

DIMITRIJE JAKOVLJEVIĆ

**The Roles of Chronobiological and
Socioeconomic Factors in the Occurrence of
Cerebrovascular Diseases**

Doctoral dissertation

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Department of Neurology,
University of Kuopio
Department of Neurology, Kuopio
University Hospital
KTL – Kansanterveyslaitos,
National Public Health Institute,
Helsinki

Distributor: Department of Neurology
University of Kuopio P.O.Box 1627
FIN-70211 Kuopio FINLAND
Tel. +358 17 162 682
Fax +358 17 162 048

Author's address: KTL –National Public Health Institute,
Department of Epidemiology and Health Promotion
Mannerheimintie 166
FIN-00300 Helsinki FINLAND
Tel. +358 9 4744 8648
Fax +358 9 4744 8661
E-mail: dimitrije.jakovljevic@ktl.fi

Supervisors: Professor Juhani Sivenius, M.D., Ph.D.
Department of Neurology, University of Kuopio

Docent Veikko Salomaa, M.D., Ph.D.
Department of Epidemiology and Health Promotion
KTL - National Public Health Institute, Helsinki

Reviewers: Professor Reijo Marttila, M.D., Ph.D.
Department of Neurology, University of Turku

Professor Pekka Jousilahti, M.D., Ph.D.
Department of Public Health, University of Helsinki

Opponent: Docent Turgut Tatlisumak, M.D., Ph.D.
Department of Neurology, University of Helsinki

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ABSTRACT

The study was designed to examine the relationship of incidence, mortality and case-fatality of cerebrovascular diseases events, and their relationship with chronobiological and socioeconomic factors in patients aged 25-99 years in the FINMONICA Stroke Register areas. The study comprised 15,320 events of subarachnoid and intracerebral hemorrhage and ischemic stroke.

The study observed a significant seasonal variation in the occurrence of cerebrovascular diseases. Ischemic stroke events were 12% more common among men and 11% more common among women in winter than in summer. For intracerebral hemorrhage, a 28% (95% CI, 3% to 58%) greater occurrence among men and a 33% (95% CI, 6% to 66%) greater occurrence among women were observed in winter than in summer. The incidence of subarachnoid hemorrhage did not vary significantly by season. The greater incidence of ischemic stroke in winter was particularly prominent among men aged 25 to 64 years though less prominent in both elderly men and women. The 28-day case-fatality of ischemic stroke showed significant seasonal variation only in women ($p=0.001$), with the lowest case-fatality in summer.

The incidence of ischemic stroke demonstrated a significant variation according to the day of the week in men aged 65-74 years but not in women in the same age span. The highest numbers of incident events were observed on Mondays in both genders (10% above the daily average in men and 8.3% in women). The incidence of both subarachnoid hemorrhage and intracerebral hemorrhage showed a significant weekly variation among men aged 25-59 years, being highest on Mondays. Among older men and women the differences were not significant.

The age-standardized incidence of subarachnoid hemorrhage among men and women aged 25-44 years was approximately three times higher in the low-income group than in the high-income group. In older individuals, differences between the income groups were less pronounced. Among survivors of the acute stage, poorer prognosis was observed in patients with low-income than in those with high-income. Similar to the findings of subarachnoid hemorrhage, the age-standardized incidence and mortality of intracerebral hemorrhage among persons aged 25-74 years were significantly higher in the low- than in the high-income group in both genders. Among men aged 25-59 years, the adjusted OR of intracerebral hemorrhage death within one year after the onset of the event was twice as high in the low-income group as in the high-income group. Incidence, case-fatality, and mortality of ischemic stroke were all inversely related to income. Furthermore, 28 days after the onset of symptoms, a greater proportion of patients with low-income than of those with high-income was still in institutionalized care and/or in need of help for their activities of daily living.

Combined analysis of chronobiologic and socioeconomic effects showed that seasonal variation in the occurrence of cerebrovascular disease events was not dependent on socioeconomic status. However, the Monday excess in the incidence of ischemic stroke tended to occur in persons with low- and middle-income only.

In conclusion, the present study showed that persons with low socioeconomic status have considerable excess morbidity and mortality from cerebrovascular diseases in Finland. This excess does not seem to vary by season, but does, to some extent, by day of the week. A reduction of this excess morbidity and mortality could markedly decrease the burden of cerebrovascular diseases to society, and thus constitute an important public health improvement.

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To Sanja and Aleksandar

Beskrajni plavi krug... U njemu zvezda

(An endless blue circle... In it a star)

”Seobe (Migration)”

Miloš Crnjanski (1893-1977)

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Helsinki, April 7th, 2005

A handwritten signature in black ink, appearing to read 'Dimitrije Jakovljević', written in a cursive style.

Dimitrije Jakovljević

ABBREVIATIONS

CI	confidence interval
CT	computerized tomography
DM	diabetes mellitus
HR	hazard ratios
ICH	intracerebral hemorrhage
IS	ischemic stroke
MONICA	MONItoring of trends and determinants of CArdiovascular disease
MRI	magnetic resonance imaging
OR	odds ratio
RR	risk ratio
SAH	subarachnoid hemorrhage
SES	socioeconomic status
TOAST	Trial of Org 10172 in Acute Stroke Treatment
TIA	transient ischemic attack
WHO	World Health Organization

LIST OF ORIGINAL ARTICLES

This study is based on the following original publications:

- I Jakovljević D, Salomaa V, Sivenius J, Tamminen M, Sarti C, Salmi K, Kaarsalo E, Narva V, Immonen-Räihä P, Torppa J, Tuomilehto J. Seasonal variation in the occurrence of stroke in a Finnish adult population. The FINMONICA Stroke Register. *Stroke* 1996;27:1774 -1779.

- II Jakovljević D, Sivenius J, Sarti C, Torppa J, Mähönen M, Immonen-Räihä P, Kaarsalo E, Alhainen K, Tuomilehto J, Puska P, Salomaa V. Socioeconomic inequalities in the incidence, mortality and prognosis of subarachnoid hemorrhage: The FINMONICA Stroke Register. *Cerebrovasc Dis* 2001;12:7-13.

- III Jakovljević D, Sarti C, Sivenius J, Torppa J, Mähönen M, Immonen-Räihä P, Kaarsalo E, Alhainen K, Tuomilehto J, Puska P, Salomaa V. Socioeconomic differences in the incidence, mortality and prognosis of intracerebral hemorrhage in a Finnish Adult Population; The FINMONICA Stroke Register. *Neuroepidemiology* 2001;20:85-90.

- IV Jakovljević D, Sarti C, Sivenius J, Torppa J, Mähönen M, Immonen-Räihä P, Kaarsalo E, Alhainen K, Kuulasmaa K, Tuomilehto J, Puska P, Salomaa V. Socioeconomic status and ischemic stroke: The FINMONICA Stroke Register. *Stroke* 2001;32:1492-1498

- V Jakovljević D, on behalf of the FINSTROKE Register Group. Day of the week and ischemic stroke; is it Monday high or Sunday low? *Stroke* 2004;35:2089-2093.

In addition, some unpublished data are presented and discussed

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1 INTRODUCTION

Cerebrovascular diseases are a serious health problem in developed countries, and they are becoming more common worldwide, causing severe disabilities and creating an enormous burden on the social and health care systems (1, 2). The increasing magnitude of the burden generated by cerebrovascular diseases on the health care systems of developed countries was recognized to its full extent until the past decade. On a global scale cerebrovascular diseases are one of the three most common causes of death after coronary heart disease and all cancers (3). Because of the aging population, the impact of cerebrovascular diseases remains considerable, despite consistently declining trends in incidence and mortality observed during the past decade in the northern Europe and Finland (4-11).

Medical chronobiology studies the implications of the temporal ordering of biological events to the enhancement of health (e.g. prevention, diagnosis and treatment of disease). The role of chronobiological patterns on health and disease is extremely complex, with both natural and artificial environmental factors having an impact. Identification of the chronorisk can thus lead to steps toward prevention. The association of chronobiology with cerebrovascular diseases has been a topic of several studies, but the relationship is still unclear mainly because of the discrepancy in results (12-16). These differences can be partly explained by the variation of methods used for study design (hospital-based studies versus population-based studies), by disparity in environmental conditions and stroke risk factor profiles among countries and by the relatively small numbers of events available for analysis. Potential risk factors for stroke, such as high blood pressure, fluctuations in platelet aggregation, fibrinogen concentrations, plasma viscosity, cholesterol level and vasoactive substances exhibit rhythmic variations that may contribute to the timing and precipitation of a stroke attack (17-23).

The relationship between SES and health status is well established; almost consistently, those with greater socioeconomic disadvantages have a worse health status regardless of the determining measures used. This inequality has been recognized for centuries (24).

In 1978, the World Health Organization (WHO), in the Alma-Ata Declaration, spelled out the dependence of human health on social and economic development and noted that adequate living conditions are necessary for health (25). Since then substantial progress has been made in understanding the mechanisms and factors involved in the socioeconomic gradient in health (26-29). During recent decades a widening of the relative gap in death rates between upper and lower socioeconomic groups has been reported for several European countries (30-32). The association between SES and cardiovascular diseases has been pointed out in several studies during the same time frame. There is reliable evidence that classical risk factors can explain a large part of the differences in cardiovascular mortality between people with different SES (27, 33-37). An inverse relationship of SES with morbidity and mortality from cerebrovascular diseases (30, 34, 38-46) has been repeatedly indicated, particularly the association between low socioeconomic status and the risk of cerebrovascular diseases (30, 40).

2 REVIEW OF THE LITERATURE

2.1 Etiology and risk factors for cerebrovascular diseases

Cerebrovascular diseases are characterized by a sudden loss of circulation to an area of the brain, resulting in a corresponding loss of neurologic function. Also termed stroke, cerebrovascular accident, apoplexy or stroke syndrome, cerebrovascular diseases comprise a heterogeneous group of pathophysiologic causes, including thrombosis, embolism, and hemorrhage. According to the WHO, stroke is defined as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin” (47).

Cerebrovascular disease may be divided into microvascular disease, macrovascular disease and vasculitis or vasculitides (a group of diseases characterized by inflammation of the wall of the blood vessels). Furthermore, cerebrovascular disease of macrovascular origin may be classified as either hemorrhagic or ischemic (48) stroke. In 70-80% of cases, stroke is caused by brain infarctions, in 9-15% by ICH and in about 10% by SAH. Hemorrhagic stroke may be secondary to spontaneous SAH or to ICH. It is sometimes difficult to distinguish ICH from IS based on clinical symptoms only, but brain imaging (CT or MRI) can usually differentiate them with certainty. However, epidemiology, pathologic process and management differ in hemorrhagic stroke and IS.

2.1.1 Subarachnoid hemorrhage

Spontaneous SAH is a particularly devastating type of cerebrovascular disease, which affects young individuals more often than other stroke types (49). SAH is defined as a bleeding, primarily in the intracranial subarachnoid space, not a secondary manifestation of some other disease (50). It represents about 10% of all cerebrovascular disease events in most western populations and the incidence decreases with age. Considerable evidence supports the role of genetic factors in the pathogenesis of intracranial aneurysms (51). The incidence rates of SAH vary from 3 to 23/100,000 in different populations (52-55). Estimates of the incidence of the different forms of

cerebrovascular disease, including SAH, depend on the population surveyed, methods used for analysis, and accuracy of classification. In a recent systematic review of the literature, the worldwide overall incidence of SAH was calculated at 10.5/100,000 person years (56). However, the highest rates of SAH are reported in Finland and Japan (up to 20/100,000 person-years), where the incidence is almost three times higher compared with many other developed countries (57). The important risk factors for SAH are smoking (58), hypertension (58, 59), and alcohol abuse (60). SAH occurs more frequently in patients older than 35 years, and more often in women than in men.

The cause of SAH is a ruptured intracranial aneurysm in 85% of the cases (56). Aneurysms are almost never found in neonates, rare occur in children and develop during the course of life (61). About 12 percent of patients die before receiving medical attention (62), 40 percent of hospitalized patients die within 30-days after the event and more than one third of those who survive have major disability problems (49).

After the onset of SAH, the outcome is determined mainly by severity of initial bleeding or early re-bleeding. Although, advances in treatment and prevention of complications have been made, these have led to only modest improvement in the overall outcome (63). Research confirms not only that identification of modifiable risk factors for SAH is of paramount necessity, but also preventive treatment methods are of almost equal importance as a means to influence the incidence and outcome of this serious disease (56, 60).

