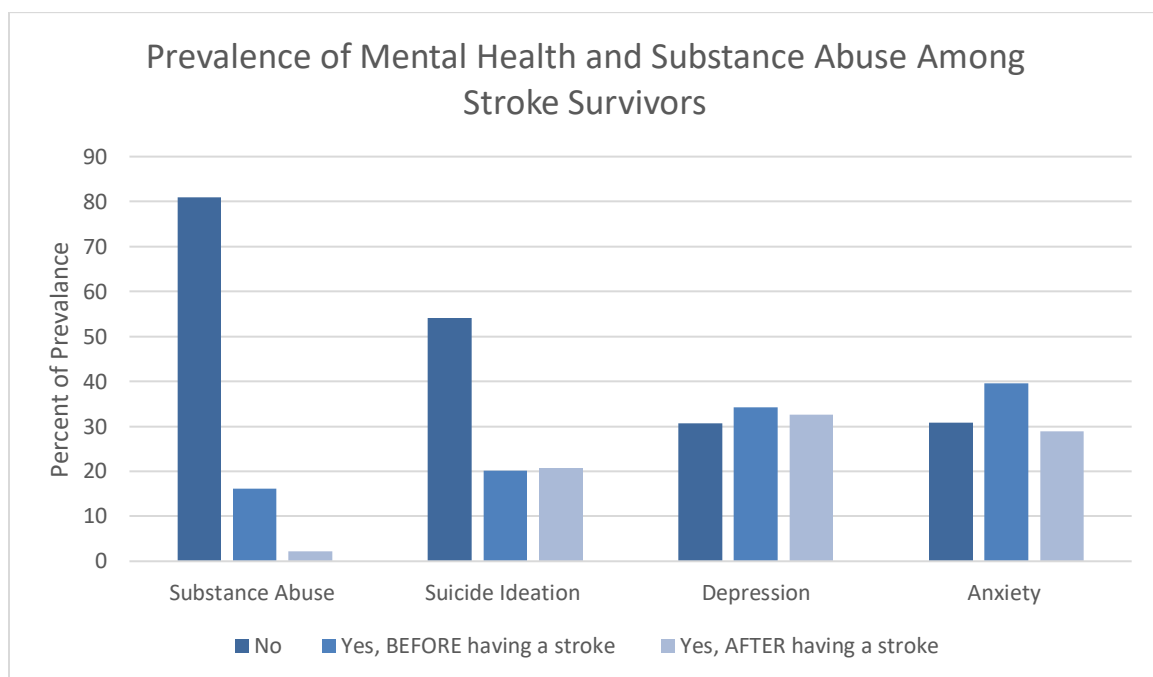


Figure 5 illustrates the prevalence of mental health conditions and substance use issues among the sample of young adults who have had a stroke (n=435). These factors were categorized as “No (absence of the condition), “Yes, diagnosed AFTER having a stroke, and “Yes, diagnosed BEFORE having a stroke”.

2.4 Discussion

To our knowledge, this study is the first to examine the pre- and post-diagnoses of stroke risk factors with the inclusion of emerging risk factors, particularly in young adults. By assessing whether individuals had a risk factor before or after their stroke, we gain a clearer and novel perspective on how these factors contribute to stroke pathophysiology, which remains largely unexplored in the existing literature. The prevalence of pre-stroke conditions, such as hypertension, substance use, sleep deprivation/disorders, and migraines provides valuable temporal insight into the importance of screening and proactive disease management, particularly related to stroke. For instance, this study indicates that majority of stroke survivors were diagnosed with PFO and arterial dissection after having a stroke. These findings suggest that these conditions may often go underdiagnosed until an individual has a stroke, reinforcing the importance of screening. Future research should consider identifying risk factors diagnosed prior to stroke onset to improve our understanding of underlying stroke mechanisms and help differentiate between those factors that contribute to stroke risk and those that may be a consequence of a stroke. Moreover, findings of the current study provide a clearer understanding of what is considered “high risk” for stroke in young adults. Although risk profiles for older adults are well-established in the literature, the findings of this study attempt to provide a clearer understanding of high risk in young adults.

Given that PFO is a congenital condition present from birth, we can assume a temporal association between PFO and stroke, suggesting that PFO may play an important role in stroke causation. Approximately 25% of the general population has a PFO (Kent et al., 2013). Research examining the prevalence of PFO in stroke patients indicates that about 30% of survivors had a PFO (Gupta et al., 2008), with this figure increasing to upwards of 50% in cases of cryptogenic strokes (Mojadidi et al., 2018). A study on ischemic stroke patients found that the highest prevalence of PFO was among those 30 years and younger, possibly indicating earlier impact of PFO on stroke (Gupta et al., 2008). Conversely, a study on young adults found that the prevalence of PFO was 21% (Lechat et al., 1988b), which

align more so with our findings. While the prevalence of PFO is high, the population-attributable risk of stroke due to PFO is relatively low (Di Tullio et al., 2007), and routine screening for PFO in asymptomatic individuals is not supported by current evidence. Randomized control trials have demonstrated that PFO closure after a cryptogenic stroke reduces the risk of stroke reoccurrence, but little evidence has shown that closure prior to first stroke is beneficial (Anantha-Narayanan et al., 2018; Homma & Di Tullio, 2010). This apparent paradox reflects the fact that closure itself may have associated risks, such as atrial fibrillation (J. Z.-J. Chen & Thijs, 2021), which may outweigh the potential preventive benefit, particularly in low-risk individuals. Thus, it may be appropriate to suggest that PFO and related factors should be identified and carefully evaluated in young stroke patients, or those at high-risk of stroke, allowing for strategies of reducing reoccurrence and prevention.

Hypertension also emerged as a highly prevalent risk factor among the sample. Findings of the study also reveal notable prevalence of hypertension among young adults who have experienced a stroke. Hypertension is widely recognized as one of the most significant risk factors of stroke risk, accounting for nearly half of all stroke cases (Poznyak et al., 2022). Physiologically, hypertension causes damage to the inner lining of arteries and increases risk of stroke through atherosclerosis (H.-L. Kim, 2023a). In young adults, research suggests that hypertension is a major contributor of intracerebral hemorrhages (Broderick et al., 2020). In our study, hypertension was one of the most reported risk factors prior to an individual having a stroke, underscoring its role in stroke risk, particularly in young adults. These findings, in addition to the literature, highlight the importance of hypertension screening, particularly among those at high risk. Alongside hypertension, sleep disorders and deprivation also emerged as a prevalent risk factor prior to stroke.

Sleep disorders/deprivation had the highest pre-stroke prevalence among etiological factors examined in this study, suggesting a potential association between sleep disturbances and stroke risk, particularly in young adults. Research highlights how sleep disorders can

impact intermediary vascular risk, such as hypertension, diabetes and obesity, which are all major risk factors for stroke risk (Wallace et al., 2012). For example, individuals with obstructive sleep apnea have shown increased stroke odds by 1.6 times in comparison to those without (Shahar et al., 2001). Chronic insomnia can also impact cardiovascular stress, contributing to metabolic abnormalities, increased inflammation, and elevated cortisol levels (Barugh et al., 2014; Bonnet & Arand, 1995; Irwin et al., 2006). Additionally, sleep disorders are linked to higher levels of prothrombic factors, increasing clot formation risk (Bikov et al., 2021). The rise in cellphone use before bed may also exacerbate sleep issues in young adults, further elevating stroke risk (Joshi et al., 2022). Although research on sleep disorders and stroke in young adults is limited, the high pre-stroke prevalence presented in our study underscores the importance of early screening, intervention, and additional research.

Regularly occurring migraines were also frequently reported before stroke onset. This study, to our knowledge, is the first to provide a prevalence rate of migraines both before and after stroke. While migraines impact 13% of the general population (Gryglas & Smigiel, 2017), limited research has examined the prevalence among young adults while considering their impact on different forms of stroke. The available research focuses primarily on migraines and risk of ischemic strokes (Lantz et al., 2015; Pezzini et al., 2014; Schwaag et al., 2003). These studies report a 20% prevalence rate of migraines and a two-fold risk of stroke in young adults (Lantz et al., 2015; Schwaag et al., 2003). The prevalence of regularly occurring migraines in our study is higher than what is typically reported in the literature. This discrepancy may result from our study focusing on various types of strokes or its emphasis on a younger population. Nonetheless, these findings suggest the need for further research to better understand the relationship between migraines and stroke risk, especially in young adults.

Similarly, history of substance use and addiction were prevalent risk factors among participants in our study. Research demonstrates that there has been a notable increase in

street drug use since the mid 1990's, with a 15% increase among young adult stroke survivors aged 20 to 54 (de los Ríos et al., 2012). A study on 422 young adults who had an ischemic stroke found that 12.1% had recently used drugs, with 4.7% having confirmed drug-related stroke causes (Esse et al., 2011). Substance abuse contributes to vascular damage, altered blood pressure and heart rate and ultimately increased stroke risk (Fonseca & Ferro, 2013). Together, these studies and our findings emphasize the high prevalence and impact of substance use among stroke survivors, suggesting a need for targeted interventions.

Lifestyle factors also play an important role in the risk of a stroke occurring and have been well documented in the literature. Consistent with previous research, our study highlights a high prevalence of obesity, poor diet, and lack of exercise among stroke survivors. A substantial proportion of participants in our study classified as overweight or very overweight, supporting the narrative that obesity is a major risk factor of early onset of stroke. Research indicates that the prevalence of obesity in young adults who have had a stroke is rising alongside increasing obesity rates in the general population (George et al., 2017; A. B. Mitchell et al., 2015). A study from 2017 found that the prevalence of obese young stroke survivors was between 14.25% and 18.35%, compared to the previous decade which was 7.25% to 10% (Jaakonmäki et al., 2022). The higher prevalence of our study suggests an increasing trend. Obesity increases the risk of stroke through various mechanisms, such as diabetes, hypertension, high cholesterol, atherosclerosis, sleep apnea, and arterial fibrillation (Kernan et al., 2013a).

Closely associated with obesity and stroke is the impact of diet. Poor dietary habits have been associated with increased blood pressure, cholesterol, insulin resistance, thrombosis, and endothelial dysfunction, all of which contribute to an increased risk of stroke (Lakkur & Judd, 2015). Similarly, lack of exercise is a well-documented risk factor of stroke risk, as it contributes to obesity and hypertension while reducing endothelial function and increasing vascular inflammation (Di Francescomarino et al., 2009; Dun et al., 2021).

According to the Canadian government, approximately 63% of individuals between 18 to 34 do not meet the recommended levels of physical activity (Canada, 2017). The high prevalence of these lifestyle factors in the young adults of the present study underscore the critical need for targeted, early interventions to mitigate lifestyle changes.

The impact of caffeine on stroke risk remains largely unexplored, particularly in young adults. The limited research on caffeine consumption and stroke risk illustrates conflicting results, suggesting that it has both potential protective (B. Kim et al., 2012) and harmful effects (Lee et al., 2013). However, to our knowledge, no study has yet to record the prevalence of average daily caffeine consumption prior to individuals having a stroke. According to researchers, the global daily caffeine intake is about 200 mg (Samoggia & Rezzaghi, 2021), which is similar to the daily intake of the controls of the present study and significantly less than the average noted among the young stroke survivors of our study. Excessive caffeine has been shown to disrupt sleep (Gardiner et al., 2023), increase heart rate and blood pressure to cause arterial stiffness and increase the risk of stroke (Gaspar et al., 2024). Given the potential harmful impact of caffeine on various risk factors of stroke, future research should further examine the role that caffeine plays in stroke risk, particularly in young adults, who are frequent consumers of caffeine products.

Mental health and stroke risk, particularly in young adults, has also been largely overlooked. Particularly, the impact of mental health factors prior to stroke in young adults is largely limited, especially in comparison to the impact of stroke survivors' mental health post stroke. The high prevalence of depression, anxiety, and suicidal ideation prior to stroke in our study suggests that these factors may contribute to stroke risk. Although research is scarce, existing literature indicates behavioural and biological factors linking mental health conditions to stroke. For instance, a decline in mental health has been shown to increase smoking and alcohol consumption, decrease sleep and exercise, and worsen eating habits (Hoang et al., 2019), all of which are known risk factors for stroke. From a biological

perspective, chronic stress and depression can increase inflammation and immune system dysregulation, elevating risk of cardiovascular diseases, including stroke (Cohen et al., 2015). Moreover, stress and anxiety have been associated with excess activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, triggering increased release of stress related hormones (Cohen et al., 2015). Prolonged overactivation of these systems contributes to increases in blood pressure, inflammation, and atherosclerosis, all of which increase stroke risk (Cohen et al., 2015). Thus, given the increasing evidence associating mental health factors to stroke risk, additional research is needed to better understand this relationship, particularly in young adults, where these risk factors are common.

2.5 Limitations

Despite the many novel findings and strengths of this study, there are some limitations. As a voluntary-based questionnaire, it is susceptible to selection and response bias. Moreover, since participants were required to have had a stroke between the ages of 18 to 50 but could still participate if they were older at the time of the study, this introduced issues of recall bias. Notably, most participants recently had their stroke, which helped mitigate this concern. Another limitation of this study was lack of validation of risk factors. Without clinical confirmation, there is a possibility of misclassification of participants either misunderstand their diagnoses or inaccurately report their health conditions. Such errors could lead to underestimation or overestimation of the true prevalences. Moreover, given that the recruitment of this study was through various stroke survivor groups, rehabilitation centres, stroke researchers, neurologists and hospitals around the world. As participation was voluntary, the number of participants from each country varied. Thus, the sample varied in representation of geographical differences and resulted in an uneven proportion of participants from each country. Additionally, because the questionnaire was only offered in English, participation was restricted to individuals fluent in the language, ultimately impacting the generalizability of the findings. Lastly, some variables had a slight reduction in

response rate as additional questions were added after the first wave of data collection to provide supplementary insight into stroke risk factors (e.g., PFO and infections), based on expert recommendation. Given these limitations, future studies should consider employing more randomized recruitment strategies and longitudinal designs to ensure more representative and accurate findings. Moreover, researchers should consider offering questionnaires in multiple languages to increase the generalizability of findings to non-English speaking populations.

2.6 Conclusion

This study highlights the complex and multifactorial nature of stroke risk, particularly in young adults. The findings reveal the significant prevalence of risk factors, such as hypertension, sleep disorders, migraines, substance use, as well as lifestyle and mental health factors. The high prevalence of these factors emphasizes the critical need for early detection, intervention, and targeted prevention strategies for policy makers, rehabilitation centres, and health care professionals. This study makes several novel and valuable contributions to the field of stroke research. Notably, it explores the pre-and post-stroke onset of risk factors, offering unique insights into whether these conditions and behaviours were present before participants experienced a stroke. Furthermore, the findings suggest that etiological risk factors, such as PFO and atrial dissections often go undiagnosed until after a stroke occurs, urging the need for additional screening protocols. This study is also the first, to our knowledge, to document the average pre-stroke daily caffeine consumption among stroke survivors, an area of research that is largely unexplored.

Future research should further investigate the role of mental health factors, such as depression, anxiety, and suicide ideation, as pre-existing risk factors for stroke. The present study also highlights a high prevalence of physical risk factors, emphasizing the need for prevention strategies that address both physical and mental health issues to be more

comprehensive and effective. Findings urge that future researchers investigate how mental health risk factors influence biological and behavioural factors related to stroke. Researchers should also consider using more complex statistical techniques to uncover the association of these risk factors and their impact on stroke risk. Overall, the findings emphasize the importance of both established and emerging risk factors for stroke prevention and intervention. Moreover, the results suggest that the risk profiles of young adults may be unique from those of older adults, underscoring the need for age-specific research, rather than relying on findings from older populations. Thus, additional multifactorial research is needed to better understand the complex nature of stroke in young adults.

Chapter 3

Stroke Risk in Young Adults: A Multifactorial Case-Control Study

Abstract

Background:

Stroke in young adults is a growing public health concern. However, research has yet to fully comprehend the risk profiles and contributing factors that may be uniquely impacting this younger population. The purpose of this paper is to examine both the established and emerging risk factors of stroke in young adults aged 18 to 50.

Method:

This case-control study was multinational and included 1,277 participants, with 435 cases and 842 controls that were matched by biological sex on a 1:2 ratio. Using a cross-sectional questionnaire, data such as individuals' demographics, lifestyle, and pre-existing health variables were collected.

Results:

Notably, the findings of the conditional logistic regression analyses indicated increased risk of stroke for individuals aged 41-50 (OR=3.908, 95% CI 2.848-5.363, $p<0.001$) and those residing in Canada (OR=2.020, 95% CI 1.233-3.307, $p=0.005$). Lifestyle factors, such as frequent marijuana use (OR=1.894, 95% CI 1.098-3.282, $p=0.023$) and ex-smokers (OR=1.650, 95% CI 1.151-2.365, $p=0.006$) had increased risk of stroke. Emerging risk factors, such as mental health depicted increased risk of stroke for those who had poor overall pre-stroke mental health (OR=1.726, 95% CI 1.196-2.492, $p=0.004$). Interestingly, individuals who had high income (OR=1.963, 95% CI 1.448-2.662, $p<0.001$), identified as

Black (OR= 0.162, 95% CI 0.093-0.282, $p<0.001$), and had moderate to heavy alcohol consumption (OR=0.402, 95% CI 0.234-0.692, $p<0.001$) had decreased risk of stroke.

Discussion:

This study is one of the first to assess stroke risk in young adults using a multifactorial perspective that includes both established and emerging risk factors. While the findings of this study largely align with the existing literature (e.g., importance of age and hypertension), there are many novel (e.g., pre-stroke mental health) and counterintuitive results (e.g., protective effect of alcohol) that emphasize the complex nature of stroke in young adults.

3.1 Introduction

Stroke is a complex cardiovascular disease traditionally associated with older adults. However, recent trends indicate rising rates of stroke cases among young adults, who now account for approximately 10 to 15% of all strokes (Yahya et al., 2020a). Although the incidence of stroke in older adults has remained stable or decreased, the global rates of strokes among young adults have steadily risen (Bukhari et al., 2023b). Despite this concerning trend, there are a limited number of studies on the risk factors of stroke in young adults, thereby highlighting gaps in the current knowledge. As such, understanding the factors that influence stroke risk in this population are crucial for prevention and intervention. There are many risk factors associated with stroke; however, there is no explicit set of factors that researchers can apply to uncover stroke causation. While some of the risk factors are shared among all age groups and are well-established in the literature, such as hypertension and obesity, they alone do not fully explain the rise in stroke incidence among young adults. Lifestyle differences, genetics, and epigenetics play an important role in stroke risk. Moreover, young adults often encounter a unique set of circumstances and exposures that differ from older adults. Therefore, research on older adults cannot be applied directly to young adults. In particular, young adults may be more affected by non-traditional or

emerging risk factors that have yet to be fully explored. Risk factors can also vary by age, with young adults facing unique challenges including stress and drug use (Nawi et al., 2021). Furthermore, emerging risk factors, such as mental health conditions may also play an important role in stroke risk among young adults, given their high prevalence in this population.

