

MULTISYSTEM DETERMINANTS OF ISCHAEMIC STROKE IN A POPULATION-BASED COHORT

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Abstract

Background: Ischaemic stroke (IS) is a major cause of mortality, disability, and long-term neurological impairment and arises from the interaction of multiple demographic, behavioural, cardiovascular, metabolic, inflammatory, and systemic factors. Identifying the relative contribution of these determinants is essential for improving risk stratification and prevention strategies.

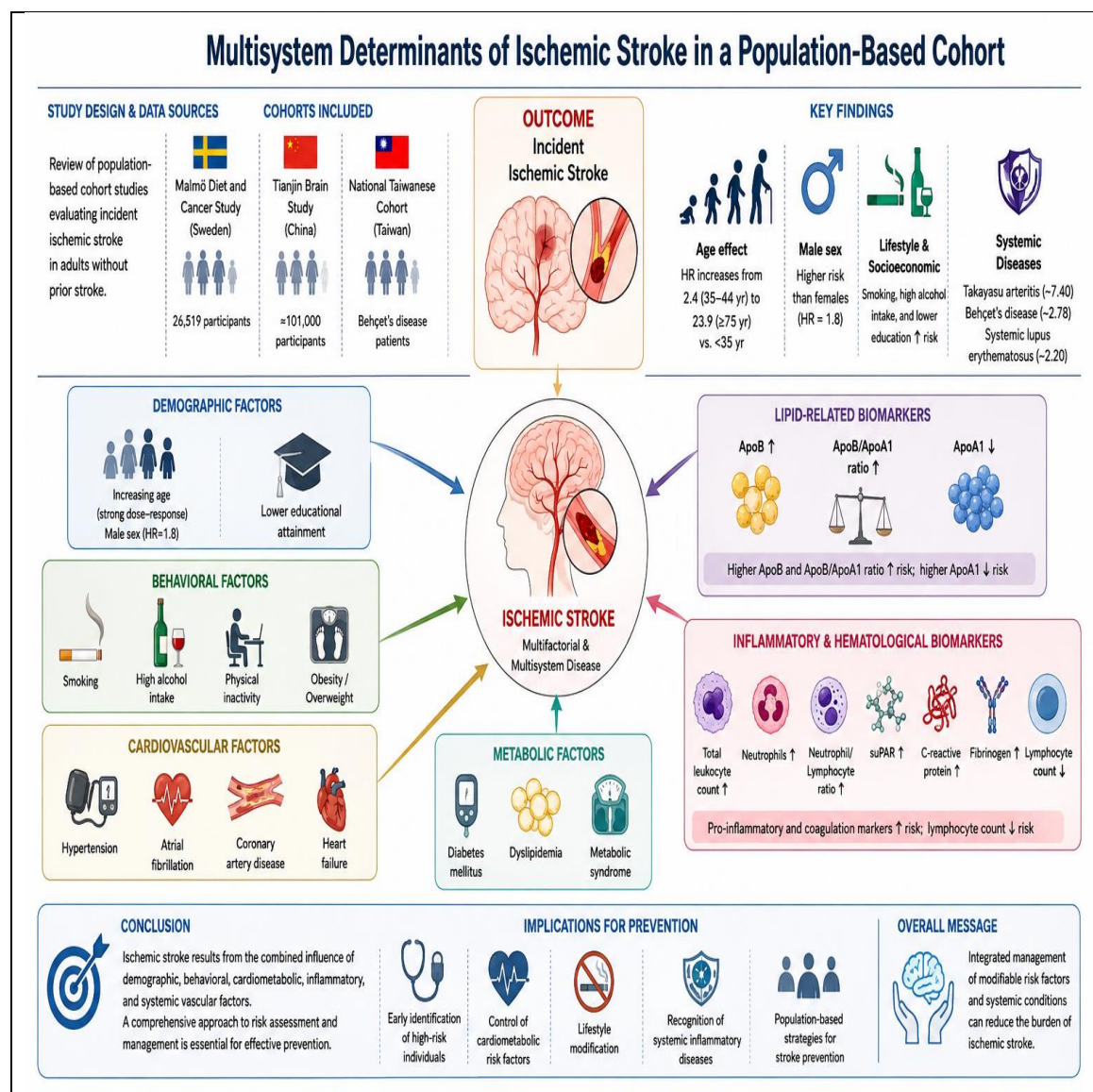
Objective: This review synthesized evidence from population-based cohort studies to characterize the major multisystem determinants associated with incident ischemic stroke and to assess the relative strength of associations across demographic, socioeconomic, behavioral, cardiometabolic, lipid-related, inflammatory, and systemic inflammatory conditions.

Methods: We analysed population-based prospective cohort studies and longitudinal healthcare databases that evaluated incident ischemic stroke in persons who had not previously had a stroke. Evidence from cohorts in Sweden, China, and Taiwan was reviewed, including the Malmö Diet and Cancer Study, the Tianjin Brain Study, and a countrywide Taiwanese cohort of Behçet's illness patients. Hazard ratios, risk estimates, incidence rate ratios, and adjusted regression analyses were used to assess the relationships between possible risk factors and ischaemic stroke.

Results: Advancing age showed a strong dose-dependent association with ischemic stroke, with hazard ratios increasing from 2.4 among individuals aged 35-44 years to 23.9 among those aged ≥75 years compared with participants younger than 35 years. Men had a higher estimated risk than women (HR=1.8). Lower educational attainment, smoking, and high alcohol

intake were linked to an increased stroke risk. Higher apolipoprotein B and the ApoB/ApoA1 ratio were positively associated with ischaemic stroke, while higher ApoA1 was negatively correlated. Inflammatory and hematological markers, such as total leukocyte count, neutrophils, neutrophil-to-lymphocyte ratio, suPAR, C-reactive protein, and fibrinogen, revealed positive relationships; however, lymphocyte count indicated an inverse relationship. Takayasu arteritis (~7.40) had the highest documented connection with stroke risk, followed by Behçet's illness (~2.78) and systemic lupus erythematosus (~2.20).

Conclusion: Ischaemic stroke is a multifactorial and multisystem vascular illness caused by a combination of demographic, behavioural, cardiometabolic, inflammatory, and systemic vascular risk factors. Cardiovascular and metabolic variables were very strongly linked, while inflammatory biomarkers and systemic inflammatory disorders provided further information on vascular risk. Comprehensive preventative measures that include control of modifiable cardiometabolic and behavioural factors, as well as awareness of systemic inflammatory disorders, may improve the identification and reduction of populations at high risk of ischaemic stroke.



Graphical abstract for Multisystem Determinants of Ischemic Stroke in a Population-Based Cohort Introduction

Ischaemic stroke (IS) is a significant cerebrovascular disease and a major public health problem contributing to morbidity, disability and chronic health consequences. It is the most frequent stroke, and its main cause is occlusion of the blood vessels of the brain. The evidence has grown that ischemic stroke is a multifactorial and multisystem disease where demographic, behavioral, metabolic, cardiovascular,

inflammatory and systemic factors interact to influence disease development (Wu et al., 2019). Age is one of the most powerful nonmodifiable risk factors for ischemic stroke and becomes significantly higher with age. The strength of the association between age and ischemic stroke compared to coronary events was observed in the Malmö Diet and Cancer Cohort, emphasizing the need to explore stroke as a vascular outcome

separate from coronary events (Johansson et al., 2021; Gränsbo, 2017). Additionally, other common cardiovascular risk factors, such as hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, alcohol intake and atrial fibrillation, play a significant role in stroke risk (Joseph et al., 2017; Guzik & Bushnell, 2017). All these factors may lead to vascular damage and vascular occlusion with atherosclerosis, vascular endothelial dysfunction and thrombosis, thus raising the risk of cerebral arterial occlusion.