2.1.2 Intracerebral hemorrhage

Spontaneous ICH is more than twice as common as SAH and is much more likely to result in death or major disability than cerebral infarction or SAH (64). ICH incidence approximately doubles with each decade of age among persons aged 35-74 years. ICH occurs slightly more frequently among men than women and is significantly more common among young and middle-aged blacks than whites of similar age (65). ICH is a multifactorial disease but advancing age, hypertension and smoking (66) are the key risk factors. The major causal factors of ICH can be broadly divided into three categories: anatomical, hemodynamic and hemostatic factors. Pathophysiological

changes in small arteries and arterioles due to sustained hypertension and atherosclerosis can lead to fibrinoid necrosis and microaneurysmal outpouchings of small end-vessels (Bouchard-Charcot aneurysms) (67), which is generally regarded as the elementary cause of ICH. These degeneratively changed vessels are prone to rupture and a frequent source of ICH. The type of underlying abnormality varies with age: below the age of 40 years, arteriovenous malformations and cavernomas are the most common single cause of ICH, whereas between 40 and 70 years of age a frequent cause is deep hemorrhage from a rupture of small perforating arteries, and in the elderly, one also finds hemorrhages in the white matter commonly attributed to amyloid angiopathy. Other causes of ICH include vascular malformations, ruptured aneurysms, coagulation disorders, use of anticoagulants and thrombolytic agents, hemorrhage into a cerebral infarct, bleeding into brain tumors and drug abuse.

The classic presentation of ICH is the sudden onset of a focal neurological deficit that progresses over minutes to hours with accompanying headache, nausea, vomiting, decreased consciousness, and elevated blood pressure. By comparison, only 5% to 20% of the various subtypes of IS and 14% to 18% of patients with SAH had gradual progression of symptoms. The early progression of neurological deficit in many patients with an ICH is frequently due to ongoing bleeding and enlargement of the hematoma during the first few hours. Despite the differences in clinical presentation between hemorrhagic types of cerebrovascular disease and IS, no collection of clinical features has sufficient predictive value to waive brain imaging. CT is an essential element of the initial diagnostic evaluation, primarily because it quickly and clearly differentiates hemorrhagic types of cerebrovascular disease from IS. In addition, it identifies the size and location of the hemorrhage and may reveal structural abnormalities such as aneurysms, arterio-venous malformations and brain tumors that have caused the ICH as well as structural complications such as herniation, intraventricular hemorrhage or hydrocephalus. On the other hand, MRI displays clear resolution of the brain tissue and therefore it is preferred in IS and plays a more crucial role in distinguishing its subtypes. CT most likely led to increased detection of less severe strokes. The validity of this conclusion is borne out by the major decline in ICH mortality rates (from 91% to 48%) between the years 1945 to 1984. The decline was especially noteworthy during the ten

years after CT was introduced (1976) and was undeniably due to the identification of smaller hemorrhages (68).

Reported incidence and mortality rates of ICH among Asian populations are higher than those reported for whites in the United States and Europe (69). A study of stroke trends in Minnesota found that the incidence rate of ICH declined from 209 to 115 per 100,000 persons between 1945 and 1975, but then increased again by 17% between 1975 and 1984 (70). A population-based study from Sweden found an increase in ICH incidence but a decrease in ICH mortality, most likely due to better detection of ICH with CT (71). A 24-year follow-up study of Japanese men in Hawaii, the Honolulu Heart Program, showed a sharp decline in stroke mortality since the late 1960s. ICH incidence declined 4.2% and mortality fell significantly. The 30-day case-fatality for ICH fell from 75% to 29%. A 9-year study of 28-day case-fatality of all strokes in Finland produced results comparable to the Honolulu study (72). Case-fatality between 1983 and 1992 fell yearly by 3.6% in men, a significant decrease, and 2.6% in women, not significant (73). ICH case-fatality registered 49% in women and 42% in men, with a significant declining trend for both genders although the observed difference in incidence rates cannot be explained by the traditional risk factors (74). The onset of the initial decline coincided with the introduction of antihypertensive therapy, while the subsequent increase in the incidence coincided with the introduction of CT.

2.1.3 Ischemic cerebrovascular disease

An ischemic type of cerebrovascular disease, simply called ischemic stroke (IS), is more frequent than hemorrhagic strokes. In the European population, IS represents up to 80% of all cerebrovascular events, is frequent in middle-aged and older individuals and often leads to prolonged hospitalization, disability, or death. It is likely that the progressive aging of Western populations will raise the number of IS events in the future. Therefore, the prevention and better treatment of IS has considerable public health significance.

Artery-to-artery embolism is the main cause of IS. The rupture of atheromatous plaques is a powerful cause of thrombosis. Indeed, the progression of atheromatous plaques

leads to arterial stenosis, formation of wall thrombus, and finally occlusion resulting in the high probability of embolism. The size and composition of emboli, and the collateral system may determine the size of infarcts. These processes may occur in large arteries (atherosclerosis) or in small penetrating blood vessels (lipohyalinosis). Data from a number of studies indicated that about 1/3 of brain embolism is due to a cardioembolic mechanism (75-77).

The etiology of IS affects prognosis, outcome, and management. There is no generally accepted way of classifying the subtypes. There are two large systems of classification which use etiology as their basis: Stroke Data Bank and Trial of Org 10172 in Acute Stroke Treatment (TOAST) (78, 79). Another option is to use the clinical localization of the infarct topography as it was used in the Oxfordshire Community Stroke Project (80). The TOAST classification (79) denotes five subtypes of ischemic stroke: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology. According to the study of Kolominsky-Rabas et al (81), the age-standardized incidence rates of IS subtypes for the European population were as follows: cardio-embolism 30.2%, small-artery occlusion, 25.8%, and large-artery atherosclerosis 15.3%. When age-adjusted to the European population, the incidence rate for large-artery atherosclerosis was more than twice as high for men as for women (23.6/100 000 versus 9.2/100 000).

The Oxfordshire Community Stroke Project (80) criteria have been widely used to categorize cerebral infarction on the basis of simple clinical criteria into four subtypes: total anterior circulation infarction, partial anterior circulation infarction, lacunar infarction, and posterior circulation infarction. This classification is reasonably predictive of etiology, prognosis and the size and site of cerebral infarction with CT scanning. Distribution of the IS subtypes among the patients in the Oxfordshire Community Stroke Project emerged as follows: 17% had large anterior circulation infarcts with total anterior circulation infarction (both cortical and subcortical involvement); 34% had partial anterior circulation infarction (predominantly cortical infarctions); 24% had posterior circulation infarction (the vertebrobasilar (posterior)

arterial territory infarctions); and 25% had lacunar infarctions confined to the territory of the deep perforating arteries.

Vasculopathies are by far the most common disorder and the cause of cerebral ischemia and infarction. Atherosclerosis mainly affects large and medium sized arteries (82, 83), which are likely to promote thrombosis (84, 85). Age is one of the main risk factors for atherosclerosis (83, 86). The small penetrating arteries of the brain are not supported by sufficient collateral circulation, i.e., the lenticulostriate branches of the middle cerebral artery, the thalamus-perforating branches of the proximal posterior cerebral artery and the perforating arteries to the brain stem. Therefore occlusion of one of these arteries is rather likely to cause infarction in a small, restricted area of the brain. Such lacunar infarction comprise about twenty five per cent of the first IS (87) and perhaps an even larger proportion of TIA (88).

The concept of the hypothesis of the lacunar infarct has been a subject of controversy. The lacunar syndromes have not been found to be exclusively pathognomonic of small-artery disease (89). Cardioembolism (90, 91) and large artery atherosclerosis (83) have been implicated as potential causes in a small number of patients with the clinical and radiologic features consistent with lacunar stroke. History of DM and hyperlipidemia are more weighty than arterial hypertension as risk factors for patients with the lacunar type of IS (92). Moya-moya disorder seems to be confined almost entirely to the Japanese and other Asians, and in most cases, the cause is unknown (93).

Although cerebral infarction is predominantly a disease of senescence, its occurs in younger age groups as well (94). IS in the young is particularly tragic because of the potential to create a long term burden for the victims, their families and the community (95). Only three percent of IS occur in patients under 40 years of age (96).

Despite efforts to arrive at an exact diagnosis, the cause of infarction in a discouragingly large number of cases remains undetermined. Although results from the stroke data bank indicated that large artery atherosclerotic occlusive disease was a less frequent cause of stroke, small vessel disease or lacunar and cardioembolic infarction were

relatively frequent while the cause for most cases of infarction could not be classified into these traditional diagnostic categories (97). This conclusion forced the creation of a separate diagnostic category for cases whose mechanisms of infarction remained unproven, known as infarct of undetermined cause or lacunar infarction (98). In patients diagnosed as lacunar infarction, risk factors were hypertension, DM and left ventricular hypertrophy. The recent study, Arboix et al, showed that DM is an essential factor in the small vessel vasculopathy underlying non-hypertensive lacunar infarction (99). Emerging technologies have led to suggestions that some lacunar infarction events may also be explained by hematologic disorders causing hypercoagulable states from protein C, free protein S, lupus anticoagulant or anticardiolipin antibody abnormalities (100, 101). White matter changes, detected by imaging techniques, are frequent in patients with IS. After an acute ischemic stroke, are associated with a higher risk of death or dependency, recurrent stroke of any type, cerebral bleeding under anticoagulation, myocardial infarction, and post-stroke dementia (102).

2.2 Summary of risk factors for cerebrovascular diseases

The risk of cerebrovascular diseases increases with age, particularly in patients older than 65. In patients younger than 60, there is a male predominance for stroke in a 3:2 ratio. There is a familial association with stroke including both a paternal and maternal history of cerebral vascular and cardiovascular disease (103, 104). Numerous factors that influence the risk of cerebrovascular diseases have been identified and an evaluation of these risk factors is important in the examination of a patient with suspected stroke. Although cerebrovascular diseases share several common risk factors, there are a number of specific differences. Detection of the specific risk factors may help to identify the cause of the type of cerebrovascular diseases (105). Elimination or minimization of those factors that are potentially treatable is essential in efforts to reduce the incidence. They may also have a prognostic effect in the acute stage of illness. The different classifications of stroke risk factors are usually divided into modifiable and non-modifiable risk factors (98, 106).

2.2.1 Non-modifiable risk factors

Non-modifiable risk factors for cerebrovascular diseases are crucial to detect, in spite of the fact that no measure can be taken to eliminate them. Their presence offers individuals at higher risk, due to non-modifiable factors the possibility of better care and justifies the implementation of vigorous treatment to reduce modifiable risk factors (98).

2.2.1.1 Age

Age is the single most crucial risk factor for stroke (98, 107). The cumulative effects of aging on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period of time substantially increase stroke risk. The risk of stroke doubles in each successive decade after 55 years of age (108). Advancing age is a more important risk factor for ICH than for SAH, which is more common in persons under 50 years (48, 98).

2.2.1.2 Gender

Gender is another important risk factor for cerebrovascular diseases, but not to the same degree as the marked male preponderance seen in coronary heart disease. IS is less common in women than in men of a similar age, but according to some recent major studies, it seems that IS is more deadly in women than in men, regardless of ethnic group. Cross-sectional studies have shown that SAH is the only type of cerebrovascular disease that is more common in women than in men, but prospective studies do not support this finding. In a meta-analysis of SAH incidence studies between 1960 and 1994 Linn et al (57), found a significant effect of gender in six studies that analyzed men and women separately, but the higher risk for women was based on only one-fifth of all patients in their review, which precluded confirmation of these findings. Labor and delivery (but not pregnancy itself) may increase the risk of SAH in women, according to a study of maternal deaths in Minnesota between 1950 and 1973 (98).

2.2.1.3 Race and ethnicity

Higher rates of cerebrovascular diseases mortality are associated with socioeconomic deprivation and ethnicity (109). Race or ethnicity is also an important determinant of the type of mechanism and the distribution of vascular occlusive lesions, thus affecting diagnostic strategies (110). According to the Northern Manhattan Stroke Study, the maximum internal carotid artery plaque thickness that increased directly with age was greater in whites and blacks than Hispanics. There was a significant interaction between race-ethnicity and low-density lipoprotein cholesterol, with a greater effect of increasing low-density lipoprotein cholesterol among Hispanics (110). Black and Asian men have more frequent occlusion of smaller brain (intracerebral) arteries than white men who have a preponderance of extracranial and large intracranial arteries (e.g. arteries of the circle of Willis). Among the Japanese population, a marked excess of strokes was reported to be due to ICH.

2.2.1.4 Genetic factors

There is solid evidence that parental history of cardiovascular and cerebrovascular diseases predict the risk independently from the other risk factors (111, 112). Khaw and Barrett-Connor (113) suggested earlier that family history of stroke may be used as a marker for high-risk subjects as well as to identify and investigate other major genetic or environmental determinants for cardiovascular disease, particularly gender differences. A recent systematic report showed that the genetic contribution is more pronounced for certain subtypes of stroke. There is also some evidence that the genetic contribution is greater for stroke occurring at a younger age, with stronger associations in analyses confined to probands or relatives aged <70 years (114). A report from the Framingham Heart Study showed that the occurrence of parental cardiovascular disease is an independent predictor of offspring cardiovascular events in middle-aged men and women (115). A study from Spain (116) has shown that the risk of all types of cerebrovascular diseases is almost two-fold higher in association with a positive history of a father with stroke and about 1.7-fold with a positive history of a sibling with stroke. In the same study, cerebral infarction was associated with a positive family history of stroke, but for ICH, the study did not show a positive association with family history of

stroke. Both twin and family history studies support a role for genetic factors at risk for cerebrovascular diseases. Some studies have indicated that environmental factors are the primary contributors to stroke and other forms of cerebrovascular disease. For example, the Honolulu Heart Study (117) evaluated the occurrence of stroke in men who had migrated from Japan to Hawaii and concluded that it was primarily environmental factors that contributed to stroke incidence. However, twin and family studies provide evidence that genetic factors play a significant role in the etiology of stroke as well (118).