Stroke risk factors can be generally classified as modifiable and non-modifiable. Modifiable risk factors are influenced by individuals' health behaviors' and lifestyle choices (Alwan et al., 2024). Modifiable risk factors include hypertension, smoking, alcohol consumption, poor diet, obesity, lack of exercise, and diabetes, which account for nearly 80% of all strokes in young adults (Aigner et al., 2017). On the other hand, non-modifiable risk factors can be characterized as inherent risk factors that individuals cannot alter, such as biological sex, race, or genetic history (Das et al., 2024). For example, young women may face higher risk of stroke due to hormonal factors, and racial minorities, such as Black individuals have higher stroke incidence and mortality (Aradine et al., 2022; Boehme et al., 2017; Das et al., 2024). Family history of stroke also significantly increases risk, with significantly higher odds of stroke amongst those with a familial stroke history (Liao et al., 1997).

Evidence also highlights the potential role of emerging risk factors, such as mental health, specifically in young adults. Young adulthood is often marked by major life transitions, such as leaving home, and/or pursuing an education or career, which can lead to feelings of anxiety, stress, and depression (Sable et al., 2011). While there is extensive research on mental health post-stroke, less is known about mental health as a risk factor, particularly in young adults. For example, depression can increase cortisol, which in turn, can result in hypertension, increased platelet aggregation and inflammatory responses that negatively impact individuals' vascular health (Halaris, 2016), and increase stroke risk.

3.1.1 Background and Research Gaps

Despite the rising incidence of stroke in young adults, our understanding of the underlying causes and risk factors remains limited. As mentioned previously, young adults account for approximately 10 to 15% of all stroke cases, and this number continues to rise (Bukhari et al., 2023a; Smajlović, 2015). However, much of the literature on stroke has historically focused on older adults, with the limited research on young adults being focused on established risk factors, such as hypertension, diabetes, high cholesterol, and smoking.

Although attention towards stroke in young adults is growing, much of the existing studies are limited in their scope, either examining specific countries or clinical subpopulations (Greenlund et al., 2004; Yi et al., 2020), or concentrating solely on established risk factors (George et al., 2017; Habibi-koolaei et al., 2018; Yandrapalli et al., 2019). While informative, these studies do not account for emerging or age-specific risk factors, which may help explain the increasing burden of stroke in young adults. For example, pre-existing mental health conditions, such as depression, anxiety, and chronic stress may uniquely impact young adults due to developmental and social transitions that are specific to this life stage (Halaris, 2016; Sable et al., 2011). These emerging risk factors may influence stroke risk through distinct biological and psychosocial mechanisms that are yet to be included in existing models.

Furthermore, studies focused only on prevalence of risk factors are inherently limited in their ability to determine whether risk factors precede stroke onset or emerge as a consequence. Without longitudinal or temporal information and approaches, it becomes difficult to identify which exposures are potentially causal, or to assess the strength of these associations as risk factors, while also accounting for confounding effects. In addition, much of the current literature on risk factors of stroke in young adults uses small sample sizes (González-Gómez et al., 2016; D. Jones et al., 2017; Leys et al., 2002), limiting

generalizability and the ability to conduct robust multivariable analyses. A broader, international lens is also lacking, despite the fact that geographic and population-level differences in stroke incidence and etiology can provide important insights into environmental and sociocultural impacts.

This study responds to the need for a more comprehensive analysis of stroke risk in young adults by addressing these critical research gaps. Specifically, it examines geographic variation and incorporates both established and emerging risk factors (including mental health and infection history). Moreover, the present research utilizes both pre-and-post stroke data to better assess risk factor association and possible temporal implications.

3.1.2 Research Aims

The aim of this study is to conduct a multifactorial, exploratory analysis of stroke risk factors in young adults, integrating lifestyle, clinical, psychological, demographic, geographic, and etiological variables. To overcome the methodological limitations of previous research, we intend on using a large, multinational, case-control dataset, and apply a conditional multiple logistic regression analysis. This approach allows for a more nuanced understanding of how these diverse risk factors collectively contribute to stroke risk, while controlling for potential confounding. Ultimately, this study aims to uncover the complex relationship among the aforementioned risk factors, while providing insight into which factors may disproportionately impact young adults in terms of stroke risk. By identifying modifiable and emerging risk factors, particularly those distinct to young adults, these findings can inform early screening protocols and targeted intervention campaigns. Moreover, this research may inform public health officials of the unique risk profiles of young adults to guide the development of age-specific prevention, intervention, and post-stroke care.

3.2 Methods

3.2.1 Study Design

This study was conducted using a matched case-control design, comparing young adults who experienced a stroke (cases) with healthy controls. The term “young adult” in the context of stroke research often ranges from 18 to between 45 to 55 years old. For this study, young adults are defined as being 18-50 years-old, aligning with prior research (Ekker et al., 2019; Bukhari, Yahi, & Bashir, 2023; Rutten-Jacobs et al., 2013). Cases were classified as those who reported experiencing an ischemic, hemorrhagic, or transient ischemic stroke between 18 to 50 years old. Whereas controls were those who were aged 18 to 50 with no stroke history. Participants were matched by biological sex, with each case matched to two controls. However, due to the uneven biological sex distribution, and a limited number of controls to achieve a precise 1:2 ratio, some of the strict matching had to be relaxed with some cases only having 1 control. Stroke cases were recruited from various avenues, including local and international hospitals, research groups, patient networks, rehabilitation centres, stroke survivor organizations, and social media platforms. The diverse recruitment approach attempted to capture a broad spectrum of stroke severity, excluding fatal cases. Conversely, the controls for the study were recruited from Prolific's online global database. Ethics approval was obtained from the University of Waterloo's Research Ethics Board in correspondence with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

The questionnaire included information on participants demographics (e.g., age, racial ethnicity, income), health history (e.g., hypertension), etiology (e.g., PFO), chronic infections (e.g., syphilis), mental health questions (e.g., depression, stress), and lifestyle factors (e.g., drug use, diet, weight). To ensure the questionnaire's validity, it was established using validated measures, such as the *National College Health Assessment-American College Health Assessment Survey* or the *Canadian Health Measures Survey*. When necessary, novel

measures were developed based on existing literature. For instance, physical activity was not assessed by just frequency of exercise, but rather by the intensity of weekly sessions (Prior & Suskin, 2018). To ensure data quality, responses that were not meaningful were filtered out, such as those completed before the minimum completion time or from participants who failed attention checks.

3.2.2 Data Analyses

As this is a matched case-control study, a conditional logistic regression was conducted with stroke status as the binary outcome variable. The covariates in the model included demographic variables (e.g., age, race), health-related conditions (e.g., diabetes and hypertension status), substance use, and lifestyle factors (e.g., exercise and diet). As missing data was minimal (less than 7%), a complete case analysis was performed.

For the regression models, age was categorized into ranges to allow for meaningful comparisons between the age at which cases experienced a stroke and the current age of the controls. The categorization of age minimized recall bias related to the age at which participants experienced their stroke and ensured that cases (who could have had a stroke at any point between ages 18-50) were matched to controls within the same age range. Since cases may be older (e.g., 55 but had their stroke within the 18-50 age range), categorizing age allowed for valid comparisons between cases and controls.

Health variables were recoded into binary responses to provide potential temporal insight. For example, high blood pressure diagnosis was originally categorized as:

“No diagnosis”

“Yes, diagnosed BEFORE having a stroke”

“Yes, diagnosed but NEVER had a stroke”

“Yes, diagnosed AFTER having a stroke”

To analyze the temporal association, the categories were recoded as follows:

“No” remained “No”.

“Yes, diagnosed BEFORE having a stroke” and “Yes, diagnosed but NEVER had a stroke” were recoded as “Yes”.

“Yes, diagnosed AFTER having a stroke” was also recoded as “No” as it does not indicate a temporal relationship prior to stroke onset.

To better understand the temporal association, participants were asked to report whether they were diagnosed with medical conditions before or after their stroke, if applicable. While a cross-sectional design limits causal inferences, this approach provides an opportunity to approximate possible temporal associations in the absence of repeated measures or longitudinal data. Given that stroke in young adults is relatively uncommon, recruitment and study designs are challenging. Future research should consider these limitations to better assess the temporality and causal associations of risk factors.

The logistic regression model was assessed for fundamental assumptions, such as multicollinearity, independence, and unmeasured confounding, to ensure that estimates were reliable. Given that participants were recruited from approximately 60 countries and through various avenues (e.g., hospitals, rehabilitation centres, and social media), responses are assumed to be independent from one another. As the study aims to explore the complex, multifactorial nature of stroke risk among young adults, a conditional logistic regression was used to analyze both known and emerging risk factors while controlling for confounding effects. To avoid overfitting, the model only included both well-established risk factors (e.g., hypertension, obesity, smoking) and relevant emerging risk factors of stroke (e.g., mental health). Considering the sample size and the absence of specific interactions of primary scientific interest, interaction effects were not considered. Additionally, variables with low response categories were collapsed to ensure reliability of estimates. All statistical analyses

were conducted in RStudio (Version 2024.12.0+467) (*Posit*, 2025) and R (Version 4.5.1) (R Core Team, 2025).

3.3 Results

3.3.1 Descriptives Statistics of Sample

Table 6 depicts the demographic characteristics of the study sample. A total of 1,277 responses were collected, including 435 participants who experienced a stroke between 18 to 50 years old, and 842 controls. Of the cases, 63% had an ischemic stroke, 30% hemorrhagic, and 7% transient ischemic attack. The average age among the cases was 39 years old, compared to 31 years old among controls. Gender and racial distributions varied between the cases and controls, with 57.8% of the cases identifying as female, compared to 45.4% of controls, and 76% of the cases identifying as White compared to 47.7% of controls.

Geographically, most cases resided in the USA (59.45%), while majority of controls were from the USA (34.31%), UK (18.37%), and South Africa (16.45%). Post-stroke income data showed that a smaller proportion of cases (25%) reported an annual income of less than \$40,000 USD, compared to controls (38.90%). Full details of demographic characteristics of both groups can be found in Table 6.

Table 6 Descriptive Characteristics of Sample

Variable	Cases (%)	Controls (%)	Total (%)
Age	Mean: 39 Years Old	Mean: 31 Years Old	
Country Of Residence:			
Australia	2.73	0.13	1.02
Belarus	0.42	0	0.14

Belgium	0.63	0.13	0.36
Canada	16.18	3.70	7.94
Denmark	0.21	0.26	0.24
Germany	1.47	0.77	1.03
Greece	0.42	1.79	1.30
India	3.36	0.77	1.73
Ireland	1.05	0.38	0.61
Netherlands	0.84	0.64	0.71
Philippines	1.68	0.26	0.81
South Africa	0.84	16.45	10.81
United Kingdom of Great Britain and Northern Ireland	6.09	18.37	13.95
United States of America	59.45	34.31	42.86
Other	4.62	22.07	14.68
Sex At Birth			
Female	57.77	45.41	49.84
Male	41.81	53.70	49.94
Prefer Not to Say	0.42	0.51	0.49
Race			
Arab	0.21	0.64	0.47
Black	2.73	35.20	22.02
Chinese	2.10	1.02	1.46
Filipino	1.89	0.51	1.06
Indigenous	1.47	0.13	0.62
Korean	0.21	0.38	0.31
Latin American	3.36	3.70	3.57
Mixed Race	3.36	4.34	3.93
South Asian (e.g., East Indian, Pakistani, Sri Lankan)	4.83	3.06	3.75

Southeast Asian (e.g., Vietnamese, Cambodian, Laotian, Thai)	1.68	1.15	1.35
West Asian (e.g., Iranian, Afghan)	0.21	0.00	0.07
White	76.05	47.70	58.76
Other	1.89	1.40	1.56
Income			
Less Than \$40,000 USD (Less Than \$53,000 Cad, €35,000 Eur, Less Than \$54,000 Aud)	25.00	38.90	33.49
Between \$41,000 USD To \$67,000 USD (\$54,000 To \$85,000 Cad, €35,000 To €56,000 Eur, \$54,000 To \$85,000 Aud)	15.12	20.79	18.49
Between \$68,000 To \$83,000 USD (\$86,000 To \$105,000 Cad, €56,000 To €68,000 Eur, \$86,000 To \$105,000 Aud)	10.92	13.65	12.90
Between \$84,000 To \$184,000 USD (\$106,000 To \$235,000 Cad, €68,000 To €155,000 Eur, \$106,000 To \$235,000 Aud)	26.68	18.37	21.55
More Than \$185,000 USD (More Than \$236,000 Cad, €155,000 Eur, More Than \$236,000 Aud)	11.13	3.57	6.47
Prefer Not to Say	11.13	4.33	6.65

Table 6 presents the demographic characteristics of the sample (n=1.277, Cases=435, Controls=842) including age, country of residence, biological sex, race, relationship status, income, and employment status.

3.3.2 Health, Lifestyle and Clinical Risk Factors

Table 7 presents the prevalence of stroke-related biological, psychosocial, and lifestyle factors. Based on pre-stroke data, cases generally reported lower physical and mental health. Of the sample, 7.14% of cases reported having excellent physical health compared to 12.26% of controls, and 5.88% of cases reported having excellent mental health compared to 14.33% of controls. In terms of body weight, cases had higher proportion of very underweight (1.8%) and very overweight (24.8%), compared to controls (0.65% and 7.09, respectively). Exercise

frequency was also lower among cases, with 28.76% reporting no activity, in comparison to 18.76% of controls. Heavy smoking (more than 10 cigarettes/day) was more common among cases (5.70%) than controls (2.19%). Frequent marijuana use was also more common in cases (7.98% daily use compared to 8.72% of controls), as was daily hard drug use (3.04% cases compared to 0.44% of controls). Regarding other health-related factors, cases generally exhibited a higher prevalence of risk factors in comparison to controls. For example, cases had higher diagnoses of hypertension (41% of cases, 16% of controls), and regularly occurring migraines (41.39% of cases, 28.09% of controls), and arterial dissection (17% of cases, 1% of controls). Full details of stroke related health factors, including their timing in association to pre and post stroke, are provided in Table 7.

Table 7 Health History, Illness, Disease and Other Stroke Related Factors Between Cases and Controls

Variable	Cases (%)	Controls (%)
Physical Health		
Excellent	7.14	12.16
Very good	21.85	33.12
Good	26.05	30.51
Average	28.99	19.00
Poor	15.34	5.21
Mental Health		
Excellent	5.88	14.33
Very good	20.79	27.47
Good	22.69	23.78
Average	25.84	22.15
Poor	24.37	12.27

Body Weight		
Very underweight	1.77	0.65
Slightly underweight	7.08	8.62
About the right weight	38.05	51.04
Slightly overweight	28.32	32.61
Very overweight	24.78	7.09
Average Weekly Moderate to Vigorous Exercise		
None	28.76	18.76
Once or twice	24.78	41.22
Three to four	29.65	29.99
More than five	16.37	10.03
Smoking		
Never	72.24	67.29
Ex-Smoker	12.55	17.72
1 to 10 cigarettes per-day	9.51	12.80
Greater than 10 cigarettes per-day	5.70	2.19
Average Monthly Marijuana Consumption		
Never	69.96	78.82
1 to 3 times a month	11.79	11.03
1 to 3 times a week	4.94	4.15
3 to 5 times a week	5.32	0.65
Daily	7.98	0.44
Average Monthly Cocaine, Opiates, or Amphetamines Consumption		

Never	92.02	96.07
1 to 3 times a month	3.04	2.18
1 to 3 times a week	0.38	0.65
3 to 5 times a week	0.76	0.65
Daily	3.04	0.44
Alcohol Use Weekly Avg		
0 grams of alcohol per-week	44.75	37.84
Between 1 to 150 grams	24.79	51.47
Between 150 to 300 grams	23.53	8.72
Greater than 300 grams	3.99	1.96
Diabetes		
No	91.39	90.10
Yes, diagnosed AFTER having a stroke	2.73	NA
Yes, diagnosed BEFORE having a stroke	5.88	NA
Yes, diagnose but NEVER had a stroke	NA	9.58
Arterial Dissection		
No	81.93	98.15
Yes, diagnosed AFTER having a stroke	16.18	NA
Yes, diagnosed BEFORE having a stroke	0.84	NA
Yes, diagnose but NEVER had a stroke	NA	1.31
Heart Disease		
No	92.02	94.86
Yes, diagnosed AFTER having a stroke	4.62	NA
Yes, diagnosed BEFORE having a stroke	2.94	NA
Yes, diagnose but NEVER had a stroke	NA	4.70

High Blood Pressure		
No	59.24	83.95
Yes, diagnosed AFTER having a stroke	17.23	NA
Yes, diagnosed BEFORE having a stroke	22.69	NA
Yes, diagnose but NEVER had a stroke	NA	13.76
Respiratory Disease		
No	88.66	86.82
Yes, diagnosed AFTER having a stroke	0.21	NA
Yes, diagnosed BEFORE having a stroke	10.71	NA
Yes, diagnose but NEVER had a stroke	NA	12.75
Chronic Kidney Disease		
No	96.22	97.83
Yes, diagnosed AFTER having a stroke	1.68	NA
Yes, diagnosed BEFORE having a stroke	1.89	NA
Yes, diagnose but NEVER had a stroke	NA	1.96
Sleeping disorder		
No	48.11	55.12
Yes, diagnosed AFTER having a stroke	18.07	NA
Yes, diagnosed BEFORE having a stroke	33.82	NA
Yes, diagnose but NEVER had a stroke	NA	42.27
Regular Migraines		
No	58.61	71.97
Yes, AFTER having a stroke	12.39	NA
Yes, BEFORE having a stroke	28.78	NA

Yes, diagnose but NEVER had a stroke	NA	26.39
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Table 7 presents the frequency and prevalence of health-related factors among the cases and controls ($n=1,277$). The factors in the table include overall self-reported physical and mental health, body weight, weekly exercise, substance use, and health history in relationship to stroke onset.