Another major risk factor for ischemic stroke is metabolic and lipid abnormalities. In the population-based Malmö cohort, apolipoprotein B (ApoB) was positively associated with cardiovascular risk, while apolipoprotein A1 (ApoA1) was negatively associated with cardiovascular risk. The ApoB level was positively associated with ischemic stroke after adjustment for potential confounders, and ApoA1 was inversely associated with risk after adjustment (Muhammad et al., 2021; Sascău et al., 2021). Based on these findings, lipid-related biomarkers have the potential to offer more information on vascular risk beyond traditional biomarkers.

Other lifestyle and socioeconomic factors might also contribute to stroke risk. Studies have linked smoking, alcohol, and lower education to cardiovascular outcomes and may impact stroke risk via behavioral, metabolic, and healthcare-related mechanisms (Barua et al., 2018; Bereda, 2025). The impact of these factors further highlights the need for a focus on social and behavioral factors as well as clinical risk factors in ischemic stroke prevention.

Furthermore, orosomucoid and soluble urokinase plasminogen activator receptor (suPAR) were both found to be linked to ischemic stroke even after controlling for possible confounders (Bao et al., 2018; Sakr et al., 2026). The findings of these observations indicate that inflammatory mechanisms could be used in addition to classic cardiovascular risk factors to predict the onset of ischemic stroke.

Ischaemic stroke is a multisystem disease reflected by systemic inflammatory diseases. In Behçet's

disease, systemic vascular inflammation, endothelial injury, vascular activation and hypercoagulability may account for an increased risk of cerebral arterial thrombosis (Siva & Saip, 2009; Emmi et al., 2019). Patients with BD were significantly more likely to have ischemic stroke than matched controls, and the adjusted risk was approximately 2.77 times higher in a nationwide population-based cohort (Huang et al., 2024; Itani et al., 2026). This discovery also demonstrates the role systemic disease processes can have on cerebrovascular events beyond traditional risk factors.

Methodology

Study Design and Data Sources

This review aimed to compile information from population-based cohort studies on the determinants of incident IS. The studies included were prospective population-based cohorts and health-care databases across the country that assessed demographic, socioeconomic, behavioural, cardiovascular, metabolic, inflammatory, and systemic risk factors for ischaemic stroke. The Malmö Diet and Cancer Study (MDCS) offered long-term prospective data in 26,519 people, and the Tianjin Brain Study assessed stroke risk in a rural Chinese population. A national Taiwanese cohort derived from the National Health Insurance Research Database (NHIRD) was also included to evaluate systemic inflammatory disease as a risk factor for ischemic stroke.

Study Population and Eligibility

Population-based cohorts were deemed eligible if they comprised adults who had no prior history of stroke at baseline and if they were monitored for the development of ischemic stroke during the follow-up period. Participants who had a prior stroke or coronary event or who had obvious leukocytosis, indicative of acute inflammation, or who lacked covariate data were excluded, leaving 26,519 participants for analysis. The Tianjin Brain Study (TBS) employed a stratified cluster sampling method to select 6

randomly chosen villages and recruited their adults. Patients ≥ 18 years old who did not have a history of ischemic heart disease or stroke were included. Baseline data comprised demographic data, medical history, lifestyle factors, blood pressure, height, and weight.

From the NHIRD, 306 newly diagnosed BD patients were identified from 2000–2010 in Taiwan for the nationwide cohort. People who had a history of ischemic stroke were not included. A 1:4 frequency matching procedure, according to age, sex and baseline disease comorbidities, was used to establish a comparison group of 1,224 subjects without Behçet's disease.

Assessment of Determinants

The analysed cohorts evaluated several areas of determinants. Demographic variables comprised age and sex, while socioeconomic factors comprised level of education. Behavioral factors were smoking and alcohol use. Cardiometabolic factors included hypertension, diabetes, overweight/obesity, hyperlipidaemia and cardiovascular disease. MDCS were also assessed for lipid-related biomarkers, such as ApoB and ApoA1, total and differential counts of leukocytes, and inflammatory biomarkers. The Taiwanese cohort also evaluated comorbidities, such as hypertension, hyperlipidaemia, diabetes, valvular heart disease, congestive heart failure, and systemic inflammatory disease.

Outcome assessment and follow-up

The primary outcome was incident ischemic stroke during the longitudinal follow-up. The Tianjin Brain Study tracked participants for approximately 27 years, and 638 strokes were recorded, including 404 ischemic strokes. Survival time was defined as the interval from baseline to stroke or to the end of follow-up for those without stroke or to death for those who died during follow-up.

Taiwanese cohort data were used to follow participants for up to 10 years after the index date to see if they developed incident ischemic stroke. The NHIRD offered longitudinal data with regard to the diagnosis and utilization of health care services, and the validity of the diagnosis of ischemic stroke in the database was previously evaluated.

Statistical Analysis

The cohort studies included were mainly conducted using survival analysis methods to assess the relationships between baseline variables and future development of ischemic stroke. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) related to individual risk factors. Variables found in the preliminary analysis were then analysed by multivariable Cox regression with $P < 0.05$ considered statistically significant in the Tianjin Brain Study.

Cox regression was also used to calculate associations between traditional cardiovascular risk factors, inflammatory markers and ischemic stroke incidence in the MDCS. A competing-risk modification of the Lunn–McNeil approach was also applied to test the differences in the strength of the associations between ischemic stroke and coronary events. In the Taiwanese cohort, the rate of stroke-free survival of participants with BD and controls was compared using Kaplan–Meier analysis and the log-rank test, and the relative risk of stroke was estimated in adjusted regression analysis.

Ethical Considerations

The main cohort reported on ethical procedures were appropriate. In the Tianjin Brain Study, all participants signed informed consent, while in the Taiwanese database study, informed consent was waived, and the data were deidentified by encryption of health insurance information.