Recent advances in neuroimaging have made it easier to identify underlying disease mechanisms and to classify cerebrovascular diseases appropriately. It is likely that the genetic risk profile at the molecular level differs according to the subtype of cerebrovascular diseases. For example, the factors leading to carotid atherothrombosis may be different from those that predispose to cerebrovascular small-vessel disease or to cardio-embolism. One explanation for this is the heterogeneity of pathophysiological mechanisms causing IS (119, 120).

While certain genes, such as those that predispose to cerebral ischemia, may increase ischemic stroke risk in all the major subtypes, other genetic factors that predispose to underlying disease mechanisms, such as carotid atherosclerosis or microangiopathy, may be relatively more important in specific etiologic subtypes (121).

2.2.2 Modifiable risk factors

Some of the risk factors for cerebrovascular diseases are classified as a "modifiable, which means there is good evidence they can be treated or controlled (98, 106).

2.2.2.1 Hypertension

The relationship between elevated blood pressure and cerebrovascular disease risk is widely accepted (58-60, 122). In the general population, 27% of cardiovascular disease in women and 37% in men is attributable to hypertension. Blood pressure, particularly systolic blood pressure, rises with age (123). The incidence of IS increases in proportion to both systolic and diastolic blood pressures. Elevated systolic pressure, with or

without an accompanying elevation of diastolic pressure, has been shown to increase stroke risk. Isolated systolic hypertension (systolic blood pressure > 160 mm Hg and diastolic blood pressure < 90 mm Hg) is a pronounced risk factor for stroke in the elderly (122, 124). Both systolic and diastolic hypertension are associated with this risk increase, but systolic blood pressure appears to be a more important determinant of cardiovascular risk than diastolic blood pressure (125).

The lifetime risk estimate for developing hypertension is 90% in patients who are 55 and 65 years old (126). There is compelling evidence that the control of high blood pressure contributes to the prevention of stroke as well as to the prevention or reduction of other target-organ damage, including congestive heart failure and renal failure. In the past 10 years, the importance of controlling isolated systolic hypertension to prevent stroke in the elderly has been underscored in clinical trials (127-129).

Hypertension is a more crucial risk factor for SAH (130) and ICH, than it is for IS. Some studies have shown that hypertension is the main cause of ICH in over 85% of the cases. Important to note is that those people who were hypertensive but had stopped taking their medication were more than twice as likely to have an ICH compared to patients with hypertension who were faithfully taking their medication (131). Although the value of treating severe hypertension has been known for sometime (132), only recently has the treatment of mild-to moderate hypertension been extensively studied (133, 134).

2.2.2.2 Smoking

Smoking is an established risk factor for cerebrovascular diseases (106, 135, 136). The mechanisms by which smoking contributes to cerebrovascular diseases are poorly understood and the role of nicotine in this process is controversial (137). Although nicotine administered transdermally and orally does not appear to have as many associated health risks as do cigarettes, nicotine does have acute vasoactive and mitogenic effects on vascular tissues (137). Nicotine might alter the function of the blood-brain barrier and disrupt normal endothelial cell function. Nicotinic acetylcholine receptor antagonists prevent some of the detrimental effects of nicotine. However,

recent studies indicate that nicotine might also interact with intracellular signaling pathways that are independent of acetylcholine receptors.

According to Bonita et al. cigarette smokers had a three-fold increase (OR 2.9, 95% CI 2.0-4.1) in the risk of stroke compared with current non-smokers (136). The risk of cerebrovascular disease exists among former smokers as well, where the increased risk persists even after cessation of cigarette smoking, which suggests the importance of early abstinence from smoking (58). The relative risk of stroke among former smokers (compared with nonsmokers) was 1.34 in the Nurses' Health Study and 1.26 in the Physicians' Health Study (138). Currently, the Centers for Disease Control and Prevention estimate that 23% of the adult population is composed of former smokers, implying a population attributable risk for former smoking of 6%. However, the stroke risk associated with former smoking has been shown to decrease substantially as time from cessation increases. As such, in the Physicians' Health and Nurses' Health studies, the 6% population attributable risk estimate is a function of the distribution of time since quitting (138). The Framingham Heart Study (139) found stroke risk to be at the level of nonsmokers at five years from cessation. Wannamethee et al (140) concluded that smoking cessation is associated with a considerable and rapid benefit in decreased risk of stroke, particularly in light smokers (< 20 cigarettes/day). However, switching to pipe or cigar smoking confers little benefit, emphasizing the need for complete cessation of smoking.

Recent studies suggest that the population attributable risk associated with all forms of exposure to cigarette smoke is substantial, with current smoking contributing to approximately half of the IS events (population attributable risk of 18% for current smoking, 6% for former smoking, and 12% for exposure to environmental tobacco smoke).

2.2.2.3 Hyperlipidemia

Hyperlipidemia is an elevation of lipids in the bloodstream. These lipids include cholesterol, cholesterol esters (compounds), phospholipids and triglycerides. Abnormalities of serum lipids (total cholesterol, triglycerides, low-density lipoprotein

cholesterol, and high-density lipoprotein cholesterol) have traditionally been regarded as risk factors for coronary artery disease but not for cerebrovascular diseases. According to the recent study, higher total and lower high-density lipoprotein cholesterol levels are associated with increased risk of IS, especially certain stroke subtypes and patient subgroups (141). In addition, the lowest levels of total cholesterol are associated with an increased risk of ICH (141).

In the Honolulu Heart Program (74), there was a continuous and progressive increase in both coronary heart disease and thromboembolic stroke rates with increasing levels of cholesterol. An inverse relationship between high-density lipoprotein cholesterol and the risk of stroke was demonstrated in both the Oxfordshire Community Study (80) and the Northern Manhattan Stroke Study (98). More recent studies utilizing ultrasound technology have established an association between lipid levels and extracranial carotid atherosclerosis and intimal-media plaque thickness.

The results from recent studies demonstrate that therapy with statins rapidly reduces the incidence not only of coronary events but also of IS, with no apparent effect on ICH, even among individuals who do not have high cholesterol concentrations (108). Allocation to 40 mg simvastatin daily reduced the rate of IS by about one-quarter and so, after making allowance for non-compliance in the trial, actual use of this regimen would conceivably reduce the stroke rate by about a third (142). Treatment of hyperlipidemia requires a multidisciplinary approach that includes lifestyle modification in addition to medical therapy. Combination drug therapy is often necessary to reach treatment goals, especially in patients with genetic hyperlipidemia and/or symptomatic coronary artery disease which increases the risk for IS (143, 144).

2.2.2.4 Diabetes mellitus

Diabetes mellitus (DM) seriously increases the risk of developing cardiovascular disease (145-147). DM (type 1 and type 2 combined) has been shown to be a strong independent risk factor for stroke and is associated with between two and six-fold increased risk of stroke (108). Subjects with DM without cardiovascular disease have a

fatal stroke risk similar to that of non-diabetic subjects with a history of prior stroke and a similar risk factor profile (148).

Patients with type 1 DM have both an increased susceptibility to and an increased prevalence of risk factors for atherosclerosis. High blood pressure is common in patients with type 2 DM, with a prevalence of 40% to 60% in adults. The development of hypertension accelerates the course of microvascular and macrovascular disease in patients with both type 1 and type 2 DM, which itself increases the risk of cerebrovascular diseases (149). In the United States, from 1976 to 1980, a history of stroke was 2.5 to 4 times more common in persons with DM than in persons with normal glucose tolerance. Among Hawaiian Japanese men in the Honolulu Heart Program (74, 150), those with DM had twice the risk of thromboembolic stroke as subjects without DM, with the increase in risk being independent of other factors (150). In the Framingham Heart Study, although the impact of DM was greatest on peripheral arterial disease, for which the relative risk was increased four-fold, coronary and cerebral artery territories were also affected. Another study from the USA indicated that DM increased the risk of thromboembolic and hemorrhagic stroke (74). The combination of hyperglycemia and hypertension has long been believed to increase the frequency of diabetic complications, including stroke. Several recent trials examining stroke and other cardiovascular outcomes favorably compared the benefit of tight control of blood glucose and blood pressure in type 2 diabetics with less stringent management (151).

2.2.2.5 Hemorheological factors

Hemorheological factors are of significance in the determination of flow characteristics of blood and play an important role in the pathogenesis of cerebrovascular diseases (152). The dynamics of blood flow in the cerebral vessels is characterized by a number of major parameters such as flow velocity, microturbulent flow, viscosity of the blood, which share stress combined with factors created by the vascular wall and vascular resistance. These factors are inseparably and dynamically interrelated (153). Increased plasma concentrations of fibrinogen cause rheological changes in blood, increasing its

viscosity, promoting increased platelet aggregation as well as inducing the formation of a blood clot rich in fibrin (154, 155).

Hemorheological disturbances may occur in more than 40% of patients with cerebrovascular diseases. According to Szapary et al, the rheological parameters measured are significantly impaired in the subtypes of IS, especially in diabetic, smoking and alcoholic patients. The severity of the carotid artery stenosis correlates with rheological parameters, but there is no association with the types of IS (156). Examination of the rheological parameters might support the choice of optimal treatment in the secondary prevention of stroke, and consequently reduce the risk of recurrent stroke (157).

2.2.2.6 Hemostatic factors, inflammation and infection

A large number of epidemiological studies provided clear evidence about the links between hemostatic variables and future risk of myocardial infarction and cerebrovascular disease (158, 159). In addition, more evidence has been provided for an early involvement of hemostatic parameters in atherosclerosis. So far, a variety of markers for hypercoagulability (i.e., factor VII, factor VIII, von Willebrand factor, platelet hyperaggregation, increased plasma levels of D-dimer, and decreased fibrinolytic capacity) plays a crucial role in the development of atherothrombotic events (160). A recent study suggested an importance of the genetic regulation of proteins involved in hemostasis and atherothrombotic disorders, including cerebrovascular disease (161).

There is increasing evidence that inflammatory processes play a central role in the pathogenesis of atherosclerosis (162). Because inflammatory cells release matrix-degrading enzymes and thrombogenic substances that may provoke plaque disruption and local thrombosis, the resulting local inflammatory process may be critically responsible for plaque destabilization manifested clinically as acute IS (163, 164).

Chlamydia pneumoniae is a common cause of community-acquired pneumonia, pharyngitis, and sinusitis. It is capable of infecting the endothelium and inflicting injury.

It has been postulated that this may increase the likelihood of platelet aggregation and CHD, including IS (165). The possibility that infection with *Chlamydia pneumoniae* is a risk factor for cerebrovascular disease may suggest an opportunity to use antibiotics to help treat or prevent atherosclerosis and thus reduce the risk for stroke (166).

2.2.2.7 Atrial fibrillation

Atrial fibrillation is known to be a major risk factor for stroke (122). Once stroke has occurred, however, it is not clear whether the subsequent short-term and especially the eventual long-term risk of death differ between stroke patients with and without atrial fibrillation (167, 168). The annual risk of stroke in unselected patients with non-valvular atrial fibrillation is 3% to 5%, with the condition responsible for 50% of thromboembolic strokes. It is estimated that approximately two-thirds of the strokes that occur in patients with atrial fibrillation are cardioembolic. The median age of patients with atrial fibrillation is 75 years. The Framingham Heart Study (169, 170) noted a rise in risk of stroke associated with atrial fibrillation and advancing age, from 1.5% for those 50 to 59 years of age to 23.5% for those 80 to 89 years of age. Kaarisalo et al reported that stroke patients with atrial fibrillation are at high risk of death both at the acute phase of stroke and during the year subsequent to the first acute stroke event. Mortality from cardiac diseases predominated in the atrial fibrillation group during the acute phase of stroke (171).

2.2.2.8 Cardiac disease

Other types of cardiac disease that contribute a small risk to thromboembolic stroke include dilated cardiomyopathy, valvular heart disease (eg, mitral valve prolapse, endocarditis, and prosthetic cardiac valves), and intracardiac congenital defects (eg, patent foramen ovale, atrial septal defect, and atrial septal aneurysm). Overall, an estimated 20% of ISs are due to cardiogenic embolism. Potential cardiac sources of emboli are associated with up to 40% of lacunar strokes in some series involving the younger population.