3.3.3 Conditional Logistic Regression

Conditional Logistic Regression

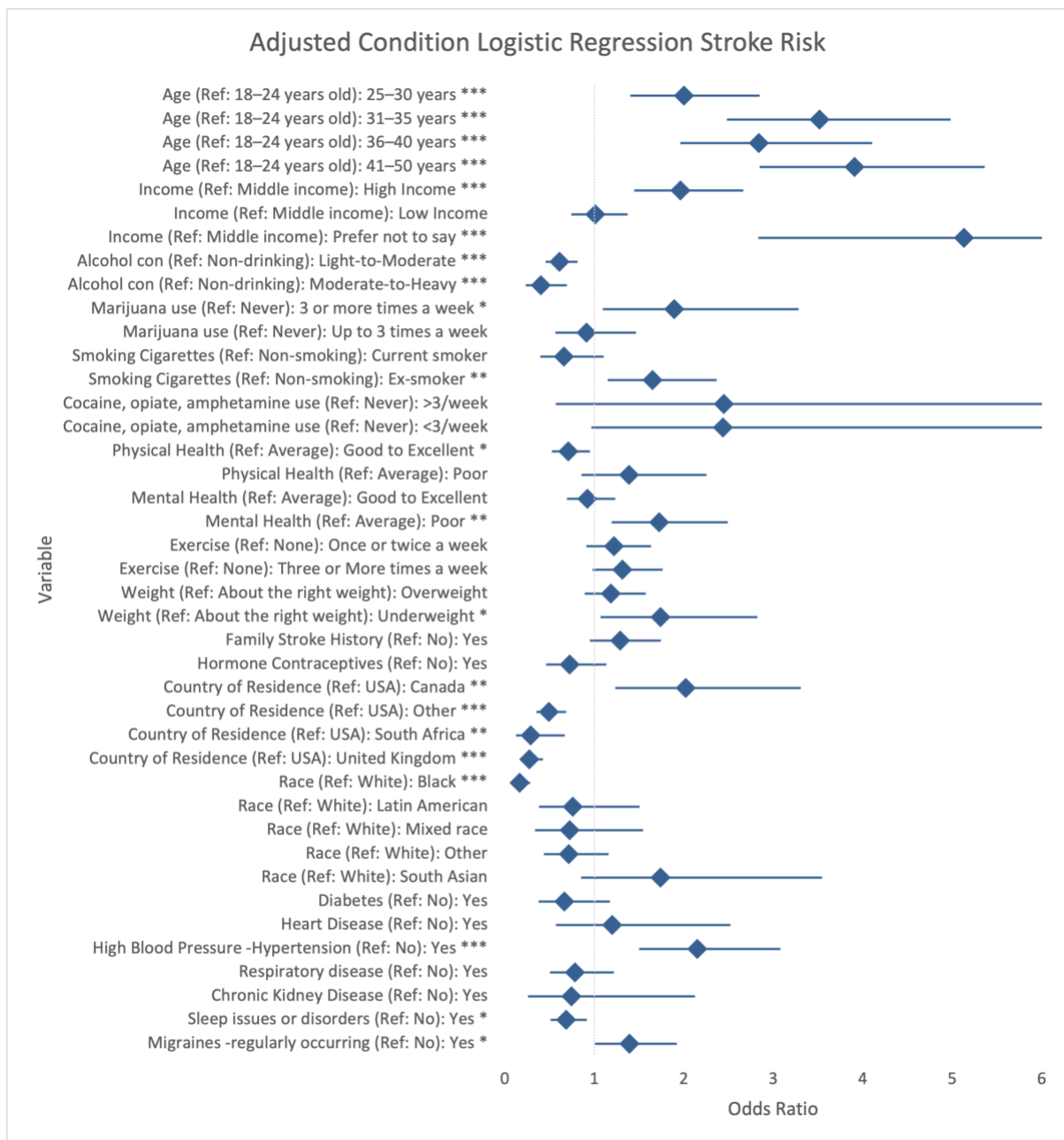
Figure 6 presents the results of the conditional logistic regression analysis based on 428 pairs. All age groups showed significantly higher odds of stroke compared to individuals aged 18 to 24, with the highest odds amongst those 41 to 50 years old (OR=3.90, 95% CI 2.848-5.363, $p<0.001$). High income (>\$84,000 USD) was associated with increased stroke risk (OR=1.963, 95% CI 1.448-2.662, $p<0.001$) and statistically significant. Likewise, those who selected “prefer not to say” were also associated with an increased risk of stroke (OR=5.131, 95% CI 2.830-9.304, $p<0.001$). In contrast, low income (OR=1.009, 95% CI 0.741-1.374, $p=0.954$) was not, compared to those with middle income. Geographic location was an influential risk factor for stroke, indicating that Canada had higher odds of stroke (OR=2.020, 95% CI 1.233-3.307, $p=0.005$), compared to the USA. Regarding race, only Black individuals showed statistically significant lower odds of stroke compared to White participants (OR=0.162, 95% CI 0.093-0.282, $p<0.001$).

Regarding lifestyle factors, alcohol consumption was a statistically significant protective factor of stroke. Light to moderate drinkers (1-300g/week) had significantly lower odds of stroke (OR=0.608, 95% CI 0.455-0.813, $p<0.001$), as did moderate to heavy drinkers (>300g/week) (OR=0.402, 95% CI 0.234-0.692, $p<0.001$), compared to non-drinkers. Compared to non-smokers, ex-smokers (OR=1.650, 95% CI 1.151-2.365, $p=0.006$) had significantly increased odds of stroke. Marijuana use depicted a dose-dependent association. Specifically, frequent use (≥ 3 times/week) was significantly associated with increased stroke

risk (OR=1.894, 95% CI 1.098-3.282, $p=0.023$), compared to those who never smoked. Similarly, individuals frequently using cocaine, opiates, or amphetamines (≥ 3 times/week) (OR=2.444, 95% CI 0.569-10.504, $p=0.230$) had increased odds of stroke, in comparison to non-users.

Health-related stroke factors also depicted influential results. Compared to individuals with average physical health, poor physical health was associated with higher, but not statistically significant odds (OR=1.388, 95% CI 0.855-2.255, $p=0.185$). Regarding mental health, those reporting poor mental health had significantly increased odds (OR=1.726, 95% CI 1.196-2.492, $p=0.004$), compared to those with average self-reported mental health. Participants classified as overweight were not a statistically significant predictor of stroke (OR= 1.184, 95% CI 0.890-1.575, $p=0.248$), while being underweight was significantly associated with increased stroke risk (OR=1.736, 95% CI 1.068-2.822, $p=0.026$). While family history of stroke, diabetes, and heart disease were not significantly associated with stroke risk, individuals who reported having sleep disorders had significantly reduced odds of stroke (OR=0.685, 95% CI 0.512-0.916, $p=0.011$), compared to those without sleep disorders. Conversely, high blood pressure was associated with significantly increased odds of stroke (OR=2.149, 95% CI 1.500-3.078, $p<0.001$).

Figure 6 Adjusted Conditional Logistic Regression of Stroke Risk in Young Adults



Significant codes: 0 '***' 0.001 '**' 0.01 '*' 0.05

Figure 6 illustrates the results of the conditional logistic regression matched based on biological sex ($n=428$ pairs). Diamonds represent the adjusted odds ratios (OR) for each variable, and horizontal lines indicate the 95% confidence intervals (CI).

3.4 Discussion

This study is the first to examine stroke in young adults using a multifactorial approach that incorporates both established and emerging risk factors of stroke, while also providing temporal insights into risk factor associations. While the results primarily align with previous literature, the study also reveals some novel findings. Notably, all age groups beyond 24 years old demonstrated increased risk of stroke, suggesting that age remains an important risk factor even within a younger population. These results reflect a possible relationship whereby long-term exposure to cardiovascular risk factors, such as hypertension, poor diet, physical inactivity, and stress can cause early vascular aging and silent cerebrovascular damage (Banach et al., 2022; Nilsson, 2008; Wright et al., 2017). These findings suggest that cardiovascular issues can manifest earlier than traditionally expected, and long-term undiagnosed exposure can result in increased stroke risk. Future research should focus on identifying early signs of cerebrovascular damage and evaluate the effectiveness of lifestyle changes, such as eating healthier, exercising, and stress management, in preventing vascular damage to reduce stroke risk.

Contrary to prior research that demonstrates that low income is associated with greater stroke risk and post-stroke mortality (Avan et al., 2019; Pantoja-Ruiz et al., 2025), this study found that odds of stroke were higher among individuals with higher income. One explanation may be that higher income in young adults often corresponds with longer work hours and high stress environments, leading to reduction in health maintenance, poor diets, and lower physical activity (Akkiraju & Rao, 2025; Wolfson et al., 2019). Nonetheless, individuals with higher income may have greater access to medical care (McMaughan et al., 2020), which could increase their likelihood of stroke diagnosis and survival, particularly given that this dataset is of stroke survivors. In contrast, individuals who selected “prefer not to say” for income also indicated elevated risk, a finding that may reflect the tendency for lower-income respondents to conceal financial information on surveys (Jabkowski & Piekut, 2024), and suggest an increase in stroke risk amongst this population. These findings

highlight the complexity of income and stroke risk in young adults and emphasizes the need for additional research to explore the relationship between income, stress, lifestyle, healthcare access, and survivor bias.

Interestingly, results indicate significantly reduced odds of stroke risk among Black individuals. These findings contradict established literature, which typically links minority populations to higher risk of stroke due to higher prevalence of hypertension and diabetes (Lackland, 2014; Lê Cook & Alegría, 2011; Sacco et al., 2001). Although the results of our study depict a protective effect of race among Black individuals, interpretations are limited due to the imbalance of Black participants between the case and control group. While genetic predispositions such as mutations to the Factor V gene may influence stroke risk (Hamedani et al., 2010), studies suggest that these variations in genetic risk do not always differ significantly by racial group (Armstrong et al., 2021). Additionally, Black young adults report lower prevalence rates of substance use (including marijuana, cocaine, sedatives, hallucinogens) (McCabe et al., 2007). Moreover, they have a reduced risk for certain stroke-related conditions, such as atrial fibrillation (Alonso et al., 2009), which may explain the lowered observed stroke risk. These findings, coupled with the results of the present study, suggest that genetic factors alone may not fully account for racial differences in stroke. Rather, other factors such as lifestyle, environmental exposures, social determinants of health, or unknown confounders may have a greater influence on stroke risk in young adults. Furthermore, given that this study is international, it is important for researchers to consider how race might influence stroke risk, as genetic factors may not be the same across regions or racial groups (Sukumaran et al., 2024). Researchers can further consider exploring how the intersection of race and geographic context influence stroke risk.

Geographical differences in stroke risk were also evident. Participants residing in Canada had higher odds of stroke compared to those in the USA, South Africa, and UK. The increased risk of stroke in Canada may be related to the shortage of primary care providers,

where nearly 20% of Canadians lack a family doctor and almost 50% are unable to see a primary care provider on the same or next day (Flood et al., 2023). Often, risk factors of stroke, such as hypertension are detected and managed by family physicians, and the inability to detect these chronic conditions early may explain these elevated risks. Notably, this study only includes individuals who survived a stroke, which may introduce survivor bias. Thus, this could explain that the apparent increase in stroke risk among Canadians may reflect higher survival of stroke among young adults in Canada, rather than true difference in underlying risk.

Several modifiable factors were significantly associated with stroke risk. Alcohol consumption appeared as a protective factor at all levels of consumption. Both light to moderate and moderate to heavy consumption were associated with reduced odds of a stroke. This finding aligns with studies suggesting that light-to-moderate alcohol use may reduce ischemic stroke (Sacco et al., 1999), though it contrasts with broader findings linking alcohol to increased cardiovascular risk, particularly in older adults (Chung et al., 2023). It is possible that the alcohol consumption may increase high-density lipoproteins and reduce certain markers of inflammation that contribute to atherosclerosis (Piano, 2017). Nevertheless, additional research is needed, particularly studies involving larger samples of heavy drinkers to better understand this association and to determine whether any potential benefits of alcohol consumption connected to stroke risk outweigh its other known health risks (e.g., liver cancer) (B. O. Anderson et al., 2023).

Consistent with previous literature, our findings depict that ex-smokers face an increased risk of stroke. Despite declining smoking rates over the past 50 years (Dai et al., 2022), and rising cessation success (Fu & Xiao, 2023), the long-term cardiovascular effects appear to persist. Ex-smokers in our study continued to show elevated stroke risk. Extensive literature supports that individuals are more likely to quit smoking after experiencing health issues or receiving medical advice (Duncan et al., 1992; Gallus et al., 2013; Pederson et al.,

1996). These findings, along with our results, highlight the residual effects of smoking on stroke risk, despite cessation.

Similarly, frequent marijuana use was associated with increased stroke risk, aligned with recent studies linking heavy marijuana use to a higher risk of stroke, particularly in young adults (Jeffers et al., 2024a; D. Liu et al., 2024). Emerging evidence suggests a possible association between prolonged marijuana use and reversible cerebral vasoconstriction syndrome (RCVS), a condition involving sudden narrowing/constriction of brain arteries, often accompanied by severe headaches (Nesheiwat & Al-Khoury, 2025). It is believed that tetrahydrocannabinol (THC) from marijuana may interact with cannabinoid receptors in the brain, which play an important role in vascular tone, to cause constriction issues of blood vessels and increase stroke risk (Burggren et al., 2019). Given that young adults represent that largest group of marijuana users (Patrick et al., 2016), they may be more susceptible to these adverse effects. However, these associations are not yet fully understood as research is still limited. Thus, additional research on marijuana use and stroke risk, particularly in young adults, is needed.

Our findings also reaffirm that both general physical and mental health are important predictors of stroke risk. Mental health plays an important, yet often overlooked, role in stroke research and may contribute through psychosocial stress, maladaptive coping, and unhealthy behaviors (Y. Liu et al., 2023; Reddin et al., 2022). It is important to note that awareness, diagnosis, and self-reporting of mental health conditions have increased in recent years compared to the past, which may also partly explain their stronger associations in contemporary studies. On the other hand, good physical health was associated with reduced stroke risk, likely reflecting healthier lifestyle behaviours. Body weight also emerged as another significant predictor as both underweight and overweight individuals had increased risk. While obesity is known to increase stroke risk through poor diet and comorbidities like hypertension, hypercholesterolemia, and diabetes (Quiñones-Ossa et al., 2021), underweight

status may reflect underlying health problems, including chronic diseases (Kwon et al., 2021), malnutrition (Di Vincenzo et al., 2023), or other undiagnosed conditions.

Sleep issues and migraines also appeared as important factors for underlying health issues that may contribute to stroke risk in young adults. The literature suggests that sleep disorders and deprivation are associated with psychosocial factors (e.g., mood disorders and stress) and biological factors (e.g., glucose imbalance), ultimately increasing stroke risk (Koo et al., 2018). However, our results indicate that sleep disorders may be a protective factor in stroke risk, contrary to most findings. Some researchers hypothesize that mild intermittent hypoxia during sleep apnea may trigger neurovascular preconditioning (low oxygen resistance), angiogenesis (improved blood flow from newly formed vessels), and cellular adaption (adaptation of cells to better survive stressful conditions such as low oxygen) (Beaudin et al., 2017; Pires Monteiro et al., 2021) to reduce stroke risk. Given that sleep deprivation and disorders are becoming increasingly more common in young adults (Chattu et al., 2018), further research is warranted to establish the positive or negative impact of sleep disorders/deprivation. In contrast, migraines were associated with increased stroke risk. Consistent with previous research, migraines, especially with aura, are believed to raise stroke risk through vascular mechanisms, such as vasospasm, endothelial damage, and clot formation (Hassan et al., n.d.; Scher & Launer, 2010). Despite this evidence, there is limited research on the potential causal relationship between regularly occurring migraines and stroke in young adults, and further exploration is needed.

Hypertension is a well-established risk factor for stroke, even in young adults. Our findings align with existing literature, demonstrating that hypertension increases stroke risk. Hypertension contributes to stroke risk through several mechanisms, including arterial and microvascular damage, accelerating atherosclerosis, and its influence on other lifestyle factors (Johansson, 1999b; Poznyak et al., 2022). The strong association between hypertension and stroke risk further reinforces the importance of managing individual blood

pressure, even in early adulthood, to reduce stroke risk. Counterintuitive to vast research, our results indicate that chronic conditions, such as heart disease, diabetes, and respiratory disease decreases stroke risk. These unexpected results may be due to the small number of participants with these conditions, which limits the statistical power to detect true effects. Future research should consider investigating the risk of these conditions, specifically in young adults.

3.5 Limitations

Despite the various novel insights and methodological gaps that our study fills in the literature, there are some limitations. Imbalances in sample characteristics, such as income, race, geographic region, and chronic conditions may have influenced some of the observed findings. Although stratification or weighted sampling techniques could be applied to address some of these imbalances, such as race, this could lead to issues of over-adjustment and loss of generalizability, especially given the matching technique already applied. Future studies should consider the inclusion of a more balanced sample in terms of the aforementioned risk factors to allow for a more accurate representation of a diverse sample.

Additionally, as this study utilizes a questionnaire, it is prone to recall bias, although most participants recently had their stroke. Similarly, given that this study uses self-reported data, there is potential of misclassification. Participants may misidentify their disease status or inaccurately report the timing of their ailment(s). For instance, participants may report being diagnosed with diabetes after their stroke, although it may have pre-existed and was just diagnosed later. Moreover, participants with significant cognitive impairments (which could limit the accuracy of their responses) were excluded from the study. Given the cross-sectional nature of this study, the ability to make causal inferences about the risk factors of interest is also limited. Future research should consider exploring how risk factors, such as

chronic conditions (e.g., hypertension), evolve over time in young adults and contribute to stroke risk.

3.6 Conclusion

Our case-control study provides valuable insights into both established and emerging risk factors of stroke, particularly in young adults, through a comprehensive and multifactorial approach. Consistent with other research, age, hypertension, poor physical and mental health, and various lifestyle factors, such as marijuana and smoking were all significant risk factors of stroke. Nonetheless, the study also uncovered various novel and unexpected findings. For example, participants who reported high-income, sleep disorders, moderate to heavy alcohol consumption, and identified as Black had lower risk of stroke. Together, these findings both support and challenge the conventional assumptions about stroke risk in young adults, further underscoring the complexity of the etiology and causes of stroke in this population.

This study makes a unique contribution to current stroke literature by integrating both established and emerging risk factors, such as mental health, lifestyle factors, chronic diseases and infections, and sociodemographic factors in a single exploratory regression model. Additionally, it is the first to examine both pre-and post-stroke data in young adults in addition to the various aforementioned risk factors; thus, offering a novel and holistic perspective on stroke risk and its temporality. By using a large international dataset and applying a conditional multiple logistic regression analysis with a matched case-control design, we provide more generalizable findings that fill methodological gaps in the existing literature.

Our findings have important implications for public health and healthcare policies. Early detection and prevention strategies are needed, especially for young adults who may be at risk. Promoting cardiovascular health, managing stress and mental health (which are

crucial to physical health), and addressing harmful lifestyle factors are essential. Policies should be aimed at expanding access to primary care, specifically for diagnosing stroke risk factors to enable early management and prevent serious health outcomes. Lastly, health education is needed to inform individuals on the increase of stroke rates in young adults and the risk factors that may be responsible for this concerning rise.

Chapter 4

Caffeine Consumption and Stroke Risk in Young Adults: A Global Case-Control Study

Abstract

Background:

Despite growing concerns of rising stroke rates in young adults, little is known about emerging risk factors that may be uniquely impacting younger populations, such as caffeine. The purpose of this study is to examine the linear and non-linear relationship between total, dose-specific, and source-specific caffeine consumption and stroke in young adults aged 18-50.