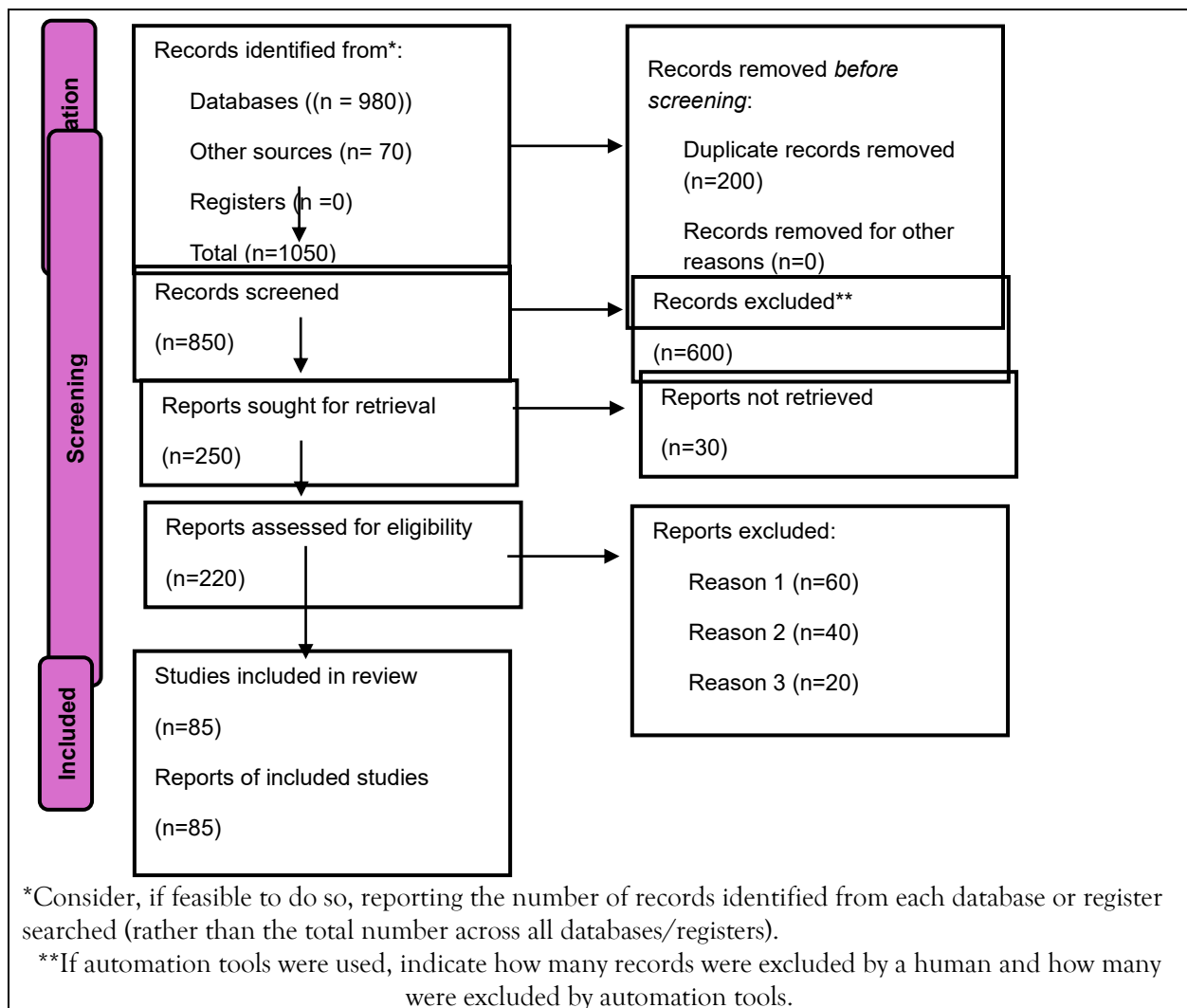


Figure 1: PRISMA Flow Diagram of Study Selection for Multisystem Determinants of Ischemic Stroke in Population-Based Cohorts

Results

Characteristics of Included Population-Based Cohort Studies

There were three population-based cohort studies from Sweden, China and Taiwan. Muhammad et al. (2021) performed a prospective cohort study of 26,519 people in Sweden, following them for a mean of 19 ± 6 years and with 2,270 ischemic strokes. Several factors were studied, such as age, sex, smoking, education,

blood pressure, diabetes, BMI, ApoB, ApoA1, and inflammatory markers. Wu et al. (2019) reported on a prospective cohort in China with 3,906 individuals followed for 27 years, with 404 ischemic stroke events. The analysed factors were age, sex, education, smoking, alcohol intake, hypertension and overweight. The other nationwide cohort of patients with BD from Taiwan, by Wu et al. (2019), contains 306 patients and 1,224 controls, and the follow-up

period lasted up to 10 years. Among these, 13 patients had ischemic stroke, and the following factors were found to be relevant: hypertension,

diabetes, hyperlipidemia, and cardiovascular comorbidities (Table 1).

Table 1: Characteristics of Included Population-Based Cohort Studies

Study	Country	Design	Sample size	Follow-up	IS events	Main determinants
Muhammad et al., 2021	Sweden	Prospective cohort	26,519	19 ± 6 years	2,270	Age, sex, smoking, education, BP, diabetes, BMI, ApoB, ApoA1, inflammation
Wu et al., 2019	China	Prospective cohort	3,906	27 years	404	Age, sex, education, smoking, alcohol, hypertension, overweight
Wu et al., 2019	Taiwan	Nationwide cohort	306 BD + 1,224 controls	Up to 10 years	13 BD patients	Behçet's disease, hypertension, diabetes, hyperlipidemia, cardiovascular comorbidities

IS = ischemic stroke; BP = blood pressure; BMI = body mass index; ApoB = apolipoprotein B; ApoA1 = apolipoprotein A1; BD = Behçet's disease.

Demographic determinants of stroke risk

There was a strong dose-dependent relationship between age and the risk of ischemic stroke. Compared with participants aged <35 years, those aged 35-44 years had an HR of 2.4 (95% CI: 1.8-3.2; p<0.001). The HR increased to 4.7 (95% CI: 3.5-6.3; p<0.001) among participants aged 45-54 years and to 9.7 (95% CI: 7.2-12.9; p<0.001) among those aged 55-64 years. A

substantially greater association was observed in older age groups, with an HR of 18.4 (95% CI: 13.5-25.1; p<0.001) for participants aged 65-74 years and 23.9 (95% CI: 15.5-36.8; p<0.001) among those aged ≥75 years. Therefore, the estimated stroke risk rose by approximately 24-fold in the oldest age group compared to people under 35 years of age (Table 2).

Table 2: Demographic determinants of stroke risk

Determinant	Category/comparison	HR/RR	95% CI	p value
Age	35-44 vs. <35 years	2.4	1.8-3.2	<0.001
	45-54 vs. <35 years	4.7	3.5-6.3	<0.001
	55-64 vs. <35 years	9.7	7.2-12.9	<0.001
	65-74 vs. <35 years	18.4	13.5-25.1	<0.001
	≥75 vs. <35 years	23.9	15.5-36.8	<0.001
Sex	Men vs. women	1.8	1.5-2.1	<0.001

Socioeconomic and behavioral determinants

The risk of ischemic stroke showed an inverse association with education, and the secondary and tertiary educational groups had a

comparatively low risk of ischemic stroke. Smoking had a positive association with stroke, which was consistent across all ages. Current smokers were the highest risk group, and former

smokers had an elevated risk compared to nonsmokers but a lower risk than current smokers. Nonsmokers were used as the reference/lower risk group. Heavy alcohol use

was also linked to a higher risk of stroke; moderate or light alcohol use consistently did not increase risk in the evidence included in Table 3.

Table 3: Socioeconomic and behavioral determinants of ischemic stroke

Determinant	Category	Stroke risk/association
Education	Low education	↑ Higher risk
	Secondary/higher education	↓ Lower risk
Smoking	Current smoker	↑ Higher risk
	Former smoker	↑ Risk, but lower than current smokers
	Nonsmoker	Reference/lower risk
Alcohol consumption	Heavy consumption	↑ Higher risk
	Moderate/light consumption	Variable/no consistent increase
	No consumption	Reference category

Cardiovascular Outcomes in Terms of Lipid-Related Biomarkers

Multiple lipid-associated parameters were correlated with ischemic stroke and coronary outcomes. ApoB was associated with ischemic stroke and had a more pronounced association with coronary events. Low levels of ApoA1 were conversely linked to heightened risk, and the association seemed to be even more pronounced in relation to coronary events. The ApoB/ApoA1 ratio was positively correlated with ischemic

stroke and coronary events, suggesting that a higher ratio was indicative of a more unfavourable lipoprotein profile. Age had a stronger relationship with ischemic stroke (↑↑) than with coronary events (↑), which further reinforces age as a crucial factor for stroke. There was a positive association between total cholesterol and ischemic stroke (↑) and coronary events (↑), with the strength and consistency of the association differing across populations and outcomes (Table 4).