The presence of cerebrovascular disease is strongly associated with the presence of symptomatic and asymptomatic cardiac disease. According to the Framingham Heart

Study (169, 170), 8% of men and 11% of women will have a stroke within six years after acute myocardial infarction. In addition, myocardial infarction is associated with the development of atrial fibrillation and is a common source of cardiogenic emboli (74, 170, 172). However, acute myocardial infarction is infrequently associated with stroke, occurring in only 0.8% of patients. The majority of these strokes (in 0.6% of patients) are ischemic.

2.2.2.9 Obesity

Obesity predisposes to cardiovascular disease in general and to cerebrovascular diseases in particular (122). However, obesity increases with advancing age, and obesity is associated with increased blood pressure, blood sugar, and blood lipids. On the basis of these associations alone, it is not surprising that obesity is related to an increased risk of SAH (130). The age-adjusted relative risk of stroke was 2.33 in a comparison of the extreme quintiles of waist-hip ratios in American men participating in the Health Professionals Follow-Up Study (173, 174).

2.2.2.10 Physical inactivity

The beneficial effects of physical activity have been fully documented for cardiovascular disease (106, 122). Moderate physical activity significantly reduces the risk of stroke and heart attacks in men both with and without pre-existing ischemic heart disease. More vigorous activity did not confer any further protection. Moderate activity, such as frequent walking and recreational activity or weekly sporting activity, should be encouraged without restriction (175, 176).

2.2.2.11 Alcohol Abuse

The effect of alcohol as a risk factor for IS is controversial and most likely dose dependent (106). For SAH and ICH, cohort studies have shown that alcohol consumption has a direct dose-dependent effect. For IS, chronic heavy drinking and acute intoxication have been associated with increased risk among young adults(106). In older adults, risk increases among heavy-drinking men (98).

Some studies have supported a J-shaped dose-response curve between alcohol intake and IS risk, with protection for those drinking up to two drinks per day and an increased risk for those drinking more than five drinks per day compared with nondrinkers (106). The dose-response relationship between alcohol and stroke is consistent with the observed deleterious and beneficial effects of alcohol. The deleterious effects of alcohol for stroke may occur through various mechanisms, including increased hypertension, hypercoagulable states, cardiac arrhythmias and reduced cerebral blood flow. On the other hand, there is also evidence that light-to-moderate alcohol intake can reduce the risk of coronary artery disease, raise high-density lipoprotein cholesterol, and step up endogenous tissue plasminogen activator (98).

2.2.2.12 Transient ischemic attack (TIA)

Transient ischemic attack (TIA) is a well-recognized risk factor for cerebrovascular disease and is associated with some of the same vascular risk factors as IS. Few studies have enumerated the risk factors for TIA compared to the number of studies that have been done on outcomes after TIA (98, 166). Despite the lack of much definitive data, it is clear that TIA and cerebrovascular diseases, particularly IS, occupy positions on a continuum of risk and that TIAs are a strong risk factor for stroke. The two events may differ in risk, with TIAs typically having a slightly lower risk for certain vascular outcomes (177).

2.3 Chronobiology of cerebrovascular diseases

Chronobiology can be defined as the study of rhythmic patterns in biological phenomena. Oscillatory fluctuations, called biological rhythms, occur in cells, tissues, organs, and more complex control systems. They are endogenous, arise within the organism, and persist under constant environmental conditions. Biological time may be linear (chronological time) and cyclical (period time). Chronobiology considers the biological events whose expression is periodic with several kinds of periodicities (biological rhythms) (178).

Chronobiological analyses of the onset of cerebrovascular diseases may throw some light on the mechanisms that trigger an event (179). Observations may generate new

hypotheses for identifying significant causal relationships. The circumstances surrounding the onset of cerebrovascular diseases are not well understood, and these events have been shown to vary by season, or even year, week, and time of the day (15, 179). Recognizing the chronobiological patterns in the occurrence of cerebrovascular diseases can provide insight into causality and eventually suggest preventive strategies (14).

2.3.1 Daily variation

A significant circadian (daily) rhythm was observed for cardiovascular diseases (180, 181). About one-third of all cerebrovascular events occurred in the morning between 7 a.m. and noon (14, 182-184).

The circadian pattern of ischemic cerebrovascular events resembles that of acute myocardial infarction (185, 186), sudden cardiac death (180), and silent or symptomatic episodes of myocardial ischemia. Thus, it has been hypothesized that some underlying pathophysiological mechanisms may be common. Proposed facilitating factors include circadian changes due to waking up and starting physical activity, and increased catecholamines. During the morning hours, plasmatic and urinary catecholamines, and renin are increased. Moreover, vascular receptors exhibit a different sensitivity, probably consequent on the increased sympathetic activity. Increased sympathetic activity may also determine an abrupt variation in blood pressure and heart rate. Thus, arterial tone increases and blood flow may be reduced, especially in the presence of concomitant preexisting stenoses.

2.3.2 Variation by the day of the week

Several studies have reported on variability in the occurrence of cerebrovascular diseases by the day of the week, but the inconsistency of findings precluded clear conclusions (179). While the underlying mechanisms are speculative and definite conclusions are difficult to draw, it seems likely that a day of the week difference in the onset of IS exists.

2.3.3 Seasonal and circannual variation

Mortality rates show strong seasonal effects, with all-cause mortality rates highest in the winter (187, 188). Over half of the excess is due to cardiovascular disease with much of the remainder due to respiratory diseases (187). The mechanisms underlying seasonal variation in mortality are not yet completely elucidated, but may include outside and inside air temperature, wind chill factors, snowfall, sunlight exposure, air pollution, activity pattern, influenza incidence, psychological conditions and/or food intake, and their effects on pathophysiological mechanisms related to disease (189-194). The influence of the seasons on the incidence of cerebrovascular disease and mortality from this condition has been reported during the last three decades, generally with some discrepancy in the results. Many studies conducted in different countries have reported a marked increase in stroke incidence, mortality and stroke hospitalization in winter-spring and a decrease in summer-autumn, related to ambient temperature (194-196). Most population-based studies have reported a marked increase of both stroke mortality (197) and stroke hospitalizations (198, 199) in the winter. This discrepancy may in part be due to the fact that the numbers of patients have been small and most of the studies have not had sufficient statistical power to analyze the subtypes of cerebrovascular diseases. Alternatively, larger studies have often been based on routine mortality statistics or hospital admission registers, in which the diagnoses are not standardized and the time of onset of symptoms is not accurately determined (198, 200, 201). Reports based on hospital or autopsy series are more variable. In many cases they are based on small numbers of events observed over short periods of time, and they were generally confounded by referral patterns and seasonal variation in hospital admission rates. Nevertheless, despite their limitations, hospital series generally support a winter excess of stroke hospitalizations.

The pattern of seasonal variation in mortality from cerebrovascular diseases has been attributed variously to differences between the incidence and case-fatality. Various explanations for such differences have been proposed. For example, numerous studies demonstrating highly significant correlations between the temporal variation in mortality from cerebrovascular diseases and various meteorological variables have concluded that stroke incidence and mortality are inversely related to temperature, and

furthermore that low temperatures or other meteorological factors cause stroke (198, 202-204).

There is also a strong and consistent seasonal pattern of high stroke and respiratory disease mortality in the colder winter months. Significant, independent research results show a positive association of cerebrovascular disease mortality with respiratory disease mortality but an inverse association with temperature (205). The underlying causes for the seasonal variations in the occurrence of cerebrovascular diseases may include rheological and hemostatic parameters such as plasma viscosity, fibrinogen (23), and factor VII activity (21). Although there are many reports which attempt to determine the effect of atmospheric and seasonal variations on the occurrence of cerebrovascular diseases, the findings are conflicting. Some of these reports include SAH and ICH (184, 201, 206), others aneurysm rupture (207, 208), and some others spontaneous SAH (209).

2.4 Socioeconomic status and risk of cerebrovascular diseases

Over the past three or four decades there has been consistent evidence of increasing socioeconomic inequalities (210-212) and due to this fact some action has been done (213, 214). The existence of a gradient of diseases has been shown also in the Whitehall study where members of the lowest social groups run at least twice the risk of serious illness and premature death of those of the top groups (215). The widening of the mortality differences between socio-economic groups in England and Wales was partly due to differences in decline of mortality from conditions related to accessibility, utilization or quality of medical care (216).

2.4.1 Measurement of socioeconomic status

There are several indicators for socioeconomic status (217, 218). The most important indicators are occupational status, level of education and income level. Each indicator covers a different aspect of social stratification, and it is therefore preferable to use all three instead of only one. Nevertheless, if one can only select one indicator, the level of education is likely to be a good choice in many circumstances, because it is easy to measure and very important in determining health status (219).

2.4.1.1 Income

Income is a common measure of SES and can be considered from the perspective of either an individual or a family. The measurement can be calculated from several approaches (219). For the most accurate comparisons, adjustment for family size should be made. Since income is a sensitive issue to people, the non-response rates are higher than those for education and occupation. Use of the taxable income as a proxy for SES provides a solution for developed countries with stable economies (220).

An alternative way of calculating income, which is commonly used in the literature, is the GINI coefficient whereby income distribution is measured (221). The GINI coefficient is derived from the Lorenz curve, which is a mechanism to represent graphically the cumulative share of the total earned income accruing in successive income intervals (222).

2.4.1.2 Education

Education is the most frequently used indicator of SES, simply because it is stable and is completed in early adulthood (219). Compared with the more personal indicators (e.g. income) education is more likely to be accurately reported (223). The major limitation for the use of education as an indicator of SES is its dependence on the birth cohort. In a certain society, more people will attain a higher level of education than preceding generations as the society develops. Ischemic heart disease an important risk factor for IS, contributed most (11.7 percent) to the difference according to education in potential life-years lost (with all cardiovascular diseases accounting for 35.3 percent) (224).

2.4.1.3 Occupation

Over the past 20 years, socioeconomic inequalities in mortality have widened (225), as job and financial security have decreased (226). In the Whitehall II study (227) the contribution of job and financial insecurity was examined. With the exception of economic depression, adjustment for job insecurity had little effect on the employment class gradients in morbidity (228). However, financial insecurity contributed substantially to gradients in self-rated health, longstanding illness, and depression in

both employed and unemployed men. According to a recent Finnish study (229), elimination of unfavorable working conditions might reduce the number of all cardiovascular deaths by 8%, myocardial infarctions by 10%, and cerebrovascular deaths by 18%. The most influential job exposures appeared to be high workload, low control, noise, and shift work. Moreover, income had a strong effect on mortality. However, inequalities observed in the study were more attributable to varying levels of education and income than to the occupational category (229).

2.4.1.4 Residential area and housing

In the absence of individual level data on social background, area-based measures of socioeconomic status are often constructed based on the social and economic aspects of the area in which the person resides (230). The neighborhoods where people live may differ in many aspects potentially related to health (217). The socioeconomic environment of neighborhoods has been shown to be related to health status and mortality as well as to health-related behavior such as smoking, dietary habits, and physical activity. For example Diez Roux et al (231), found that even after controlling for personal income, education, and occupation, residing in a disadvantaged neighborhood is associated with an increased incidence of coronary heart disease.

A comprehensive study of white men screened for the Multiple Risk Factor Intervention Trial in the USA (232, 233) found that SES, expressed as the median family income for the zip code of residence, was not significantly associated with ICH, but was associated with nonhemorrhagic type of stroke (234). This method for assessing SES may, however, involve misclassification, which usually tends to reduce the differences. In a study of civil servants in London it was shown that better characterization of socioeconomic position led to the demonstration of mortality differentials that were considerably wider than those obtained when less precise measures were used.

A recent study from the USA which included the data from elderly Medicare beneficiaries hospitalized for acute myocardial infarction and categorized by income class, using the median income of the ZIP code has shown that, despite the Medicare entitlement, there remain significant socioeconomic disparities in medical treatment and

mortality among elderly patients following acute myocardial infarction. Income was independently associated with short- and long-term mortality (235). Rao et al, using a similar model in categorizing the patients with acute myocardial infarction, found further evidence that, despite the Medicare entitlement, there remained significant socioeconomic disparities in medical treatment and mortality particularly among elderly patients (236).

2.4.1.5 Marital status

Marital status used as a gauge of SES, indicates that married people have better health status than single people, especially men (237). Marital status can be classified into four categories: married or co-habitation, divorced, widowed and never married (238).

2.4.1.6 Ethnicity and race

Ethnicity and race are widely studied as explanatory variables in health research and their independent effects are reported to explain many health variations among different groups within and between populations (239). Both, however, are associated with major problems of definition as well as confusion of social, cultural and biological concepts as to how the words, peculiar to these sciences, are defined and determined in scientific inquiry. Findings relating socioeconomic position to health status within minority ethnic groups vary (239). In the United States, ethnicity is often used as a proxy for socioeconomic position, owing, in part, to the relative absence of socioeconomic data in some routine data sources. Furthermore, the indicators of SES may have different meanings as applied to members of different ethnic groups. According to the Third National Health and Nutrition Examination Survey conducted between 1988 and 1994 most cardiovascular disease risk factors were higher among ethnic minority women than among white women (240).