Methods:

This study utilized a matched 1:2 case-control study design of 1,277 participants, including 435 stroke cases, with matching based on biological sex. Using data from a cross-sectional questionnaire, this study included questions regarding demographics, lifestyle, pre-existing health conditions, and average daily caffeine consumption. Three regression models were conducted to assess the linear and non-linear relationship between caffeine and stroke risk. The models included a crude conditional logistic regression, an adjusted conditional logistic regression, and a restricted cubic splines conditional logistic regression. Total caffeine intake was analyzed per 25 mg/day to provide interpretable effect estimates.

Results:

Crude conditional logistic regression indicated that total caffeine consumption was associated with a decreased risk of stroke (OR=0.972, 95% CI: 0.959-0.986, $p<0.001$). After adjusting

for confounders, the adjusted model also demonstrated decreased risk of stroke (OR=0.987, 95% CI: 0.976-0.998, $p<0.05$). Findings of the restricted cubic splines model indicated a possible non-linear relationship between caffeine source and stroke risk. Generally, lower levels of consumption (≤ 1 serving) of sources, such as tea, soda/pop, and other caffeine sources (e.g., energy drinks, caffeine pills/shots, and pre-workout supplements) were associated with reduced stroke risk, while higher levels of consumption (>1 serving/day) were associated with increased risk. However, lower levels of coffee consumption were associated with increased risk (OR=1.063, 95% CI: 0.977-1.157, $p=0.155$), and higher levels of consumption (>1 to 4 cups/day) decreased risk of stroke (OR=0.894, 95% CI: 0.803-0.995, $p<0.05$).

Discussion:

This study highlights the complex relationship of caffeine and stroke risk in young adults. While lower levels of caffeine may decrease stroke risk, increased consumption may increase risk; however, these effects vary by caffeine source. The findings demonstrate the non-linear relationship of caffeine and emphasize the need for additional research to further establish the possible protective or adverse effect of caffeine on stroke risk.

4.1 Introduction

The global incidence of stroke in young adults continues to increase, indicating a growing public health concern (Bukhari et al., 2023a). While rates of stroke in older adults have generally declined, younger populations are experiencing a troubling rise. For example, a cohort study in England reported a nearly 70% increase in stroke incidence among individuals aged 18 to 55 between 2002 and 2018, while rates decreased by 15% for those older than 55 during the same period (L. Li et al., 2022). Interestingly, this increase was not observed in other cardiovascular diseases, such as myocardial infarction, suggesting that the risk factors contributing to the rising stroke rates in young adults may differ from other

vascular events and older adults (L. Li et al., 2022). As such, various research has raised important questions regarding the potential influence of risk factors that may uniquely contribute to stroke risk in young adults. One such factor is caffeine consumption, which has received relatively little attention in the context of stroke research in young adults.

Globally, caffeine is the most commonly used central nervous system stimulant, often consumed through beverages, such as coffee, tea, and soda (Fiani et al., 2021). Caffeine consumption is increasing universally (Cappelletti et al., 2015), with significant increases in consumption of energy drinks, particularly among young adults (Reid et al., 2017; Tran et al., 2016). For example, United States data from the mid-2010s illustrates that 85% of adults reported consuming at least one caffeinated beverage daily (D. C. Mitchell et al., 2014), and among young adults, 86% reported caffeine consumption within the past month (Kelly & Prichard, 2016). Given the widespread consumption, understanding the potential health impact of caffeine, particularly in stroke risk, has become increasingly important.

Current evidence on caffeine consumption and stroke risk is limited and inconsistent. While some studies suggest a harmful association, others suggest a protective effect. For example, a large international case-control study found that high consumptions of coffee were associated with an increased risk of stroke (Smyth et al., 2024). Another study reported that the estimated risk of ischemic stroke nearly doubled in the hour following coffee consumption (Mostofsky et al., 2010). Moreover, coffee consumption has been associated with adverse effects, including sitting, heavy smoking, and decreased physical activity, which may all contribute to the increased stroke risk (Shao et al., 2021). Mechanistically, caffeine is an adenosine receptor antagonist, meaning it blocks adenosine, which is essential for maintaining one's blood flow and heart rate (Marcinek et al., 2024). As a result of its chemical properties, caffeine consumption can lead to increased heart rate, vasoconstriction, and increased blood pressure (Green et al., 1996), reflecting the possible increase in stroke risk.

However, some researchers have reported beneficial effects of caffeine in relation to stroke risk. A meta-analysis identified various cohort studies demonstrating a preventive effect of coffee on stroke (B. Kim et al., 2012). Similarly, a prospective large cohort study found that drinking 2-3 cups of coffee or 3-5 cups of tea daily significantly reduced stroke risk (Y. Zhang et al., 2021). Comparable findings can be noted in various other studies depicting an inverse relationship between coffee consumption and stroke risk (B. Kim et al., 2012; Kokubo et al., 2013; Larsson et al., 2008). Yet, other researchers have documented no association between caffeine consumption and stroke risk. For example, a systematic review and meta-analysis examining the dose-response of coffee consumption and stroke risk found no association between coffee intake across studies (Shao et al., 2021). Similarly, an examination of various case-control and cohort studies found no association between coffee consumption and stroke subtypes (Rui et al., 2019). In all, given the inconsistent evidence in the existing literature of caffeine and stroke, additional research is needed, particularly in young adults, who are increasingly affected by stroke and increasingly exposed to caffeine through energy drinks and other sources targeted towards younger age groups (Vercammen et al., 2019). Additional research is necessary to provide evidence that can inform policy efforts that are aimed at reducing the potential harm of highly caffeinated beverages.

4.1.1 Gaps in the Literature

As mentioned previously, research examining the impact of caffeine on stroke remains limited, particularly on younger adults, as most studies focus on older populations (Greenberg et al., 2008; Larsson et al., 2008; Silletta et al., 2007; Y. Zhang et al., 2021). Majority of research also isolates individual sources of caffeine, such as coffee (Greenberg et al., 2008; Rui et al., 2019; Shao et al., 2021), tea (Shen et al., 2012; Tian et al., 2020), or energy drinks (Alsunni, 2015; Sinha et al., 2024), rather than assessing total caffeine intake. Examining a single source of caffeine is problematic, particularly in young adults, who often consume caffeine from multiple sources, making single source analyses insufficient in capturing true effects. While some studies have examined multiple sources of caffeine, such

as tea and coffee (Y. Zhang et al., 2021), they have largely excluded other important sources, such as energy drinks. Energy drinks often contain additional supplements, including taurine, l-carnitine, guarana, and ginseng, which may negatively impact cardiovascular and cerebrovascular health (Seifert et al., 2011). The lack of research examining the combined effects of various caffeine sources presents a notable gap in the literature, especially considering the growing popularity of certain caffeine beverages (e.g., energy drinks, pre-workout supplements, and caffeine shots) in young adults.

Moreover, the majority of research fails to incorporate the complex, multifactorial nature of stroke risk. To our knowledge, limited research has adjusted for a wide range of sociodemographic, psychosocial, lifestyle, and health condition factors in their modelling approaches (Shao et al., 2021), possibly limiting their ability to detect true effects. Understanding the interactions of these factors is essential, particularly in young adults, whose stroke risk may be influenced by different environmental and biological mechanisms than those of older adults. The current lack of detailed information on these risk factors prevents researchers from truly understanding the complexity of stroke risk, especially in young adults. Furthermore, the majority of existing literature assumes a linear association between caffeine consumption and stroke, despite evidence suggesting that a non-linear pattern may exist. Considering these research gaps, a more comprehensive approach is needed.

4.1.2 Study Objectives

To address the aforementioned limitations, the present study aims to examine the impact of total caffeine consumption, dose-specific, and source-specific effects on stroke risk among young adults aged 18-50. Specifically, this study will examine the risk of stroke in relation to consumption of coffee, tea, and other highly caffeinated beverages (e.g., energy drinks, caffeine pills/shots, pre-workout supplements), that are commonly consumed in this

population. By examining various caffeine sources, this study provides a more nuanced understanding of how total daily intake and dose-and source-specific consumption relate to stroke risk.

Moreover, this study incorporates a multifactorial analysis, adjusting for covariates, such as demographic characteristics, lifestyle choices, pre-existing health conditions and emerging risk factors, such as mental health and stimulant use. This approach accounts for the complexity of stroke in young adults and aims to further clarify how caffeine may be impacted by broader behavioural and psychosocial factors. To our knowledge, this study is the first to identify and address the lack of temporal clarity in the existing cross-sectional research examining caffeine consumption and stroke risk. The timing of pre-existing health conditions will be recorded relative to stroke onset for temporal clarity. Further, the relationship between the timing of the risk factors and caffeine intake will be included to provide additional insight into how these conditions may influence stroke risk.

Apart from the novel contributions of this work, the ultimate goal of this research is to inform age-specific interventions. Given that caffeine is shown to increase stroke risk in young adults, findings of this study could support targeted education campaigns in settings of high caffeine consumption, such as universities and fitness centres. If total caffeine consumption or specific sources are found to be protective factors, our results may support its role in prevention and potential treatment strategies. However, it is possible that no statistically significant association is found between caffeine (total, source, and/or dose) and stroke risk, as some studies have found no relationship at all (Shao et al., 2021). Ultimately, this study may serve as foundational research in the assessment of source-and-dose-specific effects of caffeine, and guide future research into examining the mechanistic pathways associated with different caffeine sources and total consumption. Given the widespread use of caffeine among young adults (Kelly & Prichard, 2016), this research is essential in

understanding the potential role of caffeine as a modifiable risk factor in the early onset of stroke.

4.2 Methods

4.2.1 Study Design

This study uses a case-control design to examine the association between caffeine consumption and stroke risk in young adults. Cases and controls were matched by biological sex (male or female), with a single case matched to two controls. Given that there was an uneven proportion of males and females, as well as an insufficient number of controls to have precise 1:2 matching, some of the strict matching had to be relaxed with some cases only having 1 control. Cases included individuals who self-reported a diagnosis of an ischemic, hemorrhagic, and/or transient ischemic stroke that occurred between 18 to 50 years old. Controls included individuals aged 18 to 50 who had no history of stroke. Although the term “young adult” can vary in stroke literature, the present study defines “young adult” as being 18-50 years-old, consistent with various other research (Ekker et al., 2019; Bukhari, Yahi, & Bashir, 2023; Rutten-Jacobs et al., 2013). The stroke cases for this study were primarily recruited from local and international hospitals, stroke post-care centres, stroke survivor groups, and social media. Participants were recruited from diverse avenues to capture a wide range of stroke severity, not including fatal cases. Conversely, the controls were recruited through a research participant recruitment firm. Specifically, Prolific's global participant database was utilized for recruitment of the control group. Ethics approval was granted by the University of Waterloo's Research Ethics Board in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

The questionnaire collected comprehensive data regarding participants' demographics (e.g., age, biological sex, income), health history (e.g., hypertension), etiology (e.g., patent foramen ovale), chronic infections (e.g., syphilis), mental health (e.g., depression), and

lifestyle (e.g., substance use). To ensure the validity of the questionnaire, established instruments were utilized, including the *National College Health Assessment-American College Health Assessment*, *Canadian Community Health Survey*, and the *Canadian Health Measures Survey*. When necessary, new items were created based on relevant literature. For instance, physical activity was not assessed by frequency alone, but rather by number of weekly moderate to intense exercise sessions (Prior & Suskin, 2018). To ensure data quality, responses that were submitted prior to the minimum completion time or those who failed attention checks in the questionnaire were excluded from the analysis.

4.2.2 Data Analysis

The primary outcome of interest was stroke status, which was categorized as yes, or no. The main predictor of interest was total caffeine intake, as well as dose-and source-specific consumption. Total caffeine consumption was obtained by the sum of daily servings of caffeine beverages, such as coffee, tea, soda/pop, energy drinks, caffeine pills/shots, and pre-workout supplements. Specifically, participants were asked to report their average daily consumption in servings or cups for each source (prior to stroke onset for cases). To obtain a more accurate measure of the total caffeine consumption, each serving was converted to its estimated caffeine content (i.e., tea=40 mg, coffee=100mg, soda=25mg), based on standard references (Bunker & McWilliams, 1979; Institute of Medicine of the National Academies, 2014). By calculating a sum of average daily caffeine intake scores, we could ensure variability in caffeine concentration across different sources was accurately reflected in the total estimate.

Considering the possible linear and non-linear association between caffeine consumption and stroke risk, three types of conditional regression analyses were conducted:

1. Crude conditional logistic regression: Evaluation of the association between total average daily caffeine intake and stroke risk.

2. Adjusted conditional logistic regression: Evaluation of the association between total average daily caffeine intake and stroke risk, while controlling for various risk factors.
3. Conditional logistic regression with restricted cubic splines: Evaluation of the non-linear dose-response of specific caffeine sources and stroke risk.

Given the small response rates of high caffeine sources, such as energy drinks, caffeine pills/shots, and pre-workout supplements, these were collapsed into a single “Other Caffeine Sources” category to preserve statistical power and ensure reliable estimates. All models except the crude model adjusted for potential confounders, including demographic variables (e.g., age, race), health-related conditions (e.g., diabetes and hypertension status), drug, alcohol, and smoking status, and lifestyle factors (e.g., exercise and eating habits). As missing data was minimal (less than 7%), a complete case analysis was done.

Age was grouped into categories to allow for meaningful comparison between the age at which cases had a stroke to the current age of the controls. This approach helped minimize recall bias regarding the timing of stroke onset and allowed for more straightforward age comparisons between the cases and controls. Given that cases could currently be older (e.g., 55 but had their stroke within the age range of 18 to 50), age categorization allowed us to make meaningful comparisons between groups.

Health-related variables were converted into binary responses to gain temporal information. Specifically, participants were asked to report whether their medical diagnoses occurred before or after their stroke, when applicable. Although a cross-sectional design limits the ability to draw direct causal inferences, this approach offers a practical means to approximate possible temporal associations in the absence of repeated measures or longitudinal data. For example, heart disease diagnosis was originally categorized as:

“No diagnosis”

“Yes, diagnosed BEFORE having a stroke”

“Yes, diagnosed but NEVER had a stroke”

“Yes, diagnosed AFTER having a stroke”

To capture temporal insight, the variable was recategorized as follows:

“No, remained “No”.

“Yes, diagnosed AFTER having a stroke” was also categorized as “No” as it does not provide information on the temporal relationship prior to stroke onset.

“Yes, diagnosed BEFORE having a stroke” and “Yes, diagnosed but NEVER had a stroke” were recoded as “Yes”.

The splines model included three knots, placed at the 5th, 50th, and the 95th percentile for each caffeine source, corresponding with the typical ranges of intake for each source. However, due to the low dose consumption of “other caffeine sources” (e.g., energy drinks, caffeine pills/shots, energy drinks) these knots had to be adjusted to avoid repetition (i.e., 0 at both the 5th and 50th percentile). Accordingly, the knots of tea were 0, 1, and 3 cups, coffee were 0, 1, and 4 cups, pop/soda were 0, 1, and 3 cups, and other caffeine sources were 0, 1, and 2 servings. Ideally, four splines would provide additional information as 0 servings would be its own category; however, due to the limited sample and loss of data with the use of cubic splines, this was not possible.

All regression models were evaluated for model assumptions, including multicollinearity, independence, and unmeasured confounding, ensuring reliable estimates based on the data. As participant data was collected from various avenues (e.g., hospitals, rehabilitation centres, and social media) in 58 countries, we assume that each response is independent from one another. To prevent overfitting, the models only included well-established traditional risk factors (e.g., hypertension, obesity, smoking) and relevant emerging risk factors (e.g., mental health) that may influence stroke risk. Additionally, variables with low response categories were collapsed to ensure reliability of estimates. The

statistical analyses were performed in RStudio (Version 2024.12.0+467) (*Posit*, 2025) and R (Version 4.5.1) (R Core Team, 2025).

4.3 Results

4.3.1 Descriptive Statistics of Sample

Table 8 presents the demographic characteristics of the study sample. In total, 1,277 responses were collected, including 435 cases and 842 controls, with an average age of 39 years old for cases and 31 years old for controls. Cases were predominantly White (76%) and females (57.8%), while controls were more racially diverse (47.7% White, 35.2% Black), with a smaller proportion of females (45.4%). Geographically, the majority of cases resided in the USA (59.45%), while controls primarily lived in the USA (34.31%), UK (18.37%), or South Africa (16.45%). Full details of the sample demographic characteristics can be found in Table 8.

Table 8 Demographic Characteristics of Sample

Variable	Cases (%)	Controls (%)
Age	Mean: 39 Years old Min: 18 Max: 75	Mean: 31 Years old Min: 18 Max: 55
Country of Residence:		
Australia	2.73	0.13
Belarus	0.42	0
Belgium	0.63	0.13
Canada	16.18	3.70
Denmark	0.21	0.26
Germany	1.47	0.77

Greece	0.42	1.79
India	3.36	0.77
Ireland	1.05	0.38
Netherlands	0.84	0.64
Philippines	1.68	0.26
South Africa	0.84	16.45
United Kingdom of Great Britain and Northern Ireland	6.09	18.37
United States of America	59.45	34.31
Other	4.62	22.07
Sex at Birth		
Female	57.77	45.41
Male	41.81	53.70
Prefer not to say	0.42	0.51
Race		
Arab	0.21	0.64
Black	2.73	35.20
Chinese	2.10	1.02
Filipino	1.89	0.51
Indigenous	1.47	0.13
Korean	0.21	0.38
Latin American	3.36	3.70
Mixed race	3.36	4.34
South Asian (e.g., East Indian, Pakistani, Sri Lankan)	4.83	3.06
Southeast Asian (e.g., Vietnamese, Cambodian, Laotian, Thai)	1.68	1.15
West Asian (e.g., Iranian, Afghan)	0.21	0.00
White	76.05	47.70
Other	1.89	1.40

Income		
Less than \$40,000 USD (Less than \$53,000 CAD, €35,000 EUR, less than \$54,000 AUD)	25.00	38.90
Between \$41,000 USD to \$67,000 USD (\$54,000 to \$85,000 CAD, €35,000 to €56,000 EUR, \$54,000 to \$85,000 AUD)	15.12	20.79
Between \$68,000 to \$83,000 (\$86,000 to \$105,000 CAD, €56,000 to €68,000 EUR, \$86,000 to \$105,000 AUD)	10.92	13.65
Between \$84,000 to \$184,000 (\$106,000 to \$235,000 CAD, €68,000 to €155,000 EUR, \$106,000 to \$235,000 AUD)	26.68	18.37
More than \$185,000 (more than \$236,000 CAD, €155,000 EUR, more than \$236,000 AUD)	11.13	3.57
Prefer not to say	11.13	4.33

Table 8 presents the descriptive statistics of the demographic characteristic of the sample (n=1,277, Cases=435, Controls=842). The table includes information on participants' country of residence, biological sex, race, relationship status, income, and employment status.