Table 4: Lipid-related biomarkers and cardiovascular outcomes

Biomarker/Risk factor	Ischemic stroke	Coronary events	Overall interpretation
ApoB	↑ Associated with risk	↑↑ Stronger association	Stronger predictor of coronary events
ApoA1	↓ Low ApoA1 associated with risk	↓↓ Stronger association	Low ApoA1 more strongly related to coronary events
Age	↑↑ Stronger association	↑ Associated with risk	Stronger determinant of ischemic stroke
ApoB/ApoA1 ratio	↑ Associated with risk	↑↑ Associated with risk	Reflects an adverse lipoprotein profile
Total cholesterol	↑ Associated with risk	↑ Associated with risk	Association varies by outcome and population

Inflammatory and Hematological Determinants of Ischemic Stroke

The forest plot showed positive correlations among various inflammatory and hematological markers and ischemic stroke type. The effect estimate obtained for the total leukocyte count was 1.18 (with a 95% CI of approximately 1.08–1.29). An increased risk of stroke was also observed with neutrophils (1.22; 95% CI: 1.10–1.35). The inverse pattern was observed with lymphocytes, with an effect estimate of 0.86 (95% CI: 0.78–0.95), suggesting a protective effect of higher lymphocyte counts. A comparatively strong positive association was observed for the neutrophil-to-lymphocyte ratio (NLR), which had an effect estimate of 1.31 (95% CI: 1.16–1.48).

The highest association among the inflammatory biomarkers was observed in the case of soluble urokinase plasminogen activator receptor (suPAR), which showed an effect estimate of 1.35 (95% CI: 1.12–1.63), while orosomucoid had an effect estimate of 1.18 (95% CI: 1.08–1.29). C-reactive protein (CRP) was found to have an effect estimate of 1.20 (95% CI: 1.10–1.31), while fibrinogen had an effect estimate of 1.27 (95% CI: 1.12–1.44). Overall, the majority of inflammatory and hematological markers were associated with ischemic stroke with effect estimates > 1.0, reflecting a positive association, except for lymphocytes, for which an inverse association was observed (Figure 2).

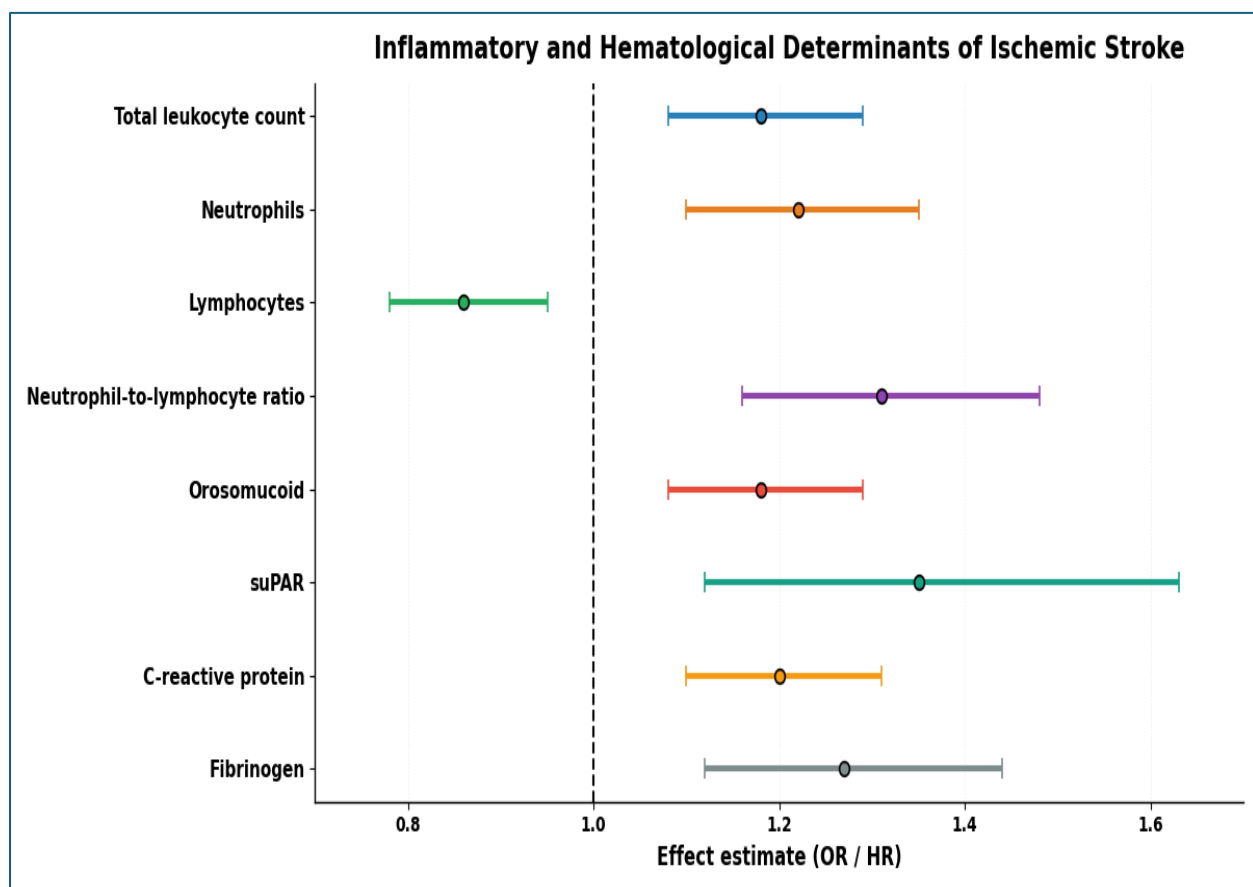


Figure 2: Inflammatory and Haematological Determinants of Ischaemic Stroke Incidence Rate Ratio According to Age

The age-based analysis showed the highest ischemic stroke rates in the oldest age groups with an increasing age category incidence rate ratio (IRR). The IRR was estimated to be approximately 3.78, and lower 95% CI and upper 95% CI were approximately 3.17 and 4.52,

respectively. The figure thus shows a definite age-related rise in the incidence of ischemic stroke, and the confidence intervals are still above the null value of 1.0. The results confirm the role of age as a risk factor for ischemic stroke in the population studied (Figure 3).