Although historically, race has been viewed as a biological construct, it is now more accurately characterized as a social category, which has evolved over time and varies across societies and cultures (241). Racial disparities in health generally do not reflect biologically determined differences in the genome or physiology (242). In this connection, several studies have drawn attention to the wealth divide (243, 244). It is

highly probable that racial prejudice as a social stress on groups of children and families can influence their health behaviors, such as eating habits and activity levels, as well as substance use and abuse, all of which might place individuals at an increased risk for both short-term and long-term health impairment and disease. According to Gornick et al, race and income have substantial effects on mortality and use of services among Medicare beneficiaries (245). Moreover a recent study showed that SES was not only directly related to perceived racial discrimination, but also to perceived gender discrimination (246).

3 AIMS OF THE RESEARCH

The aims of the present study were:

1. To examine seasonal variation in the incidence, mortality, and case-fatality of cerebrovascular diseases in the populations aged 25 to 99 years of three geographical areas of Finland, and to investigate whether this variation was dependent on SES.
2. To examine the weekly variation in the occurrence of cerebrovascular diseases in Finland, and to investigate whether this variation was dependent on SES.
3. To determine the association of SES with the incidence, mortality, acute case-fatality and one-year prognosis of cerebrovascular events.
4. To investigate whether diagnostic procedures and treatments of SAH, ICH and IS were dependent on SES.

4 MATERIALS AND METHODS

4.1 The FINMONICA Stroke Register

The main data source for this study was the FINMONICA Stroke Register, a population-based register which operated during the 1980's and early 1990's in three geographic areas of Finland: the provinces of North Karelia and Kuopio in eastern Finland and the Turku/Loimaa area in southwestern Finland (9, 247). FINMONICA is the Finnish contribution to the World Health Organization MONICA Project (MONItoring of trends and determinants of CArdiovascular disease) (248).

In all three areas the registration covered all consecutive strokes in the resident population aged 25 to 74 years. In the town of Turku, strokes occurring in persons aged 75 to 99 years were also included during the entire 10-year period. In Kuopio, persons aged 75 to 99 years were included in the registration only during 1990 to 1992. In North Karelia persons of more than 75 years were not included in the registration. The number of events of cerebrovascular diseases by gender and age-group is presented in Table 1.

	SAH	ICH	IS
Men			
25-59	434	273	1583
60-74	126	359	3606
75-99	12	91	1057
Total	572	723	6246
Women			
25-59	279	127	636
60-74	219	351	3297
75-99	45	203	2622
Total	543	681	6555

Table 1. Number of SAH, ICH and IS events in men and women 25-99 years by age-group in the FINMONICA Stroke Register

The populations of the FINMONICA areas remained stable during the monitoring period. In 1988, within the group aged 25 to 74 years, there were 53,336 men and 53,426 women in North Karelia, 77,114 men and 79,331 women in Kuopio, and 60,126 men and 67,231 women in Turku/Loimaa. In the age group 75 to 99 years, there were 2,892 men and 7,724 women in Turku and 4,283 men and 9,695 women in Kuopio.

4.1.1 The registration protocol

The FINMONICA Stroke Register followed the protocol, diagnostic criteria, and quality control procedures of the WHO MONICA project (249). Details of the registration methods have been published (10) and a full report on data quality control is available (250). The Ethical Committee of the National Public Health Institute approved the study plan of the Stroke Register.

According to the WHO MONICA protocol (251), stroke is defined “as a rapidly developing symptom of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent nonvascular cause”. All suspected acute strokes occurring in the monitored populations were registered and classified as "definite stroke," "not stroke," or "unclassifiable." This final category was restricted, with few exceptions, to fatal events occurring before arrival at hospital and when no autopsy was performed. All hospital admission and discharge diagnoses, as well as cerebrovascular deaths, were routinely checked as source data, and all suspected stroke cases were entered and validated for stroke classification (94, 252).

The subtype of cerebrovascular diseases can be distinguished fairly reliably in the FINMONICA Stroke Register Data (253, 254). Cerebrovascular diseases were classified by subtype, into three categories: SAH (International Classification of Diseases, Eighth and Ninth Revision (ICD-8/9 430), ICH (ICD-8/9 431), and IS (ICD-8/9 432 to 436). ICD-8 was used in Finland until the end of 1986 and ICD-9 thereafter. The stroke register data were cross-checked with the National Death Register for stroke deaths (ICD codes 430 to 438) using a computerized record linkage system, on the basis of personal identification numbers unique to every permanent resident of Finland. Cases

found in the National Death Register but not in the stroke register were sent to the local registration teams for evaluation.

The main sources for case finding were the admission lists to hospitals and health center wards. Hospital discharge diagnoses and diagnoses from death certificates were also routinely checked. In the main hospitals of each area the register physicians assigned the type of stroke and diagnostic category. The same specialist physicians (a neurologist in North Karelia, Kuopio, and Turku and an internist in Loimaa) performed this task throughout the entire ten-year period.

During 1983-1985, the proportion of stroke cases that had not been attended by medical personnel at the time of diagnosis was less than 2%; most of such cases died on their way to the hospital. About 8% of the stroke cases were treated at home; 81% of these were classified as cerebral infarctions (247). In the early years of the FINMONICA study, because access to CT was still limited, especially in the North Karelian study area, the classification of events by type of stroke in cases where CT or necropsy were not performed, was based on other available clinical information. From 1987, more rigorous requirements for diagnosis of SAH and ICH were adopted by the WHO MONICA stroke study. In 1983, CT was performed for 22% of men and 27% of women; in 1988 CT, MRI, angiography, or autopsy was performed on 73.3% of men and 70.8% of women. In the following years, the CT rate rapidly rose annually until it stabilized at 90% by 1993.

To confirm diagnosis of SAH, necropsy, CT scan, or bloody cerebrospinal fluid was required (55). In the present study, in 90.3% of SAH cases in the FINMONICA Stroke Register the diagnoses were confirmed either by necropsy, CT scan, or angiography. In 8.9% of cases the diagnosis was based on typical clinical symptoms and cerebrospinal fluid examination assessed by the specialist physicians of register. The remaining 0.8% of cases was diagnosed on the basis of typical clinical picture and neurological examination only. For ICH, however, the diagnosis had to be confirmed by CT scan, MRI, or necropsy. The IS category, on the other hand, was composed by combining cerebrovascular diseases of thrombotic and embolic origin. Any unspecified type of

cerebrovascular diseases (ICD-9 436) was also included in IS, amounting to 3% of all strokes and occurring mostly among elderly subjects, thus most likely IS. If it was impossible to assign a definite stroke event to one of these categories, the code "unspecified stroke" was used. In this analysis, unspecified stroke and unclassifiable cases were also combined with the IS group. In the 25- to 64-year-old group, 1.4% of patients had unspecified or unclassifiable stroke; in the 65- to 74-year group, 5% of patients fell into that classification. Throughout the years of research, the proportions did not vary between fatal or nonfatal nor between incident or recurrent events. Cerebrovascular diseases were classified as incident or first-ever event, for those occurring without any evidence of a clinically recognized previous stroke event in the patient's history. One event covered 28 days. If symptoms recurred after 28 days from onset, it was considered a new, recurrent event. Fatal events were defined as those in which the patient died within 28 days after the beginning of symptoms. Case-fatality was defined as the proportion of fatality to all events. Survival status was examined at 28 days and at one year after the onset of symptoms. Survival status at one year was obtained through record linkage with the National Death Register. The follow-up was nearly 100% complete.

4.1.2 Indicators of the socioeconomic status

Information on SES was obtained by record linkage of the stroke register with the files of Statistics Finland on the basis of the personal identification number. Taxable income, level of education, and profession for the years 1980, 1985, and 1990 were used as the indicators of SES. The income record closest to the event was used. Cutoff limits of the income categories were adjusted as necessary for the 1985 and 1990 data to take into account inflation and to keep the relative size of each category constant during the entire 10-year study period. For analyses, the income data were classified into 3 broad categories: low, middle, and high. The relationship of the SES indicators to incidence and mortality rates of cerebrovascular events was similar in all three study areas, so the data were pooled for the analysis. The income distribution was depended on age. Among male SAH patients aged 25-74 years, 29%, on average belonged to the low-, 34% to the middle- and 37% to the high-income group. Among women, the corresponding proportions were 45%, 22% and 33%. Among the ICH patients on

average, 29.5% of men belonged to the low-, 33.9% to the middle- and 36.6% to the high-income group. Among women, the corresponding proportions were 45.2%, 21.8% and 33.0%. Among the IS patients on average, 26.2% of men belonged to the low-, 31.9% to the middle- and 41.9% to the high-income group. Among women, the corresponding proportions were 38.9%, 21.4% and 39.7%. The classification of cerebrovascular diseases into subtypes was made without regard to SES. Of the events classified as IS in the FINMONICA Stroke Register, the diagnosis could be confirmed by necropsy, CT, MRI, or angiography in 72% among men of the high-income group, in 58% among men of the middle-income group, and in 47% among men of the low-income group. Among women, the corresponding proportions were 76%, 59%, and 44%. In the remainder of the events, the diagnosis of IS was made on the basis of lumbar puncture and clinical examination.

Education was stratified into two categories: basic, corresponding to nine years or less of full-time education, and secondary or higher, corresponding to above nine years of full-time education.

Occupation was classified into 5 categories: unskilled blue-collar workers, skilled blue-collar workers, farmers, private entrepreneurs and white-collar workers.

4.2 Statistical methods

In Study I, data for the ten-year period were pooled for the analyses, and each year was divided into four seasons. Winter included December, January and February; spring, March, April and May; summer, June, July and August; autumn, September, October and November. Because of the fewer days in February, the numbers were weighted by the number of days in each season, with leap years also taken into account. These analyses were stratified by area, gender and age. The findings were approximately similar in all three areas however, and therefore the data from all areas were combined. Of the 15,449 registered stroke events, 219 with MONICA diagnostic class 9 (insufficient data) were excluded from the final analyses because in these cases the information was insufficient to determine stroke subtype.

The RR comparing other seasons with summer was calculated using Poisson regression. The 95% CIs for the RRs were obtained in the usual manner: $CI = \exp(\beta \pm 1.96 \times SE\beta)$. Age, gender, and study area were added as covariates in these analyses. The distribution of SAH, ICH and IS events over time was also examined with Roger's method (47) which is sensitive to cyclic trends based on the cosine function.

In addition, meteorological data obtained from the Finnish Meteorological Institute was used to examine the association of weather parameters (air temperature, barometric pressure and humidity) with the occurrence of SAH, ICH and IS. The average monthly occurrence of SAH, ICH and IS was evaluated in relation to average monthly values of the air temperature, relative humidity and air pressure. The analysis of the association between meteorological parameters and frequency of occurrence of SAH, ICH and IS was performed using General Linear Model (GLM) procedure (255). The dependent variable was the number of events aggregated by month (in absolute and logarithmical scale). Covariates in the study were calendar year, month, and meteorological parameters.

In Study II, the annual incidence and mortality rates were age-standardized to the European standard population (256). The case-fatality were age-standardized to the age-distribution of SAH patients in the FINMONICA Stroke Register using weights 2,3,4,5,6,7,6,5,4,3 for the five-year age-groups 25-29, 30-34, ... 70-74, respectively. The 95% confidence intervals (CI) for the incidence and mortality rates were calculated using Poisson distribution for the number of events and for the case-fatality applying binomial distribution for the number of fatal events. Cox proportional hazards model was used to compute RRs of dying from SAH in the middle and low-income categories compared to the high-income category. In the analysis of a linear trend across the income categories the Mantel-Haenszel chi-square test was performed.

In Study III, the incidence and mortality rates were age-standardized to the European standard population (256). The case-fatality was age-standardized to the age distribution of the combined stroke and coronary events in the WHO MONICA Project. The 95% CI for the incidence and mortality rates were calculated using Poisson distribution and for

the case-fatality using binomial distribution. Logistic regression was used to compute ORs of dying from ICH in the low- and middle-income categories compared to the high-income category.