4.3.2 Health and Lifestyle Factors

Table 9 displays the prevalence rates of biological, psychosocial, and lifestyle factors related to participants' health and stroke risk. Pre-stroke data for cases generally indicate poorer physical and mental health. Notably, the case group indicated 15.34% and 24.37% “poor” physical and mental health, compared to 5.21% and 12.27% in the control group, respectively. Further, frequent consumption of alcohol, marijuana, and smoking was also higher in the case group. The prevalence of health-related risk factors were generally higher among cases than controls. For instance, cases exhibited higher rates of high blood pressure (39.92% in contrast to 13.76% of controls), regularly occurring migraines (41.17% in contrast to 26.39% of controls), and sleep disorders (51.89% in contrast to 42.27% of controls).

Table 9 Distribution of Sample Health history, Illness, Disease and Other Stroke Related Factors

Variable	Cases (%)	Controls (%)
Physical Health		
Excellent	7.14	12.16
Very good	21.85	33.12
Good	26.05	30.51
Average	28.99	19.00
Poor	15.34	5.21
Mental Health		
Excellent	5.88	14.33
Very good	20.79	27.47
Good	22.69	23.78
Average	25.84	22.15
Poor	24.37	12.27
Body Weight		
Very underweight	1.77	0.65
Slightly underweight	7.08	8.62
About the right weight	38.05	51.04
Slightly overweight	28.32	32.61
Very overweight	24.78	7.09
Smoking		
Never	72.24	67.29
Ex-Smoker	12.55	17.72
1 to 10 cigarettes per-day	9.51	12.80
Greater than 10 cigarettes per-day	5.70	2.19

Average Monthly Marijuana Consumption		
Never	69.96	78.82
1 to 3 times a month	11.79	11.03
1 to 3 times a week	4.94	4.15
3 to 5 times a week	5.32	0.65
Daily	7.98	0.44
Alcohol Use Weekly Avg		
0 grams of alcohol per-week	44.75	37.84
Between 1 to 150 grams	24.79	51.47
Between 150 to 300 grams	23.53	8.72
Greater than 300 grams	3.99	1.96
Heart Disease		
No	92.02	94.86
Yes, diagnosed AFTER having a stroke	4.62	NA
Yes, diagnosed BEFORE having a stroke	2.94	NA
Yes, diagnose but NEVER had a stroke	NA	4.70
High Blood Pressure		
No	59.24	83.95
Yes, diagnosed AFTER having a stroke	17.23	NA
Yes, diagnosed BEFORE having a stroke	22.69	NA
Yes, diagnose but NEVER had a stroke	NA	13.76
Sleeping disorder		
No	48.11	55.12
Yes, diagnosed AFTER having a stroke	18.07	NA

Yes, diagnosed BEFORE having a stroke	33.82	NA
Yes, diagnose but NEVER had a stroke	NA	42.27
Regular Migraines		
No	58.61	71.97
Yes, AFTER having a stroke	12.39	NA
Yes, BEFORE having a stroke	28.78	NA
Yes, diagnose but NEVER had a stroke	NA	26.39

Table 9 presents the distribution of participants overall self-reported physical and mental health, lifestyle factors, substance use, and health related factors in relation to stroke onset (n=1,277).

4.3.3 Patterns of Caffeine Consumption

The distribution of average daily caffeine consumption for cases based on different sources is summarized in Table 10. Results indicate that the consumption of other caffeine sources (e.g., energy drinks, caffeine pills/shots, and pre-workout supplements) was low among the sample. A notable proportion of participants reported consuming soda/pop (33.65%), coffee (32.94%), tea (29.10%) once per/day on average. Coffee had the highest reported consumption for more than one daily serving on average, with 33.73%, followed by tea (24.31%). Table 11 indicates a crosstabulation of the average daily consumption of caffeine based on varying sources. All caffeine data from cases reflects consumption prior to their stroke. In comparison to controls, cases reported lower average daily consumption of all caffeine sources, except coffee. Specifically, cases consumed more coffee (1.59 cups, compared to 1.29 cups for controls), but less tea (0.78 cups, compared to 1.14 cups of controls). Cases also had lower consumption of energy drinks, caffeine shots/pills, and pre-workout supplements.

Table 10 Proportion of Self-Reported Average Daily Consumption of Caffeine Sources

Variable	0 Serving (No Consumption)	1 Serving	More Than 1 Serving
Tea	46.59	29.10	24.31
Coffee	33.33	32.94	33.73
Soda/Pop	46.35	33.65	20.00
Small Energy Drink	81.25	12.47	6.27
Large Energy Drink	88.94	7.84	3.22
Caffeine Pill/Shot	95.92	2.20	1.88
Pre-Workout	86.98	8.55	4.47

Table 10 presents the proportion of average pre-stroke daily consumption of caffeine based on commonly consumed sources for cases (n=435). The distribution per-source varies between 0 servings to more than 1.

Table 11 Crosstabulation of Average Caffeine Source Consumption and Stroke Status

Stroke Status	Cups of Tea	Cups of Coffee	Cans Pop/Soda	Small Energy Drink	Large Energy Drink	Caffeine Shot or Pill	Serving of Pre-Workout
Control (No)	1.14	1.29	1.21	0.47	0.27	0.12	0.33
Case (Yes)	0.78	1.59	1.15	0.26	0.20	0.04	0.16

Table 11 presents data on the distribution of average daily serving between cases and controls based on caffeine source (pre-stroke for cases) (n=1,277, 842 controls, 335 cases).

4.3.4 Conditional Logistic Regression

Total caffeine intake was analyzed per 25 mg/day to provide interpretable effect estimates. Table 12 indicates the results of the crude logistic regression analysis. The model predicts the risk of stroke in young adults based on total average daily caffeine consumption. The results indicate that the total average daily consumption has a statistically significant, and protective association with stroke risk (OR=0.972, 95% CI: 0.961-0.982, p<0.001). Specifically, the

results indicate that for each 25 mg increase in the average daily caffeine consumption, the odds of stroke in young adults decrease by 2.8%. After adjusting for potential confounders (Table 13), including demographics, lifestyle, and health conditions, the effect of total daily consumption remained similar (OR=0.987, 95% CI: 0.974-0.999, $p<0.05$). Specifically, in the adjusted model, each 25 mg increase in daily caffeine intake was associated with an approximate 1.3% reduction in stroke risk. Although the results may be statistically significant, the effect size of total caffeine intake in the adjusted model is extremely small and the confidence interval bounds are close to the null value of 1. Nonetheless, it is important to note that caffeine is typically consumed in multi-milligram doses (e.g., typical coffee contains ~100 mg, corresponding to roughly a 5% reduction in stroke risk).

Table 12 Crude Conditional Logistic Regression Model of Predicted Stroke Risk Based on Caffeine Consumption

Variable	Odds Ratio	Lower CI	Upper CI	P-Value
Total Caffeine ***	0.972	0.961	0.982	0.000

Significant codes: 0 '***' 0.001 '**' 0.01 '*' 0.05

Table 12 presents data on the output of a crude conditional logistic regression modelling stroke risk based on per/25 mg increase for total average daily caffeine consumption (n=434 pairs).

Table 13 Adjusted Conditional Logistic Regression Analysis Predicting Stroke Risk Based on Caffeine Consumption

Variable (Reference Category)	Odds Ratio	Lower CI	Upper CI	P-Value
Total Caffeine *	0.988	0.977	0.999	0.041
Age (Ref: 18-24 years old)				
25-30 years old ***	1.848	1.288	2.652	0.001

31-35 years old ***	3.847	2.738	5.406	0.000
36-40 years old ***	3.241	2.248	4.673	0.000
41-50 years old ***	4.599	3.383	6.252	0.000
Income (Middle Income)				
High Income ***	2.366	1.751	3.199	0.000
Low Income	0.787	0.579	1.069	0.126
Prefer not to say ***	4.737	2.665	8.421	0.000
Alcohol consumption (Ref: None)				
Light-to-Moderate drinking ***	0.552	0.415	0.735	0.000
Moderate-to-Heavy drinking ***	0.371	0.216	0.636	0.000
Marijuana use (Ref: Never)				
3 or More times a week ***	3.320	1.915	5.757	0.000
Up to 3 times a week	1.220	0.764	1.951	0.405
Smoking Status (Ref: Never)				
Current smoker *	0.321	0.321	0.920	0.023
Ex-smoker *	1.450	1.020	2.062	0.038
Physical Health (Ref: Average)				
Good to Excellent *	0.739	0.550	0.992	0.044
Poor	1.202	0.745	1.939	0.450
Mental Health (Ref: Average)				
Good to Excellent	0.917	0.690	1.218	0.548

Poor **	1.658	1.161	2.367	0.005
Weight (Ref: About the right weight)				
Overweight	1.105	0.833	1.465	0.490
Underweight	1.632	0.996	2.674	0.052
Family History of Stroke (Ref: No)				
Yes	1.155	0.855	1.562	0.348
Race (Ref: White)				
Black ***	0.157	0.092	0.268	0.000
Latin American	0.897	0.456	1.768	0.754
Mixed race	0.719	0.337	1.533	0.393
Other	0.885	0.543	1.441	0.622
South Asian (e.g., East Indian, Pakistani, Sri Lankan)	1.164	0.561	2.417	0.683
Hypertension (Ref: No)				
Yes **	1.741	1.204	2.516	0.003
Heart Disease (Ref: No)				
Yes	1.483	0.709	3.101	0.295

Significant Codes: 0 '*' 0.001 '**' 0.01 '*' 0.05**

Table 13 presents the output of an adjusted conditional logistic regression modelling stroke risk based on per/25 mg increase total average daily caffeine consumption (n=434 pairs). The model adjusts for covariates such as pre-stroke medical history, lifestyle factors, substance use, and demographic characteristics.

4.3.5 Conditional Logistic Regression with Restricted Cubic Splines

Table 14 presents the results of the adjusted conditional logistic regression with restricted cubic splines. The results indicate that the dose-and source-response of caffeine consumption and stroke risk are non-linear, compared to no consumption. Tea consumption of ≤ 1 cup/day was associated with a statistically significant decrease in stroke risk (OR=0.752, 95% CI: 0.687-0.822, $p<0.001$), while >1 to 3 cups/day resulted in significantly increased risk of stroke (OR=1.311, 95% CI: 1.167-1.474, $p<0.001$). Similarly, ≤ 1 serving/day of pop/soda decreased risk of stroke (OR=0.886, 95% CI: 0.851-0.922, $p<0.001$), and >1 to 3 servings/day increased risk (OR=1.047, 95% CI: 1.019-1.076, $p<0.01$). Although ≤ 1 serving/day of other caffeine sources also decreased stroke risk (OR=0.521, 95% CI: 0.454-0.598, $p<0.001$), the increase in stroke risk was notably higher with consumption of >1 to 2 servings/day (OR=1.788, 95% CI: 1.651-1.979, $p<0.001$). Coffee consumption also depicted a non-linear association with stroke risk. However, for lower levels of coffee consumption (≤ 1 serving/day), the risk of stroke was slightly higher (OR=1.063, 95% CI: 0.977-1.157), although not statistically significant. For higher levels of coffee consumption (>1 to 4 cups/day), the risk of stroke decreased (OR=0.894, 95% CI: 0.803-0.995, $p<0.05$), suggesting that coffee may have a protective effect at higher levels of consumption.

Table 14 Adjusted Conditional Logistic Regression with Restricted Cubic Splines Predicting Stroke Risk Based on Caffeine Dose and Source

Variable (Reference Category)	Odds Ratio	Lower CI	Upper CI	P-value
Caffeine Sources				
Tea consumption ≤ 1 cup/day ***	0.752	0.687	0.822	0.000
Tea consumption > 1 to 3 cups/day ***	1.311	1.167	1.474	0.000
Coffee consumption ≤ 1 cup/day	1.063	0.977	1.157	0.155

Coffee consumption >1 to 4 cups/day *	0.894	0.803	0.995	0.040
Pop/Soda consumption ≤ 1 serving/day ***	0.886	0.851	0.922	0.000
Pop/Soda consumption >1 to 3 servings/day **	1.047	1.019	1.076	0.001
Other Caffeine Source consumption (e.g., Energy drinks, caffeine shots/pills, pre-workouts) ≤ 1 serving/day ***	0.521	0.454	0.598	0.000
Other Caffeine Source consumption (e.g., Energy drinks, caffeine shots/pills, pre-workouts) >1 to 2 servings/day ***	1.788	1.615	1.979	0.000
Mental Health (Ref: Average)				
Good to Excellent	0.955	0.732	1.247	0.736
Poor *	1.454	1.034	2.045	0.031
Age (Ref: 18-24 years old)				
25-30 years old *	1.507	1.085	2.094	0.015
31-35 years old ***	2.430	1.756	3.362	0.000
36-40 years old ***	2.039	1.449	2.869	0.000
41-50 years old ***	2.599	1.941	3.481	0.000
Income (Ref: Middle Income)				
High Income ***	1.815	1.366	2.412	0.000
Low Income	0.851	0.640	1.130	0.264
Prefer not to say ***	3.144	1.850	5.343	0.000

Alcohol consumption (Ref: None)				
Light-to-Moderate drinking **	0.648	0.496	0.846	0.001
Moderate-to-Heavy drinking **	0.417	0.251	0.693	0.001
Marijuana Consumption (Ref: None)				
3 or More times a week **	2.171	1.298	3.632	0.003
Up to 3 times a week	1.032	0.663	1.606	0.889
Smoking Status (Ref: Never)				
Current smoker	0.742	0.465	1.184	0.210
Ex-smoker	1.308	0.940	1.819	0.111
Physical Health (Ref: Average)				
Good to Excellent	0.899	0.681	1.187	0.452
Poor	1.105	0.705	1.734	0.663
Weight (Ref: About the right weight)				
Overweight	1.061	0.815	1.381	0.662
Underweight *	1.612	1.030	2.525	0.037
Family History of Stroke (Ref: No)				
Yes	1.083	0.818	1.434	0.576
Race (Ref: White)				

Black ***	0.318	0.209	0.484	0.000
Latin American	0.818	0.451	1.721	0.710
Mixed race	0.820	0.403	1.668	0.584
Other	0.847	0.534	1.345	0.482
South Asian (e.g., East Indian, Pakistani, etc.)	1.463	0.761	2.816	0.254
Hypertension (Ref: No)				
Yes ***	2.610	1.936	3.518	0.000
Heart Disease (Ref: No)				
Yes	1.627	0.934	2.834	0.086

Significant codes: 0 '***' 0.001 '**' 0.01 '*' 0.05

Table 14 presents the output of an adjusted conditional logistic regression with restricted cubic splines modelling stroke risk based on the dose and source of daily caffeine consumption (n=434 pairs). The model adjusts for covariates, such as pre-stroke medical history, lifestyle factors, substance use, and demographic characteristics.

4.4 Discussion

This study provides novel insights into the association between caffeine consumption and stroke risk in young adults, emphasizing the role of both total daily caffeine intake and the non-linear effect of dose-and source-specific caffeine. A unique contribution of this study is the exploration of how various sources of caffeine, including tea, coffee, soda/pop, and other sources may uniquely influence stroke risk in young adults. While the association between caffeine consumption and stroke has been widely debated, our findings underscore the complexity of caffeine consumption on stroke risk, specifically the quantity and the source.

Literature on the effects of caffeine on cardiovascular health have largely yielded mixed results. While some studies indicate that moderate caffeine intake is associated with

reduced risk of cardiovascular disease (Larsson & Orsini, 2011), others have suggested negative effects of excessive caffeine intake (Grasser et al., 2016). Specifically, sources such as energy drinks, have been shown to increase blood pressure and potentially increase stroke risk (Grasser et al., 2016). These studies suggest that caffeine's impact on stroke risk may be dose-and source-dependent and may further be impacted by individuals' health profiles. The findings of our study align with this ongoing discourse, suggesting that moderate levels of caffeine consumption, particularly in young adults, could have a protective effect on stroke risk.

The crude conditional logistic regression model of the present study revealed a slight reduction in stroke risk with increased caffeine consumption. These findings align with the growing body of research that suggests that caffeine may have a potential protective neurological effect (Nehlig, 2016). Similarly, the adjusted model (including factors such as age, family history of stroke, lifestyle factors, and health conditions) demonstrated a small (1.3% per/25mg decrease), yet statistically significant reduction in stroke risk. Nonetheless, this association is consistent with other studies which report similar modest reductions in stroke risk with increased caffeine consumption (Lopez-Garcia et al., 2009; Shao et al., 2021). However, it is important to note that these findings are from the models that did not include the restricted cubic splines; thus, assume a linear relationship between caffeine consumption and stroke risk. In contrast, the model containing the restricted cubic splines depicted that the caffeine dose-and source-response with stroke risk was non-linear. Ultimately, these findings suggest that linear models may oversimplify the relationship between caffeine consumption and stroke risk. The use of cubic splines reveals specific dose- and source-specific associations with stroke risk that may be overlooked using traditional linear modelling methods.

The nuanced findings of the present study align with various mechanisms that may explain the possible protective relationship between caffeine consumption and stroke risk.

Although it is well-established that caffeine can raise heart rate and blood pressure, research indicates that long-term use may mitigate these effects. Regular consumption of caffeine can often result in the development of tolerance to the acute impact of caffeine, such as blood pressure increase (Ruiz-Moreno et al., 2020); thus, potentially reducing the long-term negative effects. Moreover, various research indicates that caffeine has vasodilatory effects, particularly within the cerebral and coronary arteries (Echeverri et al., 2010; Reddy et al., 2024). Specifically, caffeine may stimulate endothelial cells to increase intracellular calcium, thereby increasing the production of nitric oxide, a potent vasodilator (Echeverri et al., 2010). The increase in nitric oxide has been shown to possibly improve blood flow in vessels within the brain and heart (Echeverri et al., 2010). As a result, caffeine-induced vasodilation, may reduce arterial stiffness and vascular damage and increase flow of blood to reduce stroke risk (Joyner, 2018). These biological mechanisms support the findings of our study, which suggest that higher coffee consumption (>1 to 4 cups/day) was significantly associated with decreased stroke risk. Given that coffee contains various antioxidant properties that reduce oxidative stress and inflammation, its consumption may help improve endothelial function and reduce stroke risk (Dludla et al., 2023).

Findings of our study emphasize the importance of caffeine sources and their level of consumption in stroke risk among young adults. For instance, consuming up to one serving of tea, pop/soda, and other caffeine sources appear to be protective factors of stroke. However, consumption of more than one serving for all these sources increased the risk of stroke. These findings underscore the potential dangers of excessive consumption of caffeinated beverages and the complexity of the benefits outweighing the potential harms. Moreover, these findings contradict findings in the current literature that suggest that high consumption (2 to ≥ 3) of caffeinated beverages, such as tea, are protective factors of stroke (Arab et al., 2009; Larsson et al., 2013; Y. Zhang et al., 2021). While antioxidants in tea can reduce stroke risk, emerging research suggests that excessive tea consumption could impair iron absorption and increase risk of iron deficiency anemia (Fan, 2016), thereby increasing

stroke risk (Mehta et al., 2012). Likewise, high levels of tea consumption can increase urinary oxalate levels, increasing the risk of kidney stones and impairing kidney function (Brzezicha-Cirocka et al., 2016), which are both associated with increased stroke risk (Nayak-Rao & Shenoy, 2017). Another possible explanation for the increased stroke risk associated with higher tea consumption could be the lower caffeine content in tea, especially considering that many varieties are decaffeinated. A standard cup of tea contains less than half the caffeine of a typical cup of coffee (Gilbert et al., 1976), which suggests that individuals may need to consume more cups of tea to experience the potential benefits of caffeine. However, consumption of more tea may also lead to increased intake of additives like creamers and sugar, which could contribute to the elevated stroke risk. With the emerging evidence and the findings of the current study, additional research is needed to further examine the impact of excessive tea consumption on stroke risk, particularly in young adults.