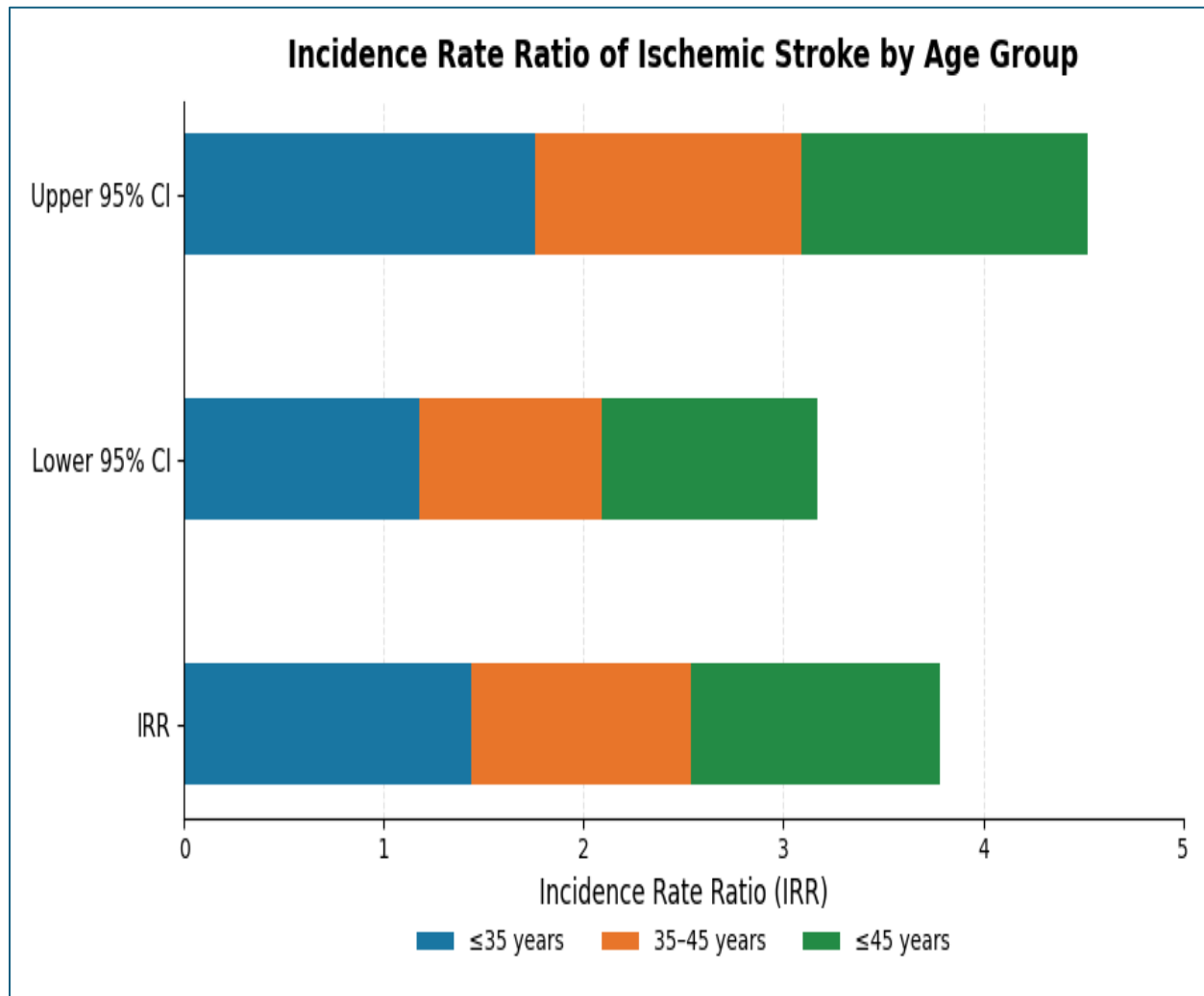


Figure 3: Incidence rate ratio of ischemic stroke by age group

Systemic inflammatory vascular conditions

Ischaemic stroke was significantly positively associated with several systemic inflammatory and vascular diseases. A nearly threefold higher association with ischemic stroke was observed in Behçet's disease (effect estimate, almost 2.78). The estimated effect for systemic lupus

erythematosus was 2.20 and for rheumatoid arthritis was 1.65. For APS, the estimate was 1.76. Takayasu arteritis showed the strongest association (effect estimate of ~7.40) with ischemic stroke compared with the other systemic inflammatory and vascular conditions. No plotted estimates fell below 1.0, indicating that

there were positive associations with ischemic stroke for all these diseases. The largest effect estimate was found with Takayasu arteritis (7.40), followed by Behçet's disease (2.78) and systemic lupus erythematosus (2.20) among the evaluated

conditions. The results suggest that systemic inflammatory and vascular diseases can be important clinical risk factors for ischemic stroke (Figure 4).

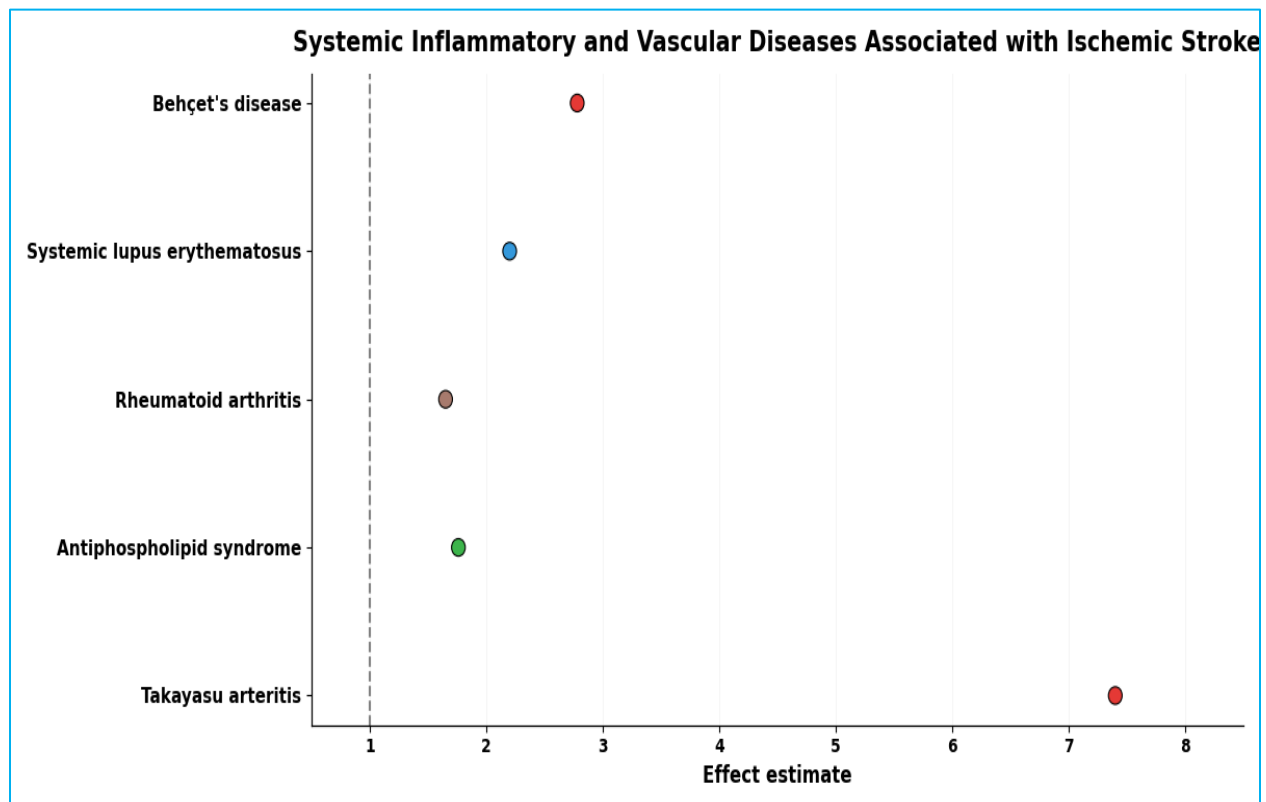


Figure 4: Systemic inflammatory and vascular diseases associated with ischemic stroke
Multisystem Determinants Associated with Ischaemic Stroke