In Study IV, SES-specific annual incidence and mortality rates were age standardized to the European standard population (249) and expressed per 100,000 persons. The 95% CIs were calculated using normal approximation of the Poisson distribution for the number of events in different age groups. Case-fatality was defined as the proportion of fatal events to all events and was age-standardized to the age distribution of the combined stroke and coronary events in the WHO MONICA Project (257). The 28-day case-fatality was age standardized by the use of weights derived from the combined age distribution of myocardial infarction and stroke patients in the WHO MONICA Project (247). The 95% CIs for the case-fatality were calculated using the normal approximation of binomial distribution for the number of deaths. Survival for different follow-up intervals was estimated using Kaplan-Meier curves, and differences between the income groups were compared using log-rank tests. Hazard ratios (HRs) for death resulting from IS were computed with Cox proportional hazards models. The 95% CIs for the HRs were calculated in the usual manner: $\exp(\beta \pm 1.96 \times SE\beta)$. Persons with a high-income were taken as the reference category, and persons with a middle or low-income were compared with them. Proportions of patients receiving different treatments and examinations were age-standardized using weights derived from the age distribution of all stroke and myocardial infarction patients in the WHO MONICA Project (257). To examine the linear trends in treatments across the income categories, the event numbers in each category were divided into two groups on the basis of the age-standardized proportions, and the Mantel-Haenszel χ^2 test was performed for the ensuing 2x3 table. The population-attributable risk of IS death and the incidence of first IS events due to low and middle income were calculated using the formula $AR = (Dt - D0)/Dt$, where AR is attributable risk; Dt is IS mortality in the population overall and D0 is IS mortality in the high-income group (258).

In Study V, data for the period from January 1, 1982 until December 31, 1992 were pooled and divided into the seven days of the week. Assuming that the sizes of the

monitored populations do not vary by weekday, we used the χ^2 tests to compare observed numbers of IS with those expected if IS events were equally distributed by weekday. These analyses were stratified by area, gender, and age. The findings were approximately similar in all three areas and therefore the data from all areas were combined. The 95% CI for the incidence rates were calculated assuming Poisson distribution for the number of events.

In all five studies the statistical analyses were carried out using SAS statistical software (255).

5 RESULTS

5.1 Seasonal variation in the occurrence of cerebrovascular diseases (Study I)

All strokes are unevenly distributed throughout the four seasons ($p < 0.001$ in men and $p = 0.003$ in women) (Table 1, Study I). The highest number of strokes occurs in winter and the lowest in summer, with intermediate values in spring and autumn.

Examination of the subtypes of stroke demonstrated that the occurrence of IS and ICH differed by season in both men and women. In contrast, SAH did not show a significant seasonal pattern. The rate of occurrence of IS events was 12% (95% CI, 5% to 20%) greater in men and 11% (95% CI, 4% to 19%) greater in women in winter than in summer. For ICH a 28% (95% CI, 3% to 58%) greater occurrence in men and a 33% (95% CI, 6% to 66%) greater occurrence in women was observed in winter than in summer. The incidence of first-ever IS and ICH followed a seasonal pattern similar to that of total IS and ICH, with the exception of the incidence of IS in women (Table 1, Study 1). The incidence of SAH did not show a significant seasonal variation.

The highest risk ratios comparing other seasons with summer were observed for ICH (Figure 1, Study 1). Among men, all other seasons showed significantly higher risk of IS than summer. Among women, only winter showed significantly higher risk of IS than summer. These risk ratios were not substantially altered when age and study area were included as covariates.

Roger's test demonstrated significant cyclic trends for ICH ($p = 0.005$) and for IS ($p = 0.003$) but not for SAH ($p = 0.20$) (Figure 2, Study 1). The incidence of first IS showed a strong seasonal variation in men aged less than 65 years ($p = 0.005$) but not in older men nor in women (Table 2, Study 1). Fatal IS showed a strong seasonal pattern in women aged more than 65 years but not in younger women or in men. The incidence of ICH showed a clear seasonal variation in men aged less than 65 years, and the variation in the occurrence of fatal ICH approached statistical significance in both men and women aged less than 65 years.

The average monthly occurrence of SAH, ICH and IS was evaluated in relation to average monthly values of the air temperature, relative humidity and air pressure (Figure 1). The air temperature was associated with the occurrence of ICH and IS among women in North Karelia ($p = 0.02$ and $p < 0.001$, respectively). In the same area, we also observed a statistically non-significant increase in the occurrence of SAH in

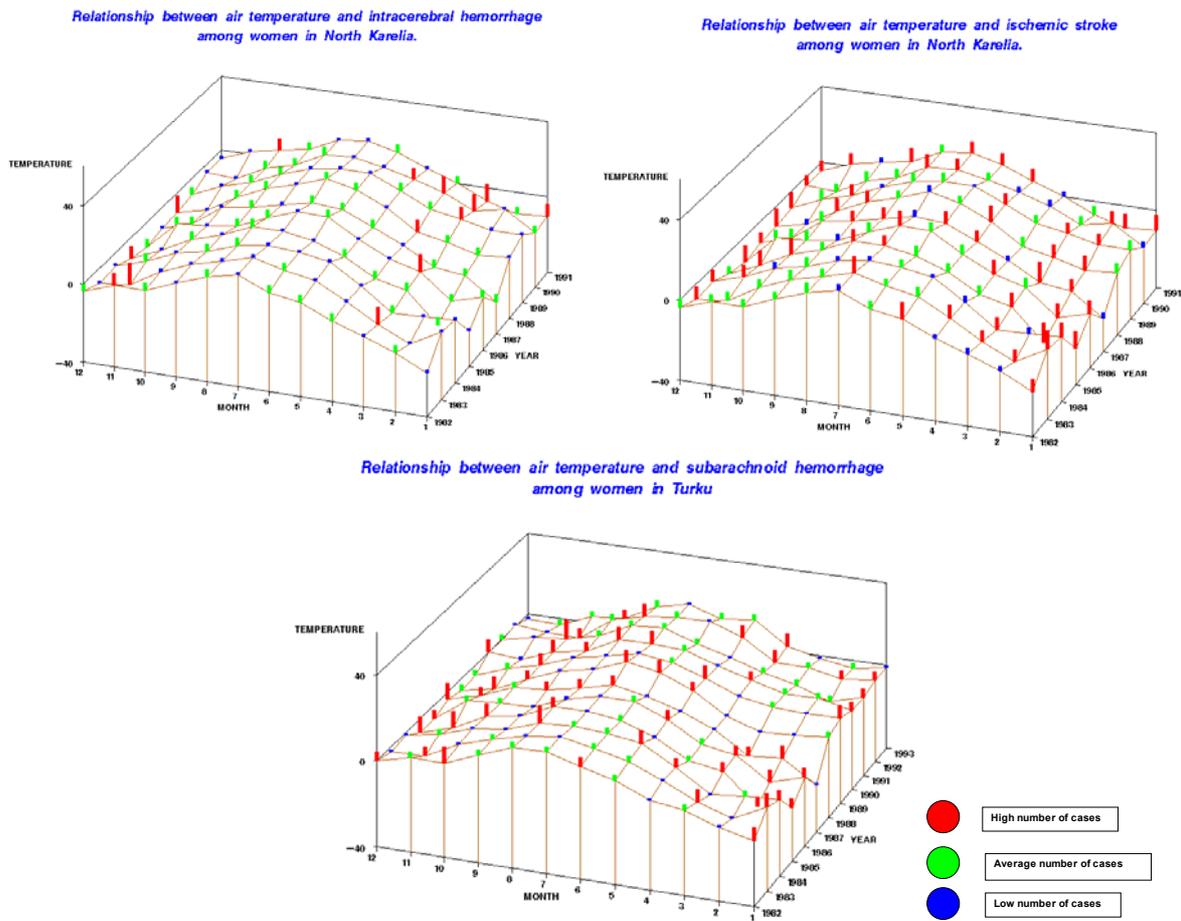


Figure 1. The average monthly occurrence of SAH, ICH and IS and the average monthly values of the air temperature ($^{\circ}\text{C}$) among women aged 25 - 99 years in the FINMONICA Stroke Register areas.

colder months. In contrast, only the occurrence of SAH was associated with air temperature ($p = 0.01$) among women in the city of Turku. There was no association between the occurrence of subtypes of stroke and temperature among men in either area. The association between stroke subtypes and barometric pressure and humidity

was not statistically significant. Data from the area of Kuopio were not included in the evaluation due to technical problems.

In summary, a significantly higher incidence of IS and ICH was observed in winter than in summer, particularly in young and middle-aged men. The greater incidence of IS in winter was particularly prominent among men aged 25 to 64 years and less prominent in both elderly men and women. The 28-day case-fatality of IS showed significant seasonal variation only in women, with the lowest case-fatality in summer. The occurrence of SAH, however, did not vary significantly by season. The study showed a significant correlation in the occurrence of SAH, ICH and IS with air temperature, in women but not in men.

5.2 Day of the week and occurrence of cerebrovascular diseases (study V)

The overall χ^2 tests showed a significant weekly variation in the occurrence of IS both among men and women ($p < 0.001$ and $p = 0.02$ respectively). IS occurred most frequently on Mondays in men (13.6% above daily average), and on Tuesdays in women (5.3% above daily average). The lowest numbers of IS events were observed on Sundays in both genders.

Further analysis by age group showed that the difference by weekday was statistically significant only in the age group 60-74 years ($p < 0.001$ in men and $p = 0.02$ women, respectively). The increase in the number of IS events from Sunday to Monday was pronounced in men (29.2 % increase from Sunday to Monday). The lowest frequency of IS events was observed on Sundays in persons aged below 75 years in both genders (Figure 1, Study V).

Among persons aged 25 - 74 years with first-ever IS we found a clear variation by day of the week in men ($\chi^2 = 19.15$, $df = 6$, $p = 0.004$), but not in women ($\chi^2 = 10.30$ $p = 0.11$). The highest numbers of events were observed on Monday (10% in men and 8.3% in women above the daily average) and they were significantly higher compared to Sunday.

A significant variation by day of the week was found in the incidence of SAH ($\chi^2 = 23.84$, $df = 6$, $p < 0.001$) and ICH ($\chi^2 = 18.15$, $df = 6$, $p = 0.006$) in men aged 25-59 years (Figure 2). Both SAH and ICH occurred most frequently on Mondays (38.7% and 48.7% above daily average, respectively). The lowest numbers of SAH and ICH events were observed in the middle of the week in men aged younger than 59 years. Among men above 59 years of age the incidence of SAH and ICH did not vary significantly by the day of the week (Figure 2).

The overall χ^2 tests did not show a significant weekly variation in the incidence of SAH and ICH among women regardless of age (Figure 2). However, the first ever event of

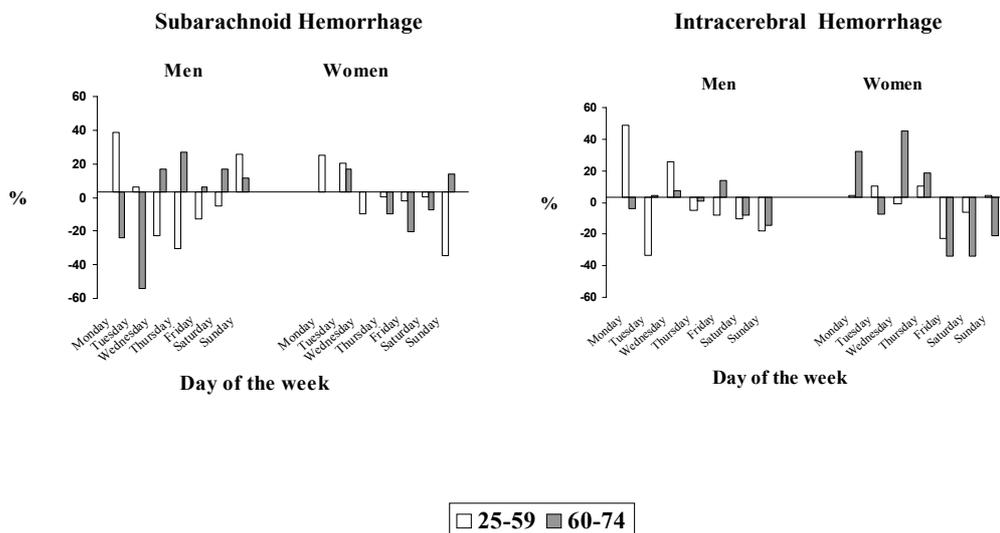


Figure 2. Proportion (%) of SAH and ICH events above and below the weekly average by day of the week and age group in men and women aged 25 - 74 years in the FINMONICA Stroke Register

SAH in women younger than 59 years old occurred most frequently on Mondays (25% above the weekly average), but the p value for weekly variation did not reach statistical significance ($\chi^2 = 11.13$, $df = 6$, $p = 0.15$). The increase in the number of SAH events from Sunday to Monday was pronounced in women below the age of 59 years (60% increase from Sunday to Monday). A similar pattern was observed in the incidence of ICH in women aged more than 59 years with the lowest frequency of ICH events on Sundays and the highest on Mondays (Figure 2).

In summary, the overall tests combining both genders and all age groups showed a clear variation in the incidence of SAH, ICH and IS by day of the week. In the analysis by gender and age group, IS demonstrated a difference by day of the week only in the age group 60-74, both in men and women ($p < 0,001$ and $p = 0.02$ respectively). In contrast, variation by day of the week in the incidence of SAH and ICH events was pronounced in men below the age of 59 years.