Similarly, low levels of pop/soda and other caffeinated sources may be associated with temporary increases in vasodilation, potentially improving an individual's blood flow and decreasing stroke risk (Echeverri et al., 2010). Moreover, energy drinks and pre-workout consumption among young adults have been associated with increased physical activity (Larson et al., 2014), a known protective factor of stroke risk. Taurine, an amino acid commonly found in energy drinks, has various neuroprotective effects (Kumari et al., 2013). For instance, taurine can play a vital role in preventing apoptosis by downregulating several molecules that trigger the cell death process that occurs in the loss of blood supply during a stroke (Kumari et al., 2013). Notably, our sample had a relatively low consumption of other caffeine sources (daily intake <0.26 servings), possibly suggesting that no consumption may represent a protective baseline. This may explain why low consumption demonstrates a protective effect, while higher intake is associated with increased risk. Future research should further explore the dose-response relationship between stroke risk and beverages containing taurine. Excessive consumption of pop/soda and other caffeinated beverages was associated

with increased stroke risk. Considering that many of these beverages contain high levels of sugar, artificial sweeteners, and other additives, they are often associated with metabolic dysfunction (e.g., obesity, diabetes, and hypertension) and increased stroke risk (Stanhope, 2016). Moreover, increased consumption of beverages containing high levels of caffeine may result in increase in blood pressure, cardiac arrhythmias, disruptions in sleep, and decreases in mental health (Grasser et al., 2016; Park et al., 2016), all of which may further increase stroke risk. Although our analyses accounted for some of these factors, large sample longitudinal studies with more diverse samples are needed to better examine the complex relationship between factors, caffeine intake, and stroke risk.

Interestingly, low coffee consumption (≤ 1 cup/day) was associated with increased risk of stroke, although this result was not statistically significant. These findings are contrary to research that suggests that any consumption of coffee decreases stroke risk (Chan et al., 2021). A possible explanation for the increased risk of stroke with low coffee consumption may be reverse causation. Participants with pre-existing health conditions (e.g., hypertension, arrhythmias, or even anxiety disorders) may limit or avoid coffee consumption, which could exacerbate these conditions and thereby increase stroke risk (Mesas et al., 2011; Voskoboinik et al., 2018). Conversely, higher consumption (>1 to 4 cups/day) was associated with reduced stroke risk, supporting findings of other research (B. Kim et al., 2012). It may also be possible that lower levels of coffee consumption may not be enough to experience the possible benefits of the caffeine. Rather, individuals may experience the negative aspects of the coffee additives, such as the sugar and cream. Previous research indicates that the protective effects of coffee are most apparent with higher levels of daily consumption (4 cups or more) (B. Kim et al., 2012). Nonetheless, additional research is needed to examine the causal relationship between various levels of coffee and stroke, particularly large cohort studies.

4.5 Limitations

While this study offers novel insight into the association between total daily caffeine intake, caffeine sources, and stroke risk in young adults, findings should be interpreted with consideration to certain limitations. This study uses a cross-sectional design. Despite the novel approach of assessing temporality of health conditions and lifestyle factors prior to stroke occurrence, this study cannot identify true causal relationships. Future research should consider examining the total average caffeine consumption in various sources over an extended period of time to better understand how long-term caffeine consumption, specific caffeine sources, and daily average impacts stroke risk in young adults. This study also utilizes self-report data from a questionnaire, which may be prone to recall bias, limiting the accuracy of pre-stroke caffeine consumption. Moreover, in our sample, the average daily consumption of most caffeine sources (tea, coffee, pop/soda) was about one cup/serving, which may limit the statistical power to accurately detect the association at higher levels of consumption. Moreover, information on decaffeinated coffee and tea, as well as additives of these beverages, such as milk, sugar, and cream was also not collected. Similarly, specific data on caffeine sources was not collected, such as whether pop/soda was sugar free or caffeine free. Future researchers should consider including all these factors into their assessment to insure reliable outputs.

4.6 Conclusion

Our study provides various novel findings into the relationship between caffeine consumption and stroke risk in young adults, which is a population that has been often overlooked in research. By examining both total daily caffeine intake as well as dose-and source-specific effects, while controlling for various confounders, the present study addresses critical gaps in the literature regarding dose, source, and the multifactorial nature of stroke. Findings of this study indicate that total daily caffeine intake reduces stroke risk even after adjusting for demographic, lifestyle and health-related confounders and risk factors.

However, the protective effect of caffeine tends to vary by source and quantity. Specifically, low intake of tea, soda, and other caffeinated beverages (e.g., energy drinks, caffeine pills/shots, pre-workouts) were all associated with decreased stroke risk. Whereas, higher levels of consumption increased stroke risk, especially for high-caffeine sources like energy drinks. Interestingly, low coffee consumption was associated with an increase in stroke risk, while higher levels of consumption were associated with a decreased risk, contradictory to some prior findings.

Results of our study suggest that the impact of caffeine on stroke is non-linear and source-dependent; thus, challenging previous research that assumes a linear relationship and focuses on only individual caffeine sources. Moreover, by incorporating a multifactorial approach and analyzing non-linear trends, our study offers a more accurate and nuanced understanding of the impact of caffeine on stroke risk, particularly in young adults. While the cross-sectional design has its limitations of potentially determining causal inferences, the findings provide various practical implications. Based on the high consumption of caffeine among young adults, targeted interventions in settings such as universities and fitness centres may be effective. Targeting common consumers of caffeine (e.g., students and athletes) could help mitigate the stroke risk associated with heavily caffeinated beverages. In conclusion, moderation is important in consideration of caffeine being a protective factor against stroke; however, excessive consumption, especially from caffeine-rich sources may increase the risk of stroke. Given the widespread availability and marketing of high caffeinated beverages, especially directed towards young adults, policymakers and public health officials should be cautious of their potential harms. Moreover, additional consideration is needed regarding regulations and educational campaigns to reduce excessive consumption of caffeine and to raise awareness of the potential health risks. This study provides valuable information for future longitudinal research to explore the role of caffeine as a possible modifiable risk factor, but also for its potential role in stroke risk reduction.

Chapter 5

Leveraging Reddit and Facebook for sampling rare and uncommon populations: A modern approach to overcoming recruitment challenges in young adults with stroke

Abstract

Recruitment of participants is a challenge faced by many researchers and becomes increasingly difficult when sampling rare or uncommon populations. Traditional methods of enrolling participants, such as third-party polling firms and recruitment from clinical settings, often involve high costs, limited reach, and lengthy ethics approval processes. These barriers often limit sample size and representativeness. This commentary highlights the challenges of traditional recruitment strategies and explores the use of social media as a promising and cost-effective approach to recruiting uncommon or rare populations. Using stroke in young adults as an example, it highlights the difficulties of conventional strategies and demonstrates the use of targeted social media outreach on Reddit and Facebook to successfully recruit participants. While this commentary illustrates the potential benefits of this strategy, it also highlights the limitations, such as potential sampling biases and issues with disease status verification. As the use of social media becomes more prominent, it serves as a promising method, particularly for researchers early in their career or with limited funds, to advance research on rare and uncommon populations.

5.1 The Difficulties of Recruiting Rare and Uncommon Populations

One of the most difficult aspects of primary research is recruiting participants, a challenge that is exponentially greater when studying rare populations. High costs, limited resources, and lack of community or professional network connections often complicate recruitment efforts and limit the ability to obtain large, representative samples. This is a particular challenge among students, junior researchers, and early investigators. In recent years, social

media platforms, including Reddit and Facebook have emerged as promising and innovative approaches to overcoming these barriers. This commentary explores the use of social media platforms for recruiting rare or uncommon populations. To illustrate this modern approach, we draw on the example of examining stroke risk in young adults.

5.2 Defining “Rare” and “Uncommon” Populations

The definition of what is considered a ‘rare population’ varies across studies. Some researchers define it broadly as a population with low numbers (McDonald, 2004), while others describe it as a population where the presence of a particular trait is very low (Christman, 2009). For the purpose of this commentary, we will consider the latter definition, considering a rare population as one in which the prevalence of a trait of interest is very low. Similarly, the threshold for what is considered a “rare disease”, varies with definitions of prevalence ranging from 5 to 80 cases per-100,000 individuals (Rakesh & Swathi, 2024). Although an outcome may not be within the definition of a rare disease, it can still be uncommon enough to complicate recruitment. Stroke among young adults provides a relevant example. While stroke is generally considered common in the general population, it is much less common in young adults. For instance, Canada’s crude incidence rate for 2022-2023 was 936 per 100,000, while in young adults aged 20-49 years was 74 per 100,000 (Canada, 2024). This low prevalence presents significant recruitment challenges for research amongst this population.

5.3 The Challenges of Traditional Recruitment Methods: A Focus on Stroke in Young Adults

The examination of the traditional and emerging risk factors of stroke in young adults provides a relevant example of recruitment challenges. With such a research question, traditional methods such as cross-sectional surveys are often used due to their simplicity and effectiveness in examining associations of risk factors. However, survey collection for an

uncommon outcome like stroke in young adults can be challenging due to difficulties in identifying and reaching enough eligible participants. A common strategy for completing such work is through third-party research polling firms. Upon approaching these firms, we were met with expectedly high costs. Due to the low prevalence rate of the outcome, the estimated expenses from recruitment services ranged from \$10,000 CAD to over \$65,000 CAD, often with no guarantee of recruitment or quality of data. Monthly fees for research advertisement or introductions to collaborators similarly ranged from \$2,500 to \$25,000 CAD, without guaranteed partnerships. These substantial costs prohibit many researchers, especially those in earlier stages of their career or with limited funding, to conduct such research. It may also be considered a (mis)use of valuable resources, from funding agencies, limiting funds that may be better spent in answering research questions, graduate student training, and knowledge dissemination and translation activities.

Recruitment through traditional methods such as hospitals and rehabilitation centres introduce additional challenges. For instance, most hospitals require time-consuming ethics reviews that may be redundant to approvals obtained by the academic research board. These additional processes of reviews, combined with long wait periods, significantly delay the research process. Acute care centres and clinical settings may also not offer access to particular patient groups if contact is minimal after an event. For example, in stroke research, young adults are frequently underrepresented in rehabilitation settings, where older patients are often prioritized. While some younger patients with severe outcomes are admitted, many are reluctant to participate in research during recovery, further limiting participation. On the other hand, recruitment via collaboration with other researchers in the field may be hindered by gatekeeping of knowledge, data, and research connections. For instance, datasets were not shared for monetary or privacy issues, or assistance was contingent on authorship or compensation. Unfortunately, research and academia can be exclusive, particularly, it can be advantageous to those with pre-existing connections or large research grants/funds, thereby limiting the opportunities for emerging researchers to develop.

Together, these conventional recruitment methods highlight the broader limitations of traditional approaches, particularly when targeting uncommon or rare populations. However, we achieved some success from survivor support groups and rehabilitation centres who generously shared our research. Unfortunately, this support, while meaningful, was not sufficient to build a large enough sample size. Faced with growing challenges, we recognized the need for a more effective approach for recruiting participants.

5.4 The Use of Social Media for Recruitment of Rare and Uncommon Populations

The solution to our recruitment challenges came through targeted social media posts, primarily on Reddit and Facebook. Subreddit communities such as r/stroke and r/StrokeRecoveryBunch provided invaluable support. These groups were largely composed of young adults who had recently suffered from a stroke and recognized the value of the research, expressing a strong willingness to support. Moreover, many members had loved ones affected by stroke who were also happy to help. These communities were enthusiastic and openly shared our study in other support groups across multiple platforms, helping to facilitate recruitment beyond just our reach. The young stroke survivor group is unique, given that this outcome is not common, and survivors have created supportive online environments to share experiences, ask questions, and find commonality. On Facebook, groups such as Stroke Awareness and Support, Stroke Survivors, and Stroke Survivors Support Group similarly helped with dissemination of the questionnaire. Similar to Reddit, members of these groups happily and actively participated or shared our study with eligible contacts.

While a promising opportunity for recruitment, researchers must consider several important factors prior to recruiting participants from social media. Some of these factors include platform-specific user demographics, access requirements, and researcher privacy.

Although there is limited information on user demographics of these platforms, researchers must consider their differences when looking for participant recruitment. For instance, it is estimated that 22% of all American Adults aged 18 to 29 are Reddit users (Chew et al., 2021). Based on a sub-sample study of Reddit users, approximately 31.7% of the sample was aged 13-17, 29.8% aged 18-20, and 38.5% aged 21-54 (Chew et al., 2021). For the sake of stroke research on young adults, this population distribution closely aligns with the target population. Little is also known about the demographics of Facebook users. The most recent, albeit dated, data shows that the average Facebook user is 30.34 years-old (McAndrew & Jeong, 2012), however, we believe that this average may be much higher now. Given that this demographic is largely part of the minority of users on Reddit, it is complementary benefit for our recruitment purposes. Moreover, both Reddit and Facebook require permission to post research-related content within the group. On Reddit, we were often required to provide proof of research ethics approval before posting. In contrast, Facebook was generally more lenient, although it required posts to be made using personal Facebook profiles and thus required a member of the research team to create a personal profile. Reddit, however, allowed us to create profiles dedicated to research, allowing researchers to maintain privacy. The choice between these platforms, or other platforms such as Instagram or X (formally known as Twitter) should be guided by the research question and target population. Investigating the target population for these platforms, as well as how they are used, is a first step in determining the right platform(s) for accessing the target population.

5.5 Considerations for Using Social Media Platforms for Recruitment

By no means does this commentary suggest that social media can be used as a universal tool to collect data on any/all rare or uncommon populations, as it is not a “one-size-fits-solution” to recruitment challenges. For example, research examining rural West African elderly individuals with late-stage dementia would likely not benefit from using social media. Instead, the use of social media for recruitment depends on whether the research question(s) and the characteristics of the population of interest align with its use. For instance, many

young adults actively use social media platforms, such as Reddit and Facebook, making targeted recruitment of this population through social media appropriate. Additionally, a significant proportion of young adults have a cryptogenic stroke (stroke with an unknown cause) (Putala et al., 2017), resulting in many young adults gathering on social media communities seeking answers and support. This collective interest from survivors may enhance their interest and willingness to participate in research, increasing the usefulness of targeted social media recruitment. Nonetheless, in addition to these considerations there are also limitations in using social media as a recruitment technique. For instance, disease status verification is not feasible, although it is unlikely that individuals in support groups would falsely claim being a stroke survivor, especially given that participation was voluntary and not compensated. This is particularly a consideration in research whereby compensation is provided for research participation. Moreover, researchers must acknowledge that this approach can lead to issues of sampling bias and non-representativeness. These concerns can cause the sample to become skewed based on the specific demographics of the social media platforms. Additionally, sampling from social media groups can introduce self-selection bias and possibly impact the validity of the research.

5.6 Conclusion

Despite these limitations, the use of social media for recruitment makes possible what otherwise may feel impossible. Recruiting rare or uncommon participants presents substantial challenges due to low prevalence, high costs, limited resources, and restricted access to potential participants. Traditional recruitment methods such as third-party polling firms or researcher collaborations are often expensive or difficult to navigate. Our experience with examining stroke risk factors in young adults illustrates these challenges. However, leveraging the use of social media offered an accessible and affordable way of collecting meaningful data, ultimately, helping advance our understanding of these understudied groups.

Chapter 6

Conclusion

The purpose of this thesis was to investigate the complex nature of stroke risk in young adults. Through four studies, this research advances our current understanding of stroke risk within this population. Specifically, this thesis:

1. Identified the frequency and distribution of stroke and its associated risk factors across different demographic groups, providing an overview of those who experienced a stroke between 18 to 50 years old.
2. Explored the established and emerging risk factors of stroke using a matched case-control design with a conditional logistic regression, enhancing our understanding of the complexity of stroke risk.
3. Examined the linear and non-linear dose-and source-specific association of caffeine consumption and stroke risk.
4. Illustrated the value of recruiting rare or uncommon populations using social media platforms, such as Reddit and Facebook.

6.1 Summary of Findings

6.1.1 Study One Summary

Study one utilized a holistic approach to investigate young adults who had experienced a stroke, utilizing medical, epidemiological, and psychosocial perspectives. The study focused on identifying the prevalence of both established and emerging risk factors. Specifically, it examined stroke types, comorbidities, demographic characteristics, and mental health profiles, as well as the pre-and-post prevalence of these factors. The primary goal of study one was to describe this population in detail and identify how it differed from young adults without a history of stroke. This study provided critical insight into the prevalence and/or influence of various risk factors in young stroke cases and guides the direction of future research. Overall, the findings from study one suggested that several risk factors are commonly present before the onset of a stroke in young adults. These factors included hypertension, sleep disorders, and regularly occurring migraines, stressing the need for early

screening and risk factor management. Moreover, certain congenital and acquired conditions, such as patent foramen ovale (PFO) and arterial dissections, were often diagnosed only after an individual has had a stroke. These findings suggest that these factors may be underdiagnosed and that early detection may be a method for prevention, particularly in young adults. Factors such as obesity, unbalanced diets, physical inactivity, and substance use were all highly prevalent among young adults who had experienced a stroke. These findings also emphasized the importance of targeted prevention strategies and rehabilitation care for young adults. Emerging risk factors such as an individual's mental health also depicted an important role in young stroke survivors. Factors including depression, anxiety, and suicidal ideation were frequently reported prior to individuals having a stroke. These results indicated that mental health factors may play a potential role in increasing stroke risk through behavioural, biological, and psychosocial mechanisms. Ultimately, study one highlighted that stroke in young adults is multifactorial, including a combination of pre-existing medical conditions, lifestyle factors, and mental well-being. Moreover, this study demonstrated that many of these factors are often underrecognized or undiagnosed until after an individual has a stroke, reinforcing the need for early identification and comprehensive prevention strategies tailored to young adults.