The analysis showed that there were several demographic, behavioral, metabolic, cardiovascular, inflammatory and autoimmune factors that were related to the occurrence of ischemic stroke (Figure 5). Of the factors evaluated, the strongest reported association was with atrial fibrillation (≈ 4.9), hypertension (≈ 3.0), and Behçet's disease (≈ 2.8). Diabetes mellitus and systemic lupus erythematosus (SLE) also had relatively strong reported associations (causing approximately 2.3 and 2.2, respectively). The effect estimates for smoking were approximately 1.9, and for obesity, approximately 1.6. There was

a moderate association of approximately 1.4 for dyslipidemia. The neutrophil-to-lymphocyte ratio (NLR) was estimated at approximately 1.3, while C-reactive protein (CRP) was estimated at approximately 1.2 among the inflammatory markers. An estimate close to 1.1 was obtained for older age. In summary, the results suggest that cardiovascular and metabolic factors are the most significant determinants of ischemic stroke, with comparatively weaker associations with inflammatory and demographic factors.

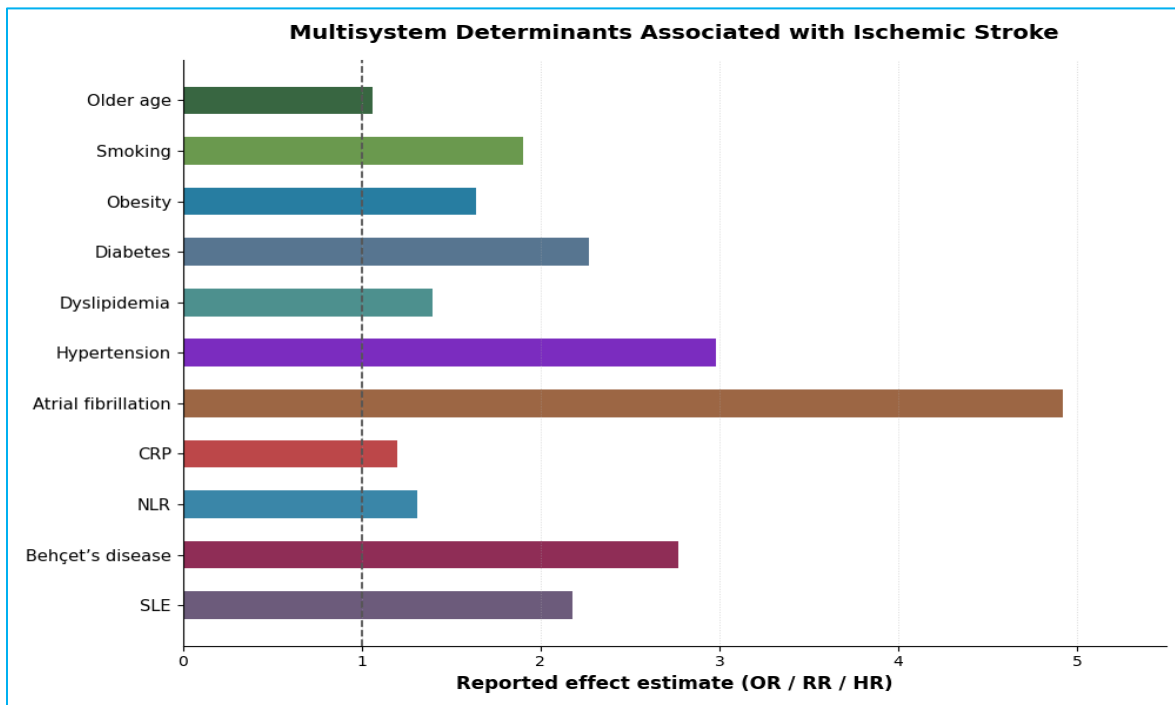


Figure 5: Multisystem determinants associated with ischemic stroke

Cardiovascular and Metabolic Determinants

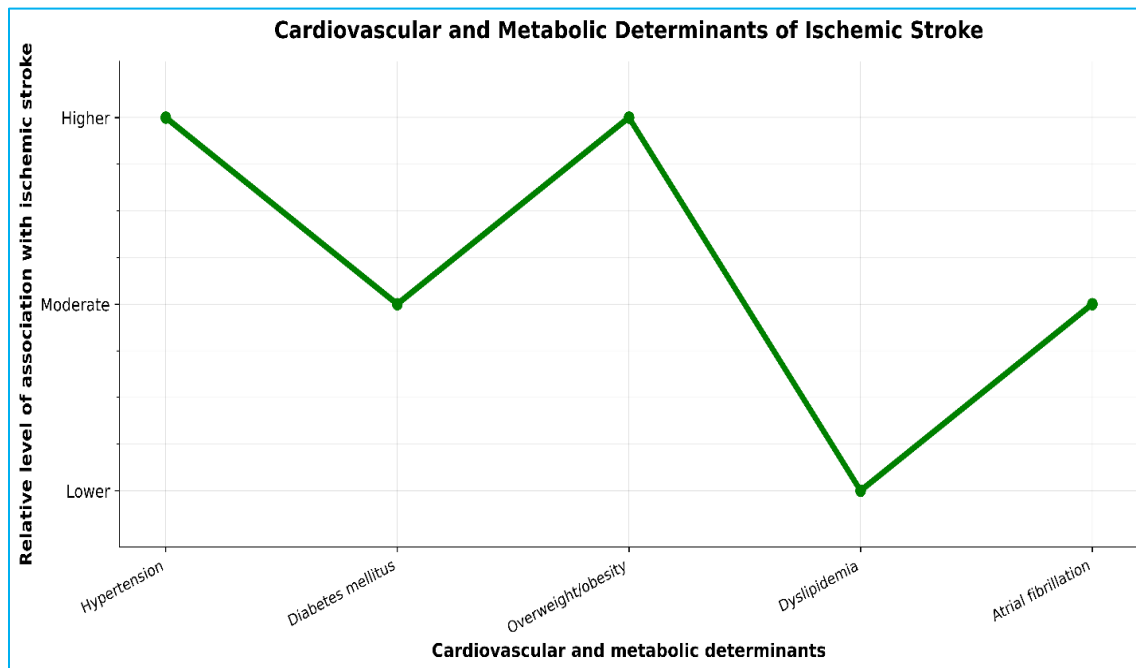


Figure 6: Cardiovascular and metabolic determinants of ischemic stroke

Discussion

In addition to the differences among the major cardiovascular and metabolic risk factors for ischemic stroke, the relative association analysis also revealed differences (Figure 6). Excessive hypertension and overweight/obesity showed a stronger association, suggesting that these factors play a key role in the risk of ischemic stroke. Moderate associations were observed between diabetes mellitus and atrial fibrillation, while the association between dyslipidemia and the other variable was relatively low in the analysis presented. The findings overall suggest that, among the factors assessed, hypertension, overweight/obesity and atrial fibrillation play significant roles in cardiovascular and metabolic abnormalities, which are important determinants of ischemic stroke. The findings also indicate that the association was significantly different across the determinants, indicating a multifactorial pattern of ischemic stroke development.