5.3 Socioeconomic status as a risk factor for cerebrovascular diseases

5.3.1 Subarachnoid hemorrhage

The age-standardized incidence of first ever SAH event was approximately three times higher in the low-income group than in the high-income group among men and women aged 25-44 years. Among older individuals the differences between the income groups became less pronounced. With regard to mortality, significant differences among all three income groups were observed among young men as early as seven days after the onset of symptoms and those differences remained significant throughout the one year follow-up time (Table 1, Study II). Among young women, the mortality at seven days after the beginning of symptoms was higher in the low-income group than in the high-income group and this difference remained significant at 28 days and at the one year follow-up. Among middle-aged women as well, mortality was higher in the low-income group than in the high-income group at day 28 and at one year from the onset of symptoms. Among older women, the high-income group tended to have the lowest mortality, but the 95% CIs overlapped with other groups.

At seven days after the onset of symptoms, the age-standardized case-fatality among men aged 25 - 44 years was 51.1% (39.3 - 62.9%) in the low-income group and 16.5% (6.6 - 26.3%) in the high-income group (Table 2, Study II). During the period of days 7 - 365, no deaths were observed in the high-income group, whereas in the low-income group the age-standardized case-fatality was 10.8% (0.0 - 22.1%). Among women of the younger age-group, the seven-day case-fatality also tended to be higher in the low-income group than in the high-income group, but the difference did not reach statistical significance (Table 2, Study II). After the initial seven days there were very few deaths

among women. No significant differences by income level were observed in case-fatality of persons aged 45-74 years.

A considerable proportion of the high seven-day case-fatality among young men was due to pre-hospitalization deaths. Their age-standardized prehospital case-fatality was 20.7% (11.4-29.9%) in the low-income group, 12.6% (6.0-19.3%) in the middle-income group, and 3.9% (0.0-9.2%) in the high-income group. Among young women and older persons there was also a trend towards higher pre-hospital case-fatality in the low-income group, but the differences between the income groups were not statistically significant.

In multivariate Cox proportional hazards models, the risk of fatal outcome from an event of SAH among men aged 25-44 years, measured at different points in time, was three to four times higher in the low-income group than in the high-income group (Table 3, Study II). These risk estimates were adjusted for age, study area and urban/rural residence. Further adjustment for living alone vs. with a family member did not change the estimates substantially. Among men aged 45-74 years the risk ratios did not differ from one. There was a significant age-group/low-income group interaction ($p = 0.01$ for the interaction term), but the age-group/middle-income group interaction did not reach statistical significance ($p = 0.32$). The RRs of fatal outcome among women aged 25-44 years in the low and middle-income groups exhibited no difference from those in the high-income group of the same age group (Table 3, Study II). In contrast, among older women, the risk of SAH death within 28 days and at one year from the beginning of symptoms was significantly higher in the low-income than in the high-income group. No significant age- /income group interaction was observed among women.

The association of income level with treatment and examination practices was analyzed for those SAH patients who reached the hospital alive and stayed alive for at least two days. Women with middle or high-income were significantly more often treated at a university hospital than women with low income (p for trend = 0.001) (Table 4, Study II). A CT-scan was administered to SAH patients with high income more often than

those with low income in both genders. In addition, approximately half of the male and female SAH patients with low income were still hospitalized 28 days after the beginning of symptoms, whereas in the high-income group this proportion approached one third among men and a quarter among women.

In summary, SAH mortality and morbidity vary according to SES. If the mortality and morbidity of the low and middle-income groups could be brought to the level of the wealthiest group, a considerable number of young persons would be saved from death or disability. Thus, there exists the potential to reduce SAH mortality and morbidity markedly by focusing more attention on the risk factors and also on the diagnosis and treatment of SAH in lower socioeconomic levels.

5.3.2 Intracerebral hemorrhage (Study III)

In the age-group 25 - 59 years the age-standardized incidence of first ever ICH event was approximately three times higher among men and four times higher among women in the low-income group than in the high (Table 2, Study III). Among older individuals the differences between the income groups were not significant. Among men aged 25 - 59 years, the 28-day mortality rate was approximately five times higher in the low-income group than in the high, and the differences were similar at the one-year follow-up (Table 2, Study III). Among women aged 25 - 59 years as well, the largest differences were found at the 28-day and at the one-year follow-up with about three times higher mortality in the low-income group than in the high-income group. In the older age groups differences in mortality among the income groups were smaller, especially among women.

The 28-day case-fatality of ICH was almost two times higher in the middle-income group than in the high-income group among men aged 25 - 59 years. The proportions (percentage % and 95% CI) of fatal outcomes within 28 days from the onset of ICH were 51.6% (41.8-61.4%) in the middle-income group and 28.5% (16.2-41.3%) in the high-income group. A similar trend towards higher case-fatality was observed for men of the low-income group, but the 95% CIs overlapped with those of the other groups

(48.0% (37.9-58.1%)). Among women and in the older age group of both genders, no SES differences were observed in the case-fatality of ICH.

The prognosis of patients who had survived the acute stage, i.e. were alive at day 28 also depended on the income category. The case-fatality between days 28 and 365 in the high-, middle-, and low-income groups was 31.2 % (18.6 - 43.8%), 57.8% (48.1 - 67.5%), and 52.3% (42.1 - 62.5%), respectively, among men aged 25-59 years. In contrast, no significant differences between the income groups were observed among women and older subjects of both genders.

The age-specific, multivariate adjusted ORs of fatal outcome of an ICH event at day 28 and at one year comparing the low- and middle-income groups with the high-income group are shown in Table 3, Study III. The ORs are adjusted for age, study area, and urban/rural residence. The OR of ICH death among men of the low-income group aged 25-59 years was 2.10 (1.00 - 4.42) at day 28 and 2.19 (1.02 – 4.40) at one year. Among men aged 60-74 years the ORs did not differ from one, except for one-year deaths in the low-income group (2.40 (1.04 - 5.55)). Among women of all age groups the ORs did not differ from one.

In summary, the present study showed that the age-standardized incidence and mortality of ICH vary significantly by SES in both genders. Among men aged 25 - 59 years, the adjusted OR of ICH death within one year after the onset of the event was twice as high in the low- as in the high-income group.

5.3.3 Ischemic type of cerebrovascular diseases (Study IV)

The age-standardized incidence of first IS events was almost two times higher among persons with a low or middle income than among those with a high-income, both in men and women and in all age groups (Table 1, Study IV). In the incidence the widest gap was observed between the high- and middle-income groups, whereas in mortality, there was a gradual decrease from the low- to the middle- and high-income groups. Among men aged 25 to 59 years, the 28-day mortality rate ratio was 5.7 (95% CI, 3.2 to 10.0) in the low-income group and 3.5 (95% CI, 2.0 to 6.3) in the middle- compared

with the high-income group. Among women aged 25 to 59 years, the 28-day mortality rate ratio in the low-income group compared with the high-income group was 2.9 (95% CI, 1.3 to 6.7).

Among older men and women, the findings were consistent with those observed in the younger age groups. Differences in mortality between the two groups, divided on the basis of education, were somewhat smaller than differences between the two extremes of the three income groups (Table 1, Study IV). However, persons with only a basic education had significantly higher incidence and mortality rates than did persons with a secondary or higher education.

The 28-day case-fatality of IS among men aged 25 to 59 years was nearly three times higher in the low- (13.6%) than in the high-income group (5.1%) (Table 2, Study IV). At the one-year follow-up, the difference in case-fatality between the low- and high-income groups remained stable. A steady trend, but with a smaller gap, was observed among older men at day 28. Among women of all age groups, the low-income group had a marginally higher case-fatality than the high-income group (Table 2, Study IV). Only at the one-year follow-up among older women was the difference between the low- and high-income groups more significant.

The association between income, on the one hand, and diagnostic and treatment patterns, on the other, was analyzed for IS patients who reached a hospital alive and survived for \geq one day after the onset of symptoms. Both male and female IS patients with a high-income were more often treated at a university hospital and less often at a health center ward than were their counterparts with a low-income (Table 4, Study IV)). Accordingly, patients with a high-income were more often examined by a specialist in neurology than were patients with a low-income. The high-income group was more often examined with CT or MRI, whereas the low-income group was more often examined with a lumbar puncture. Almost half of the IS patients with a low-income were still in institutionalized care 28 days after the onset of symptoms. Among men with a high income, the proportion remaining in an institution was significantly less (37.3%), while among women, a significant trend existed in inverse proportion to

ascending income. Almost 60% of IS patients with a low-income needed help in the activities of daily living at day 28. Among patients with a high-income, this proportion was significantly lower: 43.5% in men and 46.5% in women.

The population-attributable risk was estimated by designating the high-income group as the nonexposed category and the combined low- and middle-income groups as the category exposed to low SES. Accordingly, the population-attributable risk of the incidence of first IS event due to low SES was 36% for both genders. Corresponding estimates for the death from a first IS within one year from the onset of the event were 56% for both genders.

In summary, the incidence, case-fatality, and mortality rates for IS were all inversely related to income. Furthermore, 28 days after the onset of symptoms, a greater proportion of patients with low-income were still in institutionalized care and/or in need of help for their activities of daily living. Population-attributable risk of the incidence of first IS due to low socioeconomic status was 36% for both genders. For death from first IS, it was 56% for both genders.

5.4 The combined effects of chronobiological and socioeconomical factors of the occurrence of cerebrovascular diseases

Study V showed that the highest average incidence of IS occurred among men aged 60-74 years, 788 (per 100,000 per year), in the middle-income group, almost as high, 742, in the low-income group and clearly lowest, 489, in the high-income group. In the low-income group the incidence peaked on Monday being 17.9% above the weekly average (Table 2, Study V). This was significantly different from Sunday, which was 13.9% below the weekly average. A similar significant difference between Monday and Sunday was found in the middle-income group (14.4% vs. - 15.5%), but another peak (20.7%) was observed on Thursday. In the high-income group no Monday peak was observed, but the incidence was clearly lowest (- 38.3%) on Sundays. Sunday, did not, however, differ significantly from any other day of the week in the high-income group.

The pattern for women aged 60 - 74 years was similar to that for men. The incidence of IS was highest in the middle- and low-income groups (470 and 465, respectively) and

Table 2. Incidence rates* (and their 95% confidence intervals) of first ever ischemic stroke events by season, age group, income group and education level in men and women aged 25 - 74 years in the FINMONICA Stroke Register

Season	25 – 59					60 – 74				
	Income group			Education level		Income group			Education level	
	Low	Middle	High	Basic	Higher	Low	Middle	High	Basic	Higher
Men										
Winter	123 (99 to 147)	135 (113 to 157)	64 (50 to 78)	115 (100 to 131)	80 (63 to 96)	797 (720 to 875)	806 (692 to 919)	575 (431 to 720)	797 (131 to 862)	672 (548 to 796)
Spring	145 (119 to 171)	161 (137 to 184)	65 (51 to 79)	139 (123 to 156)	84 (67 to 101)	760 (686 to 834)	687 (583 to 791)	405 (284 to 525)	749 (686 to 812)	486 (381 to 591)
Summer	110 (87 to 132)	121 (100 to 141)	42 (31 to 54)	101 (87 to 115)	68 (53 to 83)	669 (599 to 740)	792 (681 to 904)	464 (335 to 593)	722 (660 to 784)	500 (394 to 606)
Autumn	99 (78 to 120)	123 (103 to 144)	61 (48 to 75)	107 (80 to 121)	73 (57 to 89)	741 (666 to 815)	870 (752 to 987)	515 (379 to 651)	777 (712 to 841)	637 (517 to 756)
Women										
Winter	43 (31 to 54)	44 (28 to 59)	31 (22 to 40)	52 (41 to 63)	20 (13 to 27)	512 (469 to 556)	420 (308 to 532)	256 (158 to 355)	505 (463 to 547)	356 (279 to 433)
Spring	49 (37 to 62)	56 (39 to 73)	21 (13 to 29)	47 (38 to 57)	28 (19 to 37)	470 (429 to 510)	489 (370 to 609)	246 (150 to 341)	475 (435 to 515)	327 (254 to 400)
Summer	58 (44 to 72)	32 (19 to 45)	25 (16 to 34)	44 (34 to 53)	30 (20 to 39)	425 (386 to 463)	446 (333 to 560)	331 (220 to 441)	455 (416 to 495)	242 (179 to 304)
Autumn	45 (33 to 57)	53 (36 to 69)	22 (14 to 31)	41 (32 to 51)	20 (20 to 39)	452 (413 to 492)	524 (400 to 649)	309 (202 to 415)	473 (432 to 513)	341 (266 to 417)

* per 100,000 inhabitants

lowest in the high-income group 285. In the low-income group there was a clear incidence peak on Monday, which was significantly different from Sunday (12.6% vs. - 9.1%, Table 2, Study V). In the middle- and high-income groups the event numbers were small among women and the 95% CIs became wide.