6.1.2 Study Two Summary

Building on the gaps identified in study one, study two utilized a multifactorial, exploratory approach to examine the risk factors of stroke in young adults. Using a conditional logistic regression and a case-control design, this study assessed the associations between the established and emerging risk factors of stroke in young adults. The findings indicated that despite stroke becoming more common in younger adults, age remains an important risk factor of stroke, even amongst young survivors. This suggests that vascular aging is very relevant and may occur at earlier stages in life than traditionally expected. Moreover, the findings highlighted the cumulative impact of risk factors, including hypertension, lack of exercise, and an unbalanced diet on cerebrovascular health. Demographic factors such as race

and country of residence played an influential role in stroke risk. Compared to White individuals, those who identified as Black had lower odds of stroke, a finding that contradicted much of the existing literature. This unexpected result suggested a potentially complex interaction between genetics, lifestyle, and geographic context; however, it requires additional research. Country of residence also played an important role in stroke risk. Individuals residing in Canada had higher odds of experiencing a stroke. These results may reflect systemic challenges, including limited access to primary care and a higher prevalence of undiagnosed risk factors. Lifestyle factors such as alcohol consumption, cigarette smoking, and drug use were associated with significantly increased stroke risk, emphasizing their relevance in young adults. Physical health factors were also important. Factors such as being underweight or overweight increased risk of stroke, while good overall self-reported physical health was protective. In relation to comorbidities, conditions including pre-existing hypertension and regularly occurring migraines significantly increased stroke risk, reaffirming their importance, even in young adults. Emerging risk factors such as mental health, particularly poor self-reported mental health, were associated with an increased risk of stroke. Nonetheless, study two depicted some unexpected findings. For example, sleep disorders, diabetes, and respiratory disease depicted no significance or decreased risk of stroke. However, these findings likely reflected small sample sizes in these subgroups and should be interpreted with caution. Ultimately, the results of study two highlighted the complex interaction of demographic, lifestyle, physical health, and mental health factors that influence stroke risk in young adults. While some findings were consistent with previous literature and others were contradictory, the results suggested that findings differ from traditional assumptions. Thus, age-specific prevention and intervention strategies targeting modifiable risk are necessary.

6.1.3 Study Three Summary

Study three examined the linear and non-linear source-and dose-specific impact of caffeine on stroke risk in young adults. Specifically, this study used a matched case-control study

design, applying a conditional logistic regression, and a conditional logistic regression with restricted cubic splines. The results suggested that total caffeine intake (when examined linearly and independent of source) had a statistically significant decrease in stroke risk. That is, as total daily caffeine increased, stroke risk decreased. These findings suggested a potential protective effect of caffeine consumption and cerebrovascular health. However, dose-and source-specific consumption revealed more nuanced, non-linear patterns. Specifically, low intakes (less than or equal to one serving/day) of tea, pop, as well as energy drinks, caffeine pills/shots, and pre-workouts supplements were associated with decreased stroke risk. In contrast, higher intake (greater than one serving/day) of these sources increased stroke risk. The results implied that while low consumption may result in decreased risk of stroke, excessive consumption, possibly due to high levels of sugars, additives, and other chemical compounds in these sources, may counteract or reverse the potential protective effects of caffeine. Interestingly, coffee intake demonstrated the opposite pattern. Specifically, low intake (less than one serving/day) of coffee was associated with increased stroke risk, whereas intake greater than one to four servings/day was associated with reduced risk. These findings indicated that lower intake of coffee might reflect avoidance of coffee and caffeine due to pre-existing health issues. Alternatively, the increased risk with low consumption may indicate that a threshold level of intake is necessary to achieve the vascular benefits of coffee. Ultimately, these findings suggested that the protective effects of caffeine on stroke risk may be related to their vasodilatory and antioxidant properties, which can improve vascular health. However, excessive consumption, particularly from sources high in sugar and additives, may negatively influence blood pressure, metabolic regulation, and other mechanisms, and ultimately increase stroke risk. Despite the results of this study highlighting the novel risk of caffeine in young adults, these associations need further investigation, especially considering the vast marketing of caffeinated beverages and high level of consumption in this age group.

6.1.4 Study Four Summary

The final study of this dissertation highlighted the recruitment challenges involved in sampling rare or uncommon study populations, a consistent issue experienced in the present thesis. Traditional recruitment methods such as hospitals, rehabilitation centres, and research polling firms proved difficult and resulted in limited recruitment after months of persistent efforts. However, this barrier was overcome through the use of targeted social media posts. This paper demonstrated how social media platforms such as Reddit and Facebook can be effective in reaching rare or uncommon populations, using the recruitment of young adults who had experienced a stroke as an example. Despite its utility for recruitment, this study also acknowledged the limitations of using social media as a recruitment tool, such as participation bias and the generalizability of results. The chapter emphasized that while this approach was effective for this thesis, it is not a “one-size-fits-all” solution to recruiting rare or uncommon populations. This study offered important insight and considerations for future researchers facing similar recruitment challenges.

6.2 Comparison of Thesis Findings to Literature on Older Adults

Although the primary focus of this dissertation was not to directly compare the findings of this study to those observed in older adults, the results offered important insight. Specifically, these studies highlighted the distinct difference in risk between the young stroke survivors recruited for the present research and older populations documented in the literature. The differences presented in this thesis emphasize that the risk profile for stroke in young adults does not represent that of older adults, highlighting the need for age-specific research, prevention and intervention, as well as post-stroke care. With consideration to the sample size of this study ($n=1,277$; cases= 435, controls = 842), and the possible differences in modelling techniques and covariates, the results indicate notable differences in health-related factors, lifestyle behaviours, stroke-specific factors, and demographic characteristics related to stroke risk between young and old stroke survivors. For instance, in our study, 61% of stroke cases were ischemic, while 31% were hemorrhagic. In comparison, the proportion of

ischemic strokes in older adults has been documented to be higher in research. For example, a large scale study examining the National Inpatient Sample database over a 15-year period found that 81.6% of strokes in older adults were ischemic (Khan et al., 2021b). These findings align with general population statistics that are inclusive of all ages, which indicate that approximately 87% of all strokes are ischemic (Saini et al., 2021). Our findings are also consistent with other literature suggesting that hemorrhagic strokes are more common in younger adults. For instance, researchers found that the highest proportion of hemorrhagic strokes (35.9%) occurred in young adults (Khan et al., 2021b), which closely aligns with our findings. The increased proportion of hemorrhagic strokes in young adults may be attributed to the early onset of hypertension, substance use (particularly, cocaine and amphetamines), and traumatic vascular injuries, such as arterial dissections (Yahya et al., 2020b). Together, the differences in stroke type between young and old stroke survivors reinforced the distinct etiology and risk between age groups. Thereby, further emphasizing the need for age-specific approaches to prevention and intervention.

Based on the sample of this study, stroke etiology appears to vary between age groups. For instance, 18% of young adults were diagnosed with an arterial dissection after their stroke, while only 2% had been diagnosed beforehand. These findings align with other research on young adults, which reports that 10-25% of ischemic strokes are attributable to arterial dissection (Bukhari et al., 2023c). In contrast, arterial dissections account for only about 2% of strokes in older adults (Bukhari et al., 2023c), depicting that stroke risk factor prevalence can vary considerably by age. Similarly, PFO is also more commonly present in young adult stroke survivors. While in our study about 19% of cases had a PFO, other studies have higher prevalence. For instance, research on young stroke survivors have found that 43.9% of patients with a cryptogenic stroke had a PFO, compared to 28.3% in older adults (Handke et al., 2007). These findings support the role of PFO as an important stroke mechanism in young adults and the potential advantage of its closure in those who may be at

risk of having a stroke. Moreover, it may be beneficial to target and test those with additional risk factors for early detection of these mechanisms for stroke prevention.

Traditional risk factors of stroke also appear to vary between the older stroke survivors in the literature and the younger stroke survivors in the present research. For instance, the prevalence of hypertension among our sample was about 23% pre-stroke. In contrast, the prevalence of hypertension is substantially higher in older adults, with some studies reporting up to 70% of older stroke survivors having pre-existing hypertension (Yu et al., 2020). Similarly, 25% of our sample was overweight pre-stroke, whereas the prevalence of obesity among older stroke survivors ranges from 18-44% based on BMI, and 36% using central measures (Kernan et al., 2013b). To date, research has yet to examine pre-existing mental health factors in older adults. However, evidence from research on the general population indicates that young adults are more likely to report worse mental health, with higher rates of depression and severe anxiety (Sikström et al., 2023; Udupa et al., 2023). Based on these findings, it can be hypothesized that pre-existing poor mental health may be more common and potentially more influential among young adults, impacting both stroke risk and post-stroke outcomes. The differences in mental health factors between age groups demonstrates the need for additional consideration of non-established stroke risk factors for future researchers. While established risk factors such as hypertension and obesity are highly prevalent and influential, these factors alone do not account for the complex risk of stroke in young adults, as demonstrated by our findings. Public health officials should consider the influence of psychosocial factors in stroke risk for this population. Particularly, individuals with traditional risk factors, such as hypertension should also be screened for mental health factors, as these factors may be influential and increase stroke risk. Moreover, these findings highlighted the need for integrated mental health interventions for post-stroke care in addition to physical rehabilitation. Nonetheless, additional long-term research is needed to further establish the relationship between mental health factors and stroke risk.

Findings of study two indicated that stroke risk increases significantly with age, even among young adults, particularly when compared to those aged 18 to 24. For example, the odds of stroke were approximately twice as high among 25 to 30-year-olds and almost four times higher among 41 to 50-year-olds in our sample. In contrast, studies on older adults report much smaller increases in stroke risk with increases in age. For example, researchers found that among individuals aged 80 years and older, there was only a 3-4% increase in odds as individuals aged (Ness et al., 2000). These findings suggest that although age is a critical risk factor throughout one's life, in young adults the relative increases are sharper. Ultimately, these findings emphasized the importance of early intervention and prevention, even within what is often considered a low-risk age group. Interestingly, study two found that higher income was associated with almost twice the odds of stroke, compared to those who reported having average income. These findings contradict much of the existing literature, which consistently depicts that lower socioeconomic status is associated with increased risk of stroke. For example, a study with American adults aged 65 years and older found that individuals age 65-74 in the lowest education and income group had more than double the risk of stroke, compared to those in the higher socioeconomic group (Avendano et al., 2006). These findings highlighted the need for additional consideration of socioeconomic and psychosocial factors when examining stroke risk in younger populations.

Substance use also emerged as a significant risk factor for stroke among young adults. Although the impact of substance use as a risk factor exists across all age groups, the use of drugs are more prevalent in younger adults (Nawi et al., 2021). In our study, frequent marijuana use was associated with nearly double the odds of stroke, whereas research on older adults found a odds ratio of 1.42 (Jeffers et al., 2024b). Although Jeffers et al. excluded participants older than 65 years old, the mean age of their study was 45.4 years old (Jeffers et al., 2024b), which nears the upper limit of the young adult definition used in the present research. As such, these findings still provide meaningful context, suggesting that the relative impact of drug use on stroke risk may be amplified in young adults. Another possible

explanation for this result may be that young adults may generally have fewer risk factors, resulting in a lower baseline risk of stroke. Consequently, non-traditional risk factors, such as substance use may appear more influential in younger adults. Physiological differences between young and older adults might also contribute to these differences. It is hypothesized that young adults have arteries that are more elastic and less impacted by chronic vascular damage, making them more susceptible to acute changes induced by drugs (Qureshi et al., 2001). For example, substances like cocaine can induce intense vasospasm and acute hypertension, which may have a more dramatic effect on healthy, responsive arteries than those already stiffened or narrowed (Qureshi et al., 2001). Together, these findings suggested that substance use may disproportionately impact young adults, further emphasizing the need for targeted prevention strategies. Similarly, findings of our study indicated that young adults diagnosed with hypertension prior to experiencing a stroke had more than double the odds of stroke, compared to those without hypertension. While these findings depicted a significant increase in risk, it is notably lower than the risk reported in older populations. For instance, researchers found that hypertension increases stroke risk up to four times amongst those 65 and greater (Arboix, 2015). These findings suggest that while hypertension significantly increases stroke risk in young adults, its associated risk may be higher in older adults. The differences in stroke risk may be attributed to the cumulative vascular damage caused by the prolonged effects of factors, such as hypertension. Studies indicate that chronic hypertension leads to arterial stiffness, atherosclerosis, inflammation, and endothelial damage, which worsen over time as an individual ages and increase stroke risk (H.-L. Kim, 2023b).

As mentioned previously, differences in modelling techniques and covariates included in our analyses compared to those in the referenced studies above are not directly comparable. However, these comparisons highlight the broader differences of stroke risk between younger and older adults. Collectively, the noted differences between our findings with young adults and research on older adults highlight the importance of age-specific research. The findings illustrate that risk factors may manifest differently and have varying

levels of influence at different ages of one's life. Consequently, relying only on stroke research that is conducted on older adults may overlook these differences and important mechanisms that uniquely impact young adults. Rather, researchers should be cautious and use research with older adults as a guide, serving as reference, rather than a strict model. In addition to research, policy makers and public health may use these findings to create more tailored prevention, intervention, and rehabilitation care for young adults. For example, post-stroke care for young adults should consider a greater emphasis on mental health in addition to physical rehabilitation. The incorporation of age-specific interventions in health care prevention and planning has the potential to reduce the long-term impacts of stroke and improve outcomes of young survivors. The importance of these age-related differences in shaping prevention, intervention, and post-stroke care will be discussed in greater detail below.

In summary, stroke in young adults is influenced by various factors, with complex associations between established, emerging, and age-specific risk factors. Similar to older adults, established risk factors such as hypertension, obesity, smoking, poor diet, as well as sedentary lifestyles remain highly prevalent pre-stroke and influential in stroke risk. However, the findings of this thesis suggest several factors disproportionately impact younger populations. For example, congenital and vascular conditions such as PFO and arterial dissections, as well as substance use factors, may have more acute vascular effects in younger, otherwise healthy arteries. Additionally, mental health factors, such as depression, anxiety, and suicidal ideation are more common in young adults and may influence stroke risk through biological stress pathways and associated unhealthy behaviours. Similarly, caffeine consumption is more prevalent in this age range, particularly from highly caffeinated beverages, and was found to have both protective and harmful effect in young adults, depending on source and dose. Collectively, these findings highlight that while young adults may share many stroke risk factors with older populations, the possible influence, prevalence, and detection of many factors remain different. Recognizing these differences

may assist clinicians move beyond reliance on traditional risk profiles towards those that are more tailored to young adults. For example, a checklist with age-specific risk factors may help guide health care providers with earlier identification and intervention. Ultimately, by recognizing these differences, health care providers may develop and/or refine targeted prevention strategies and reduce the growing burden of stroke in young adults.

6.3 Limitations and Future Directions

Despite the various novel findings of this thesis, it is not without limitations. A key limitation was the uneven distribution of demographic characteristics between the case and control groups. For example, 35% of controls identified as Black, compared to 2.73% of controls. Ideally, for greater generalizability and accuracy of results, case and control groups should have more even distribution of demographic characteristics. However, this is often difficult to achieve, especially for an uncommon outcome, such as stroke in young adults. Although sample weighting was a possible solution, it was not applied given the relatively small sample size and small number of Black cases. Applying sample weights could have possibly introduced statistical instability and increased variance in the model estimates, potentially compromising the reliability and interpretability of our results. Nonetheless, the multiple regression models included demographic characteristics, such as race, to adjust for their potential confounding effect. Future research should consider matching participant characteristics more evenly. Previous large-scale stroke studies have recruited controls from similar hospitals and communities to increase ethnic matching and control geographical differences (O'Donnell et al., 2010). Specifically, researchers tried to recruit one control per-case at each recruitment site to ensure comparable case-control groups differences (O'Donnell et al., 2010).

Another limitation of this thesis was the large variations in participants country of residence. These differences limited the international generalizability of our findings. The

majority of the study's cases were from the United States of America, Canada, United Kingdom of Great Britain and Northern Ireland, Australia, and India. Thus, results from our study were likely most applicable to populations from these countries. While the international scope of this research was valuable, the uneven distribution of participants country of residence restricted broad, international representativeness of the results. Given the challenges of recruiting uncommon populations, such as cost, recruitment was limited to voluntary participation. In addition, cases were not provided compensation for their participation, this may have limited the time and effort they spent on the questionnaire. However, we believe that this is a notable strength of this study. The willingness of participants to contribute without any incentives underscore their genuine interest and willingness to support this research. Nonetheless, future studies could benefit from targeted recruitment to diversify geographic representation.

Participant stroke severity was not measured in this study, resulting in the lack of information on the full spectrum of stroke severity. This study screened for those with severe cognitive impairments and as such, they are not represented in the data. Future research should consider examining the experiences, risk factors, and impact of stroke amongst those with severe cognitive impairments. Similarly, this study only included stroke survivors, excluding those who had a fatal stroke. Thus, the results of this research only reflected the survivor population, and not all individuals who experienced a stroke.

As a case-control study, this thesis was inherently impacted by selection and participation bias. Many participants of this study were recruited from social media, which may not accurately represent the general population. Users of these platforms may differ from the general population in terms of age, socioeconomic status, education level, race, and health behaviours. While social media was effective and cost-efficient, future researchers should place greater emphasis on diversifying recruitment sources, such as hospitals, rehabilitation centres, and survivor groups to enhance representativeness. Moreover, this

study utilized a self-reported questionnaire as the main measure, which introduced possible issues of recall bias and misreporting of stroke history and risk factors. Thus, future researchers should consider verifying stroke occurrence through medical records or clinical recruitment of participants. However, we believe that this is unlikely, given that participation for cases was voluntary and unpaid, reducing reasons to participate outside of interest.

Establishing temporal associations using a cross-sectional study design is challenging. Although this study collected data on pre-and-post-factors and diagnoses, fully establishing precise temporal relationships was not possible. Moreover, the accuracy of reported answers was limited by recall bias and incomplete medical histories. Additionally, some conditions may have been present prior to having a stroke, but were diagnosed after the onset, leading to a misclassification of the temporal sequence. Future researchers should consider conducting longitudinal studies to follow participants over time with routine medical assessments to capture the impact and onset accuracy of these risk factors and stroke. Moreover, integrating biomarker data and neuroimaging can strengthen the accuracy of the self-reported findings.

Although this study included multiple risk factors in the modelling approaches to control for the impact of confounding, other missing or unknown confounders may have influenced the observed associations. Therefore, future research should consider collecting detailed data on as many confounders as possible without fatiguing participants and overfitting the data. Researchers should also consider gathering large samples to avoid issues of overfitting, as well as ensuring that subgroups of the sample are well populated. For instance, this thesis had an insufficient number of cases who had been diagnosed with diabetes prior to having a stroke, which impacted the inferences of this important variable. Thus, researchers should ensure sufficient sample sizes for such clinically important risk factors to enhance statistical power, and the reliability of their findings.

Lastly, some inconsistencies exist between the various papers of this thesis regarding the impact of some covariates. The inconsistencies arise from differences in study objectives, scope, and statistical analysis, which are inherent in the sandwich structure of this thesis. For instance, study one identified a high prevalence of pre-stroke sleep difficulties or disorders, whereas study two suggested a potential protective effect. In study one, sleep disorders were discussed primarily as a risk factor, given their high pre-stroke prevalence in cases, whereas study two assessed associations and observed a protective effect. These differences highlight the importance of interpreting the findings within the context of each study, with consideration to the distinct aims and methods.