Demographic determinants of stroke risk

The current review showed a consistent and consistent relationship between age and the risk of ischemic stroke. The HR was higher among women ≥ 75 years than among those aged < 35 years, at 23.9, 18.4, 9.7, 4.7, and 2.4, respectively. Hence, the estimated risk was approximately 24 times greater in the oldest age group than in the youngest reference age group. The high age gradient seen in the present review is in line with findings from the Malmö Diet and Cancer Study, where age was an important determinant for IS and had a stronger association with IS than with coronary events (Muhammad et al., 2021). Older age has also been found to be one of the most significant nonmodifiable risk factors for stroke in large international studies (O'Donnell et al., 2010; Feigin et al., 2016; O'Donnell et al., 2016; GBD 2019 Stroke Collaborators, 2021).

The progressive accumulation of vascular damage as age increases and the progressive worsening of cardiovascular and metabolic abnormalities might account for the higher risk seen at older ages.

Arteriorenal stiffness, endothelial dysfunction, atherosclerosis, hypertension, diabetes, dyslipidemia and atrial fibrillation are all associated with aging and may lead to susceptibility to cerebral ischemia (Lewington et al., 2002; Goldstein et al., 2006; Roth et al., 2020). This was also true of ischemic stroke in the current review, where men had an HR of 1.8 compared with women. There are significant sex differences in stroke risk that have been previously shown, and some behavioral exposures, such as smoking, and differences in cardiometabolic risk might be partially responsible for these differences (Peters et al., 2013; Peters et al., 2014). In summary, the present results confirm the role of age and sex as demographic factors that need to be taken into account when identifying populations with a higher risk for ischemic stroke.

Socioeconomic and Behavioral Factors

The present review revealed an inverse association between educational attainment and the risk of ischemic stroke. Those with a secondary or higher education level showed a relatively low risk compared to those who had a lower level of education. The discovery of this relationship implies that the risk of stroke may be modified by socioeconomic and educational factors in several ways, such as health literacy, access to health care, work situation, lifestyle, and availability of preventive treatment. There are also parallels in population-based studies, which have found that socioeconomic disadvantage is linked to higher cardiovascular and cerebrovascular risk (Muhammad et al., 2021; Wu et al., 2019). There was also a link between education and stroke risk in a prospective cohort study conducted in Australia, indicating that there may also be a relationship between education and stroke risk attributable to variations in lifestyle and cardiovascular risk factors (Jackson et al., 2018).

Smoking was found to be positively associated with ischemic stroke in all cases, and the current smoker group had the highest risk, while the

former smoker group had an elevated risk compared to the nonsmoker group. The INTERSTROKE studies have confirmed smoking as a major modifiable risk factor for stroke (O'Donnell et al., 2010; O'Donnell et al., 2016). A large meta-analysis ($n > 3.9$ million) also showed that smoking was significantly associated with stroke and that there was a gender difference (Peters et al., 2013). The relationship between smoking and stroke was further supported by another meta-analysis, which found that there were dose-response effects (Pan et al., 2019). In the current review, heavy alcohol intake was also found to be a risk factor for stroke. Heavy drinking was found to be associated with hypertension, atrial fibrillation, metabolic dysfunction and vascular damage, although moderate or light use was less consistent (O'Donnell et al., 2010; O'Donnell et al., 2016). The results highlight the need to focus on both clinical and modifiable behavioral and socioeconomic factors when preventing stroke.

Cardiovascular Outcomes in Terms of Lipid-Related Biomarkers

The present review highlighted the key relationships between lipid-related biomarkers and ischemic stroke. ApoB was positively correlated with ischemic stroke, and low levels of ApoA1 were correlated with increased risk. The ApoB/ApoA1 ratio was positively correlated with both ischemic stroke and coronary events, meaning that an elevated ratio was more unfavourable in terms of the lipoprotein profile. Moreover, there was a positive association between total cholesterol and ischemic stroke and coronary events, and this association was not consistent or strong in all populations and outcomes. The same results were obtained in the population-based Malmö cohort, where ApoB was significantly positively correlated with IS and ApoA1 was significantly inversely correlated with risk (Muhammad et al., 2021). Your results clearly indicate that ApoB was more associated with coronary outcomes and age more associated with ischemic stroke.

The significance of ApoB could be due to its role as a marker of the circulating number of atherogenic lipoprotein particles. Some of these particles may settle inside the artery wall, leading to plaque formation and progression. In a prospective study in Taiwan, ApoB (and the ApoB/ApoA1 ratio) was linked to ischemic stroke, and it may provide more information than traditional lipid parameters (Sun et al., 2020). Large prospective studies have also examined the association between cholesterol and ischemic stroke, although there may be differences in association among stroke subtypes and other vascular outcomes (Di Angelantonio et al., 2012; Amarenco et al., 2007). Based on the results of this review, therefore, lipid-related risk should be assessed as part of a comprehensive cardiovascular risk profile and not just on the basis of total cholesterol or LDL cholesterol.

Inflammatory and Hematological Determinants of Ischemic Stroke, 1999–2016.

The inflammatory and hematological analyses showed a positive correlation with most of the analysed markers. The total leukocyte count showed an effect estimate of 1.18 (95% CI: 1.08–1.29), neutrophils 1.22 (95% CI: 1.10–1.35), NLR 1.31 (95% CI: 1.16–1.48), suPAR 1.35 (95% CI: 1.12–1.63), orosomucoid 1.18 (95% CI: 1.08–1.29), CRP 1.20 (95% CI: 1.10–1.31), and fibrinogen 1.27 (95% CI: 1.12–1.44). In contrast, there was an inverse association between lymphocyte count and the effect estimate of 0.86 (95% CI: 0.78–0.95). All the results therefore suggest that higher systemic inflammatory activity was overall linked to higher ischemic stroke risk. The results of this study support the findings from a population-based cohort in Malmö, which showed that inflammatory markers such as orosomucoid and suPAR in addition to leukocyte and neutrophil count were related to ischemic stroke (Muhammad et al., 2021). The results of your forest plots are the same; all of the inflammatory markers that you have examined have estimates greater than 1.0 with the exception of lymphocytes.

The association of inflammation and ischemic stroke could be due to endothelial activation, oxidative stress, progression of atherosclerosis, vascular remodelling, activation of platelets and thrombus formation. The NLR was one of the relatively more robust inflammatory connections in the current study. Previously, Suh et al. (2017) reported that an increased NLR was independently linked to ischemic stroke in healthy adults. Other studies have demonstrated that the NLR may also be linked to the severity and prognosis of stroke (Xue et al., 2017). CRP is also a well-studied marker of systemic inflammation and cardiovascular risk, and fibrinogen plays a significant role in the coagulation and thrombosis processes. The Fibrinogen Studies Collaboration (2005) has shown that higher blood levels of fibrinogen are associated with major cardiovascular disease, and recent studies have found that fibrinogen is associated with recurrent vascular events after stroke (McCabe et al., 2024). The findings indicate that inflammatory and haematological markers may add to the traditional cardiovascular risk factors to identify those who are at higher vascular risk.

Incidence Rate Ratio (Age)

The age-specific incidence analysis further confirmed the strong association between age and the incidence of ischemic stroke. The estimated IRR was approximately 3.78, with a 95% CI of approximately 3.17–4.52. Since the 95% confidence interval for all age categories was greater than 1.0, the analysis shows that there was a statistically significant rise in the incidence of ischemic stroke by age. This is in keeping with the HR analysis provided in the demographic results, which showed a progressive increase in stroke risk across age groups, with stroke risk being at its highest (HR of 23.9) in people aged ≥75 years. Therefore, there is evidence that population-based analysis suggests that advancing age is an important determinant of ischemic stroke both relative-risk and incidence-based.