6.4 Contributions and Implications for Rehabilitation, Health Policy, Promotion, and Practice

6.4.1 Methodological Contributions

This dissertation led to various methodological contributions that advanced the current field of stroke research; namely, methods to examine temporal associations of risk factors, social media as a tool for recruitment of rare and uncommon populations, and expanding the current understanding of risk profiles in research. Collectively, the research design provided a comprehensive and novel approach for investigating and understanding stroke risk in young adults. To our knowledge, this thesis was the first cross-sectional study in stroke research to incorporate temporal insight, identifying whether specific risk factors were present before or after stroke onset. This distinction was crucial, as it allowed for a more accurate assessment of which risk factors may contribute to stroke risk, or which factors may be consequences of the stroke. More importantly, this provided valuable information for future researchers and serves as foundational knowledge that can guide mechanistic research. For instance, the high prevalence of poor self-reported mental health factors pre-stroke suggests the need for researchers to consider longitudinal analyses between cerebrovascular risk and mental health. This thesis also demonstrated the use of social media platforms as a cost-effective and

accessible alternative to traditional recruitment methods for studying rare or uncommon populations. The use of online communities on Reddit and Facebook offers a practical framework for researchers who face financial and institutional barriers in recruiting participants, particularly for an uncommon population, such as young adults with stroke. In addition, this thesis also expanded on the traditional risk profiles of at-risk patients of stroke. Specifically, this thesis integrated both established and emerging risk factors, including hypertension, obesity, substance use, mental health, and caffeine to present a more holistic examination of stroke risk in young adults. Ultimately, this integrative approach demonstrated the need for age-specific prevention strategies, early diagnosis, and intervention strategies.

6.4.2 Implications for Post-Stroke Care

Findings of this research emphasized the critical need for age-targeted rehabilitation and care for young adults who experience a stroke. Given the etiological and risk factor differences between young and older stroke survivors, rehabilitation needs are also likely to be different. As mentioned above, the findings of the current study demonstrated high prevalence of poor self-reported mental health factors, an issue often overlooked in existing rehabilitation programs (Terrill, 2023). Despite many rehabilitation options being available, stroke survivors often report that their mental health is not prioritized (Terrill, 2023). Most rehabilitation programs remain outdated and are primarily focused on older adults. Research indicates that young stroke survivors report more unmet rehabilitation needs compared to older survivors (Huang et al., 2025). Given the increasing incidence of stroke among young adults, it is essential to develop age-targeted rehabilitation and recovery strategies that reflect the distinct challenges faced by this population. Findings of this thesis suggest that rehabilitation programs should consider the incorporation of mental health support. Moreover, rehabilitation programs should also include the incorporation of sleep disorder management, substance use counseling, and psychosocial support to address the full spectrum of important stroke risk factors in young adults. Given that young stroke survivors are uncommon, they may feel isolated and disconnected from existing services. Many young

stroke survivors suffer from loss of identity, independence, and purpose due to life-altering changes caused by their stroke (Zheng et al., 2023). A qualitative study examining the needs of young stroke survivors identified that the gap in post-stroke care and support was the lack of psychological and long-term support tailored to young adults (Huang et al., 2025). Specialized recovery and rehabilitation programs for young adults could foster a sense of community, provide peer support, and offer age-specific counselling. These programs can help address mental health concerns, such as depression, anxiety, and suicidal ideation, all of which were commonly reported both before and after stroke in the present study. The creation of young adult only rehabilitation and recovery centres can also help reduce the stigma that they face. Developing young adult only rehabilitation programs and integrating psychosocial support, creates real potential to reduce the mental health burden associated with stroke and improve their recovery outcomes.

6.4.3 Implications for Health Policy, Promotion, and Practice

This thesis provided many important implications for health policies and planning. Public health officials should consider the findings of these studies as evidence to inform health policy recommendations and reforms aimed at prevention, early detection, and health education. One major recommendation is the implementation of early and routine checkups for young adults who may be at an elevated risk of having a stroke. Although universal screening of young adults for conditions like PFO may not be economically realistic, targeted screening for at-risk individuals could be developed. Moreover, the development of targeted screening tools could also serve as possible alternatives. For instance, various states in the United States utilize the ABCD and ABCD2 risk scores to assess stroke risk following a TIA and adjusts for factors, including age, blood pressure, and diabetes (Bhatt & Jani, 2011). Although this tool is designed for assessing stroke risk following a TIA, the framework itself demonstrates the use of a multifactorial model to assess risk and prevention. Researchers should consider creating a similar framework that is age-specific to screen individuals with known risk factors such as elevated blood pressure, substance use, and/or regularly occurring

migraines. Individuals identified as “high-risk” using such a model could be referred to further testing, such as an echocardiogram for PFO (Montessuit et al., 1997). This recommendation offers a feasible option for early detection and intervention.

Despite the potential benefits of screening guidelines, they will not be enough on their own, especially if access to care is limited. Thus, such screening policies must be paired with increased access to primary care services and providers, particularly in countries such as Canada. Findings of the current study indicated that Canada faced a higher risk of stroke in young adults. Primary care providers, such as family physicians, play a critical role in reducing cardiovascular disease by providing preventative care and screening (K. Li et al., 2023). However, in Canada, access to these services is limited, with 55% of individuals in the territories, 21.5% in Quebec, and 17.7% in British Columbia not having a family physician (K. Li et al., 2023). Limited access to such services, combined with a growing and aging population, may result in inadequate screening and delayed diagnosis of stroke-related conditions, ultimately increasing stroke risk (K. Li et al., 2023). To address this gap, health policies must prioritize increasing access and availability of primary care to improve preventive services. These disparities must be addressed to reduce the burden and occurrence of stroke, especially among young adults.

Stroke is no longer a disease that occurs almost exclusively in older adults. With increases in stroke cases among young adults, increased public health investment is urgently needed to target youth preventative programs and services, including improved health education. These programs should emphasize the importance of traditional modifiable risk factors, including exercise, diet, and weight, while also highlighting the importance of more unique risk factors that may be impacting young adults, such as mental health and caffeine consumption. Public health campaigns should raise awareness that stroke is becoming more common in young adults and management of both traditional and emerging risk factors is essential in its prevention. Given the use of social media in the current study and its

widespread use amongst young adults, advertisements from national health departments could target this population on social media platforms to maximize engagement. Although research on the percentage of social media users based on age group is limited, findings indicate that nearly 98% of young adults in America used at least one form of social media regularly (Shannon et al., 2022). Thus, policy makers should consider advertising the risk factors of stroke using targeted ads on platforms, such as Reddit, TikTok, Facebook, X, and YouTube to increase awareness and prevention. Federal departments, including Health Canada have run various health campaign ads, such as the 2024 Canadian Dental Care Plan that reached nearly 650,000 Canadians (Health Canada, 2024). While this campaign reached many Canadians, these advertisements were largely conducted on streaming services and television, largely without utilizing social media. The reach of these advertisements could have been much greater, especially among young adults if conducted on social media.

Lastly, this research highlighted the potential danger of caffeine as an emerging risk factor of stroke, particularly among young adults with high daily consumption. Social media, television, and retail stores, such as convenience stores and gas stations are saturated with advertisements for highly caffeinated products. These products often include energy drinks, caffeine shots, and pre-workout supplements, many of which contain caffeine levels that exceed daily recommended limits. Moreover, these products are often promoted by fitness influencers and marketed as physical and cognitive enhancers, contributing to their widespread use among youth and young adults. While implementing cigarette-style warning labels or banning advertisement of these products may reduce consumption, such measures may not be practical or enforceable. Several countries have adopted regulatory mandates on the consumption of caffeinated products. For example, in Canada energy drinks must contain less than 180 mg of caffeine per-serving and must contain cautionary labelling such as: “Not recommended for those under 14 years old, pregnant or breastfeeding women or individuals sensitive to caffeine” (Government of Canada, 2023). Similarly, various European countries mandate high-caffeine content labeling on energy drinks with 150 mg or more of caffeine

(Breda et al., 2014). Nonetheless, other countries, such as Denmark, Turkey, Norway, and Uruguay have outright banned the sale of energy drinks due to their health risks (Breda et al., 2014). While banning the consumption/sale of energy drinks may not be feasible, additional awareness on its negative health impacts is needed. Particularly, individuals should be made aware of the health risks (e.g., stroke) associated with frequent high consumption of caffeinated beverages. Moreover, policy makers should consider applying mandates similar to countries like Poland, which have banned the sales of energy drinks for minors (under 18 years old) (Mularczyk-Tomczewska et al., 2025). In addition, health care professionals should be trained to routinely screen and educate young patients, especially those with other risk factors for stroke. Targeted public health intervention advertisements in high-consumption environments, such as at colleges and universities, long work hour environments (e.g., hospitals and construction sites), and gyms could reduce consumption. Together, these measures may help address the growing concern related to caffeine consumption and stroke risk in young adults.

6.5 Conclusion

The findings of this research provide valuable contributions to inform public health, clinical practice, and policy development. Notably, the results highlight age-specific differences in stroke risk and emphasize the distinct biological, psychosocial, and lifestyle factors that drive these risks, some of which were amenable, while others were not. Although stroke among young adults are increasing, clinical guidelines and research continue to focus predominantly on older adults. This research underscores the urgent need for age-specific interventions, research, and post-stroke care tailored to younger survivors. Furthermore, this dissertation demonstrates the need for policy approaches that address behaviours associated with risk, but also prevention efforts. In conclusion, this dissertation advocates for the recognition of young stroke survivors as a distinct group of stroke survivors who deserve tailored policies, intervention, post-stroke care, and research.

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Appendices

Appendix A

SEEKING RESEARCH PARTICIPANTS

Attention Young Adults Who Have Experienced a Stroke!

Are you a young adult who has experienced a stroke between the ages of 18 to 50 years old?

We want to hear from you!

Stroke in young adults is a rare phenomenon, yet its impact can be profound and life-altering. We understand the unique challenges and struggles that come with being a young stroke survivor. Thus, we want to improve our understanding of stroke etiology and risk, as well as improve the current prevention strategies for young adults.

Your experience and insight matter to us!



Your Participation Matters

Stroke significantly impacts survivors as well as the lives of their families and loved ones. Your participation in this study can make a real difference by preventing future young adults from experiencing the devastating effects of stroke all over the world.

How to Participate



Participation in this study is easy! Simply complete our online survey, which should take you approximately 10-15 minutes. Your survey responses are collected anonymously. You will not be asked to include any information that could identify you such as "your name".

Criteria

Must have had a stroke (ischemic, hemorrhagic or transient ischemic attack) between the ages of 18-50 years old

Did not have brain surgery PRIOR to having a stroke

Do not suffer from any cognitive impairments that may impact your ability to participate in the survey (i.e., inability to understand or read text)

This study has been reviewed and received ethics clearance from a University of Waterloo research ethics board.

Ready to help make a difference?

Please scan the QR code below (with your phone's camera) to take the survey.



https://uwaterloo.ca/qualtrics.com/jfe/form/SV_5A6B07tWZHqTicY

As a token of our appreciation, participants will have a chance to win 1 of 4 \$50 Amazon gift cards.

Thank you for your courage, strength, and willingness to help others.

Together, we can create a brighter, healthier future for young adults everywhere.

Should you have any questions or concerns, please contact us at : support.uwstrokestudy@uwaterloo.ca

Appendix B

Email Outreach

This email is being sent on behalf of the researcher team at the University of Waterloo.

Dear stroke survivor,

We hope this email finds you well.

As part of our ongoing research in the field of stroke epidemiology, we are excited to share an opportunity for you to participate in a meaningful research study we are collaborating on.

Researchers at University of Waterloo are conducting a study focused on strokes in young adults. As part of their research, they are seeking input from individuals who have experienced a stroke. This study aims to better understand the factors contributing to strokes in young adults and ultimately improve our understanding of stroke etiology and risk, as well as improving current prevention strategies for this demographic.

Your experiences and insight as a stroke survivor are incredibly valuable. Given that the prevalence of strokes in young adults is rare, your participation is crucial in our understanding of the risk factors that contribute to stroke risk. In comparison to older adults, stroke uniquely impacts the lives of young adults and poses many long term physical and cognitive impairments, marked by emotional and social challenges. Your experiences and insights will provide valuable information that can help researchers and health care professionals identify stroke risk and create targeted prevention programs.

Participation in the study involves completing an online survey, which typically takes about 10 to 15 minutes to complete. All survey responses are collected anonymously. You will not be asked to include any information that could identify you, such as your name. This survey will be completed online through Qualtrics and the link can be found below. The survey will begin with more information about the study and your rights as the participant. If at any time you wish you withdraw from the survey, please close your browser.

The criteria to participate in the study is the following:

- **Controls (those who have not had a stroke):** Any young adult between the ages of 18 to 50 years-old who have NOT suffered from a stroke.
- **Cases (those who have had a stroke):** Must have had a stroke (ischemic, hemorrhagic, or transient ischemic attacks) between the ages of 18 to 50 years old (cases CAN be older than 50 years old, as long as they had a stroke between 18 to 50 years old).

- Did not have brain surgery PRIOR to having a stroke
- Do not suffer from any cognitive impairments that may impact your ability to participate in the survey (i.e., severe/global aphasia).
- Individuals who may have had cardiovascular surgery (heart surgery), intracranial surgery (brain surgery), and carotid endarterectomy (surgery to remove plaque from the carotid arteries) will not be included in our study.
- Lastly, participants must be able to complete the survey in English (be able to read and understand English)

If you qualify for participation, here is a link to our survey:

https://uwaterloo.ca/1.qualtrics.com/jfe/form/SV_5A6B07tWZHqTiCy

Your participation would be greatly appreciated and could have a significant impact on the lives of other young stroke survivors.

Thank you for considering this opportunity to contribute to stroke research and make a difference in the lives of others. Again, if you have any questions, please contact a member of the research team at: support.uwstrokestudy@uwaterloo.ca

This study has been reviewed and received ethics clearance from the University of Waterloo Research Ethics Board (46461).

Warm regards,

University of Waterloo Stroke Research Team

Appendix C

Introduction to Study and Consent to Participate

Study Title: **A comprehensive analysis of the stroke risk and causes in young adults**

University of Waterloo, Canada. School of Public Health, Epidemiology and Biostatistics

What is the study about?

Dear Participant,

Thank you for taking the time to participate in this research study. Your contribution is invaluable and will immensely contribute to advancing the understanding of the risk factors associated with strokes. Given that the prevalence of strokes in young adults is rare, your participation is crucial in our understanding of the risk factors that contribute to stroke risk. In comparison to older adults, stroke uniquely impacts the lives of young adults and poses many long term physical and cognitive impairments, marked by emotional and social challenges. Strokes can have devastating effects on individuals and their families, and understanding the factors that contribute to the onset of stroke is crucial for developing effective prevention strategies.

This study is a case-control design. Thus, it will involve both young adults who have not experienced a stroke (controls) and those who have had a stroke between 18 to 50 years-old (cases). This survey is designed to gather information about various risk factors that may be associated with strokes in young adults. Thus, the survey consists of several sections, each focusing on different aspects related to stroke risk. These sections include but are not limited to demographic questions and questions related to medical history, lifestyle factors, and any pre-existing conditions you may have.

What does participation involve?

Controls – Those who have NOT experienced a stroke (Prolific, Amazon Mechanical Turk, or Other Polling Companies)

This survey will ask you questions about your demographic characteristics (i.e., age, sex, country of residence), as well as your physical, mental, and social health and well-being. On average, this should take you approximately 5-10 minutes to complete.

Cases – Those who HAVE experienced a stroke

This survey will ask questions similar to those in the control group, along with additional questions about your stroke and its impact on your life. We understand that your time is valuable, and we have designed this survey to be as efficient as possible. However, given that stroke is a complex disease, multiple factors must be considered to make as accurate conclusions as possible; thus, this survey is detailed and consists of multiple subsections. On average, it should take approximately 10 to 15 minutes to complete. Your thorough and thoughtful responses are greatly appreciated and will contribute significantly to the success of this study.

Who may participate in the study?

The criteria to participate in the study is the following:

- Controls: Any young adult between the ages of 18 to 50 years-old who have not suffered from a stroke.
- Cases: Must have had a stroke (ischemic, hemorrhagic, or transient ischemic attacks) between the ages of 18-49 years old
 - o Did not have brain surgery PRIOR to having a stroke
 - o Do not suffer from any cognitive impairments that may impact your ability to participate in the survey (i.e., aphasia).
 - o Individuals who may have had cardiovascular surgery (heart surgery), intracranial surgery (brain surgery), and carotid endarterectomy (surgery to remove plaque from the carotid arteries) will not be included in our study.
- Lastly, participants must be able to complete the survey in English (be able to read and understand English)

Will I receive anything for participating in the study?

As mentioned previously, this survey will not ask for any personal/identifying information. In appreciation of the time you have given to this study, you can enter into a draw for 1 of 4 \$50 Amazon gift cards. Your odds of winning one of these prizes is approximately 1 in 250. Information collected to draw the prizes will not be linked to the study data in any way, and this identifying information (your email address) will be stored separately, then permanently deleted after the prizes have been provided. The amount received may be taxable. The emails entered in the draw will not be stored, nor contacted, unless you are the winner.

What are the possible benefits and risks of the study?

Though there are no risk and direct benefits to you, the data collected from this survey will provide valuable information for researchers to further the discussion of stroke in young adults. Some questions may cause discomfort. There are no other known or anticipated risks. Please feel free to select “prefer not to answer” for any questions you do not feel comfortable answering. Your responses will remain deidentified, confidential, and will only be used for research purposes. This questionnaire will not ask for your name or other identifying information. As described above, email addresses will be separately collected to enter your name in the draw. This survey is hosted by Qualtrics, which has multiple safeguards in place, although no Internet transmission is ever fully secure. Qualtrics will collect IP address, but this will be removed, and all data will be de-identified. Collected data will be securely stored on password-protected computers for at least 7 years. If at any time you wish you withdraw from the survey, please close the browser. Moreover, removing your responses once they have been entered is not possible as the researchers will not have any way of which responses belong to you, as they are completely anonymous.

This study has been reviewed and received ethics clearance through the University of Waterloo’s Research Ethics board (46461). Should you have any questions or concerns regarding your participation or this study, please feel free to contact a member of the research team at: support.uwstrokestudy@uwaterloo.ca

Once again, thank you so much for your willingness to participate in this study. We sincerely appreciate your time and willingness to share your experiences. We hope that together we can shape future interventions and ultimately improve the health outcomes of young adults that are at risk of having a stroke.

Thank you for your time and contribution. Warm regards,

University of Waterloo Stroke Research Team

Followed by consent question:

By providing your consent, you are not waiving your legal rights or releasing the investigator(s) or involved institution(s) from their legal and professional responsibilities.

☐ I agree to participate in this study

☐ I do not agree to participate in this study