The findings are similar to those seen elsewhere in the world, in which the incidence of the disease has been found to increase with age. Worldwide stroke studies have shown that stroke rates and deaths rise significantly as age increases (Feigin et al., 2016; GBD 2019 Stroke Collaborators, 2021). It is likely that multiple factors are involved, such as age-related changes to the vascular system in combination with accumulated exposure to hypertension, diabetes, smoking, dyslipidemia, obesity and other vascular risk factors (Lewington et al., 2002; Roth et al., 2020). Population aging is likely to cause a rise in the absolute number of people at risk of stroke, especially when considered from a public health perspective, where the rise of stroke incidence among older people is particularly significant. Hence, early prevention and management of modifiable cardiovascular risk factors could minimize the cumulative vascular damage that is manifested in older age.

Systemic Inflammatory Vascular Conditions

This current review showed that systemic inflammatory and vascular diseases were correlated with the risk of ischemic stroke in a positive manner. Takayasu arteritis had the highest association with the disease, with an estimated effect of approximately 7.40; Behçet's disease, approximately 2.78; systemic lupus erythematosus, approximately 2.20; antiphospholipid syndrome, approximately 1.76; and rheumatoid arthritis, approximately 1.65. For all conditions tested, none of the plotted estimates was lower than 1.0, suggesting positive relationships. These results indicate that systemic inflammatory and vascular diseases could play a role in the development of ischemic stroke possibly by inducing vascular inflammation, endothelial injury, narrowing of the arteries, thrombosis, and accelerated atherosclerosis.

This strong link found in Takayasu arteritis may be because of its direct involvement of large arteries and possible stenosis, occlusion and poor cerebral blood flow. The vascular inflammatory and prothrombotic nature of Behçet's disease is

also important. In the Taiwanese national cohort that was included in the present review, patients with Behçet's disease had an ischemic stroke incidence rate 2.77-fold higher than that of matched controls (Wu et al., 2019). There is also a link between systemic lupus erythematosus and stroke. Indeed, a meta-analysis of population-based cohort studies found that there was an approximately 2-fold higher risk of ischemic stroke in patients with SLE (Holmqvist et al., 2015), and a recent systematic review of the literature showed that the risk for cerebrovascular disease among patients with SLE was increased (Bello et al., 2023; Yazdany et al., 2020). These results highlight the need to consider systemic inflammatory diseases as an important clinical risk factor for ischemic stroke, especially in younger age or in people without typical cardiovascular risk factors.

Multisystem Factors Associated with Ischaemic Stroke

ISC was determined to have determinants across multiple domains, as revealed from the integrated multisystem analysis. The strongest association reported was for atrial fibrillation (approximately 4.9), hypertension (approximately 3.0) and Behçet's disease (approximately 2.8). Diabetes mellitus had an approximate association of 2.3, and SLE had an approximate association of 2.2. The estimated associations for smoking were approximately 1.9, obesity was approximately 1.6 and dyslipidemia was approximately 1.4. The NLR was ~1.3, and the CRP level was ~1.2 for inflammatory markers. As a result, the associations of cardiovascular and metabolic determinants were generally stronger than those of individual inflammatory and demographic determinants.

The magnitude of the effects are similar to the mechanisms by which these determinants are thought to relate to stroke. Cerebral embolism may be caused by atrial fibrillation, chronic vascular injury by hypertension, endothelial dysfunction and atherosclerosis by diabetes, and oxidative stress, inflammation and vascular

damage by smoking, all of which may be seen in the patient (Hart et al., 2007; Odutayo et al., 2016; O'Donnell et al., 2016). This risk profile may be exacerbated by systemic inflammatory diseases, which can cause vascular inflammation and hypercoagulability. Most importantly, these are often all working together. Diabetes and hypertension can occur together, smoking can exacerbate atherosclerotic processes, and dyslipidemia can occur. Hence, the present results suggest that ischemic stroke is caused by the interplay of several interacting risk factors and not by any single risk factor.

Cardiovascular and Metabolic Determinants

The cardiovascular and metabolic analysis showed variations in the strength of associations between the primary risk factors. Overweight or obesity and hypertension were the factors that were most significantly associated, and diabetes mellitus and atrial fibrillation were moderately associated. In the present analysis, the association with dyslipidemia was relatively low. These results confirm the need for hypertension and metabolic disorders to be considered in the etiology of ischemic stroke. This observed pattern aligns with major international studies that have identified high blood pressure, diabetes, obesity and dyslipidaemia as some of the major modifiable risk determinants for stroke (O'Donnell et al., 2010; O'Donnell et al., 2016; GBD 2019 Risk Factors Collaborators, 2020).

These connections are intermingled with regard to the mechanisms involved. Hypertension might affect the vascular endothelium and lead to arterial remodelling, and obesity could be a risk factor for hypertension, insulin resistance, diabetes, and systemic inflammation. Diabetes is associated with a greater risk of developing atherosclerosis and with higher levels of thrombotic susceptibility; atrial fibrillation is an important cardioembolic pathway (Lewington et al., 2002; Emerging Risk Factors Collaboration, 2010; Odutayo et al., 2016). Although the relatively lower association seen in the present analysis does not mean that lipids are not

important, lipid effects may differ by stroke subtype, age, population and lipid measure. In general, these results suggest that there is a multifactorial cardiovascular and metabolic pathway that culminates in ischemic stroke and that all these blood parameters should be treated simultaneously.

Conclusion

This study indicates that ischaemic stroke is a complex multisystem condition influenced by a variety of demographic, socioeconomic, behavioural, cardiovascular, metabolic, inflammatory, and systemic vascular risk factors. Age indicated a significant and progressive connection with stroke incidence, while male sex, poorer educational attainment, smoking, and high alcohol intake were also linked to increased risk. Hypertension, atrial fibrillation, diabetes, overweight/obesity, and dyslipidemia were identified as significant cardiometabolic risk factors. Lipid-related biomarkers, particularly ApoB, ApoA1, and the ApoB/ApoA1 ratio, revealed additional information about an abnormal vascular profile. Inflammatory and haematological markers such as NLR, CRP, fibrinogen, suPAR, leukocyte count, and neutrophil count were all positively linked with ischaemic stroke; however, lymphocyte count was inversely associated. Systemic inflammatory and vascular disorders, including Takayasu arteritis, Behçet's illness, and systemic lupus erythematosus, also showed clinically significant relationships with stroke risk. Overall, the findings emphasize that ischaemic stroke cannot be fully explained by a single risk factor; rather, it is caused by the cumulative and interactive impacts of numerous biological and behavioural variables. Ischaemic stroke prevention requires integrated risk assessment, early detection of high-risk patients, and effective control of modifiable cardiovascular, metabolic, behavioural, and inflammatory variables.

Declarations

Consent for publication

All subjects gave their “informed consent” for the publication of details within the text (“informed consent”) to be published in the above Journal and Article. Written “informed consent” was obtained from all authors for the publication of this manuscript.

Availability of data and materials

Data are provided within the manuscript or supplementary information files.

Competing Interest

All authors declare that there are no competing interests.

Conflict of interest

All the authors declare no conflicts of interest.

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