Table 3. Incidence rates* (and their 95% confidence intervals) of first ever ischemic stroke events by season, age group and profession in men and women aged 25 - 74 years in the FINMONICA Stroke Register

Season	25 – 59				60 – 74			
	Manual Workers	Retired	Office workers	Farmers	Manual Workers	Retired	Office workers	Farmers
Men								
Winter	104 (82 to 127)	128 (104 to 152)	86 (64 to 109)	85 (61 to 109)	1185 (570 to 1800)	731 (671 to 791)	752 (296 to 1208)	1046 (686 to 1405)
Spring	136 (110 to 161)	149 (123 to 175)	78 (56 to 99)	115 (88 to 143)	1490 (729 to 2251)	671 (614 to 728)	758 (276 to 1241)	919 (550 to 1289)
Summer	102 (80 to 124)	103 (82 to 124)	49 (33 to 66)	84 (61 to 108)	1326 (640 to 2012)	637 (582 to 693)	2592 (215 to 4969)	1033 (653 to 1414)
Autumn	110 (87 to 134)	120 (98 to 143)	70 (49 to 91)	64 (44 to 85)	5203 (420 to 9986)	710 (650 to 769)	3113 (223 to 6003)	1061 (678 to 1444)
Women								
Winter	54 (31 to 71)	44 (29 to 59)	30 (30 to 39)	31 (13 to 48)	2369 (0 to 5132)	474 (436 to 513)	394 (76 to 713)	621 (193 to 1048)
Spring	45 (30 to 60)	51 (35 to 68)	30 (20 to 40)	37 (18 to 55)	2361 (0 to 5074)	444 (407 to 481)	1098 (0 to 2690)	922 (398 to 1446)
Summer	41 (26 to 56)	58 (40 to 76)	29 (19 to 39)	29 (12 to 45)	1400 (0 to 3330)	404 (369 to 439)	507 (156 to 858)	620 (242 to 999)
Autumn	48 (32 to 65)	49 (32 to 66)	32 (21 to 42)	32 (15 to 50)	3819 (451 to 7188)	414 (378 to 450)	2279 (0 to 4560)	1709 (900 to 2517)

per 100,000 inhabitants

When the incidence rates of IS were stratified by season and age group no consistent differences in seasonality were observed among the income, education and profession

groups (Tables 2 and 3). Similar to the incidence rates, the mortality rates of IS (28 days and one year) did not show consistent differences in seasonality. A statistical analysis for SAH and ICH was not carried out due to the small number of events after stratifying by SES and age group.

6 DISCUSSION

The aim of the current study was to investigate whether chronobiologic and socioeconomic factors and the interactions of these factors increase the risk and fatality of cerebrovascular diseases among persons aged 25 and above, in the areas of the FINMONICA Stroke Register in Finland. The study included 15,320 events of SAH, ICH and IS, during the period from 1982 until the end of 1992. From this number 9,303 were incident (first ever events) of cerebrovascular disease (253).

6.1 Study population

The study population consisted of inhabitants aged 25 and above in the monitoring areas of the FINMONICA Stroke Register; i.e., the former provinces of North Karelia and Kuopio in eastern Finland and the Turku/Loimaa area in southwestern Finland. Since the study was population-based, every effort was made to register all clinically symptomatic cerebrovascular events in the monitored populations during the ten-year study period. The main sources of case finding were hospital admission diagnoses registered at the outpatient clinic of the hospital. Completeness of case finding was ascertained by means of an annual record linkage of the study data with the National Causes of Death Register.

A limitation regarding the study population was that the oldest age group (75 to 99 years) was registered during the entire study period only in the town of Turku and only from 1990 in the province of Kuopio and not at all in Northern Karelia. Therefore, the oldest age group represents only the populations of these areas in these years. Since Turku is a coastal town with smaller seasonal variations in temperature than Kuopio, the highest age group was analyzed separately for Turku and for the province of Kuopio, but the results did not differ substantially and for simplicity of presentation pooled results are shown. Since the study population was representative solely for the study areas, the results from the study can be generalized to the whole the population of Finland only with great caution.

6.2 Methods and quality control

In the FINMONICA Stroke Register, the emphasis was on strict application of clinical criteria in classifying cerebrovascular disease events according to the WHO MONICA Protocol (251, 253). The use of clinical criteria by the same specialist physicians provided consistency of diagnostic classification even though the availability of diagnostic examinations improved considerably during the ten-year study period. The quality control procedures of the WHO MONICA project were rigorous and the results of the FINMONICA Stroke Register were generally solid (250).

A limitation of the present study in relation to SES was lack of access to household income, which may have caused some misclassification of the income category among women. This factor was mitigated by the fact that a considerable proportion of Finnish women are economically independent; according to Statistics Finland, 85% of Finnish women aged 35 to 59 years were working outside of the home in 1997. Therefore, the possible misclassification is not as substantial as it might have been in some other countries. Furthermore, the results for income were similar to those for education, which were not biased by the lack of family income.

The fact that the diagnosis of cerebrovascular events was not always based on CT or MRI was an added limitation of the study. Since in North Karelia the number of CTs performed during the early years of registration was very low, it is possible that some of the mild cerebrovascular events were classified as TIAs and therefore not included in the register. The proportion of CT examinations was highest in Kuopio and lowest in North Karelia. Another problem was the classification of the unspecified type of cerebrovascular disease (ICD-9: 436), which was usually included in IS. This comprised about 3% of all strokes, and occurred mostly among elderly subjects (11, 254), and most probably was IS.

The strengths of the present study include its population-based design and the large number of cerebrovascular events collected according to a standardized protocol and under rigorous quality control of the WHO MONICA Project. The team put considerable effort in registering the date of the onset of the stroke event according to

the first presentation of symptoms rather than according to hospital admission; for this reason the stroke register data are suitable also for analyzing the day of onset of the cerebrovascular event. Another major strength was the possibility of record linkage with the files of Statistics Finland, which provided us with accurate information on taxable income, education and occupation for each patient prior to the cerebrovascular disease event.

6.3 The role of chronobiological factors in the occurrence of cerebrovascular diseases

6.3.1 Seasonal variation (Study I)

Studies on chronobiology of cerebrovascular events indicate that the onset of cerebrovascular disease is not a random event and suggest that identifiable factors play a role in the causation of these events. Results presented in the study are generally consistent with findings from related studies. For example, in a population-based study from Japan, Shinkawa et al found significant seasonality in the incidence of all strokes, ICH(194), and cerebral infarctions (198). In a community-based stroke register study from Italy, cerebral infarctions were more frequent during winter and primary ICH during autumn (195). Some studies have, however, obtained different results for ICH. Most of the studies in this field have been performed in countries with cold (201) or temperate climates, but in a study from Israel the average daily incidence of stroke was approximately twice as great on hot days as on relatively cold days (259, 260). This suggests that exposure to extreme temperatures, whether cold or hot, may increase the risk from cerebrovascular diseases. In contrast, a recent study from Greece showed that cardioembolic stroke which is the most frequent type of cerebrovascular disease among Greek patients, has a clear temporal pattern with a peak during winter and a decline of stroke occurrence during summer (261).

Interestingly, a report from the Oxfordshire Community Stroke Project (196) did not find a seasonal variation in the incidence of IS in the United Kingdom, although a nonsignificant trend toward higher mortality in winter emerged. The authors concluded that the reported winter excess in the mortality from IS could be due to the

complications of IS, such as pneumonia, which also shows seasonal variation. However, our study was much larger than the British study and clearly shows that, at least in Finnish conditions, the incidence of IS also has significant seasonal variation in men aged < 65 years. The higher case-fatality of IS during seasons other than summer observed in our study in women aged 65 years or more may, however, be due to complications of stroke, as was hypothesized by British investigators. Our findings for ICH are consistent with those of the British study, although the seasonal variation did not reach statistical significance in Oxfordshire, presumably because of the small number of ICH events.

In the present study, no significant association was found between season and the occurrence of SAH, which aligns with findings from Japan (198), Portugal (262) and Russia (201). Some other researchers have reported significant association (263, 264), however, and it should be noted that in this study the occurrence of SAH also tended to be higher during the winter months than during the other months. At least in part, these controversies may be due to the small numbers of patients in these studies and to the relative rarity of SAH. This study was larger than most other studies that have examined the seasonal variability of SAH. However, the study had only 50% power to detect a significant difference at a level of $p < 0.05$ between the seasons with the highest and the lowest occurrence of SAH (e.g. between winter and autumn in men). Therefore, seasonal variation in the occurrence of SAH cannot be excluded on the basis of the data from this study.

In this study, the seasonal differences in the occurrence of IS were most prominent among men aged 25 to 64 years, with the older men and women showing smaller or non-significant differences. Previous literature has reported that the seasonal differences in mortality from cerebral and myocardial infarction are greater in older than in younger age groups (265). Our finding is, however, in agreement with the results of from Japan (198), who also found a more prominent seasonal variation in younger than in older persons. In contrast, Sheth et al from Canada found that persons above the age of 65 demonstrated a greater winter increase in acute myocardial infarction and stroke mortality than younger individuals because elderly persons, with their reduced

physiologic reserves, may be more vulnerable to these influences (266). Britain has a large burden of excess winter deaths, much of which is attributable to the effects of cold. According to a recent study, it seems that excess winter death in elderly people cannot be explained by socioeconomic factors (267). Increased winter mortality(268) in southern and western Europe could be reduced through improved protection from the cold indoors, increased public spending on health care, and improved socioeconomic circumstances resulting in more equitable income distribution (268). For example in Finland, effective insulation of houses and adequate heating may protect older persons, since the indoor temperatures do not vary substantially by season in Finland (269).

The potential deleterious effect of low temperatures on cardiovascular (270-272) and cerebrovascular incidence (204, 273) and mortality (274) is supported by numerous studies in various countries (191, 268). Seasonal and temperature variations of blood pressure (275, 276), serum lipid, and fibrinogen levels (23) have also been described (17, 18). The present study showed a significant correlation in the occurrence of SAH, ICH and IS with air temperature, in women but not in men. The difference between men and women may be due to the difference in dressing and protection from cold weather (277). The finding in this study may suggest the importance of climatic factors, particularly temperature, in causing seasonal variation.

A number of studies have suggested that infections may trigger cerebral infarction, particularly in young patients (278-280), although plausible underlying pathogenetic mechanisms remain to be determined. In particular, of all acute infections, respiratory infections have been most commonly implicated as risk factors for acute cerebral ischemia (278, 279) and respiratory infections represent the majority of acute infections preceding such IS (205). Unfortunately, most of the available studies have been case reports or uncontrolled case series, but several case-control studies have been published which supported these associations. Most of these case-control studies indicate that infection strongly increases the risk of stroke compared with controls in people under 50 (278, 279), but reported risks are less consistent and weaker for the older age groups which is most prone to IS.

6.3.2 Variation according to the day of the week (Study V)

The present study demonstrated a clear variation by day of the week in the occurrence of IS, which is consistent with findings from other studies (281-283). The greater IS incidence on Mondays was consistently pronounced among persons aged 60 to 74 years and subsisting on low SES. Because IS incidence is much higher in persons with low SES, the Monday excess is of substantial public health interest. The Monday excess may also suggest reasons for the higher IS incidence in persons with low SES and open up possibilities for prevention.

In a community-based stroke register from Japan, Wang et al (283) found among persons > 60 years of age a considerable weekly variation in the incidence of cerebral infarction, with a peak of 26% among men on Monday compared with the weekend, whereas in women, most events occurred on Thursday and Friday. In the Framingham Study (282), a significantly higher number of strokes occurred on Monday (17.2%) than on any other day. Johansson et al (284) found that cerebral ischemic events resulting from thrombosis of large vessels had their highest peak of frequency between Tuesday and Thursday and lacunar infarctions on weekends. Pasqualetti et al (179) reported a zenith of IS and hemorrhagic events on Saturday, Sunday, and Monday and a nadir on Wednesday and Thursday. On the other hand, in the community-based study, Brackenridge (285) found that the highest frequency of events (35%) occurred on Wednesday and the lowest (14%) during the weekend, without stratifying data by gender and subtypes of stroke. In contrast, Passero et al found no association in occurrence of ICH by day of the week (194).

6.3.3 Daily (diurnal) variation

Several studies suggest a daily rhythm for cerebrovascular diseases, with a peak of onset in the morning (184, 195, 206). The daily variation in onset of cerebrovascular disease is of both practical and physiological interest. According to Tsementzis et al, all three subtypes of cerebrovascular diseases exhibited a peak of incidence in the morning hours, specifically, between 10 and noon (184). Only lacunar infarctions were more

common during sleep (195). However a recent study from Greece suggested that in some populations a second peak occurs in the afternoon which may be due to different habits (261, 286). Endogenous physiological variables that show diurnal rhythms such as blood pressure (287), blood coagulation (288) and platelet activation (289) have been suggested as possible explanations for the observed daily variation in the onset of cerebrovascular disease (288).

Unfortunately, the time of onset of cerebrovascular disease was not recorded regularly in the FINMONICA Stroke Register, and therefore diurnal variation in the occurrence of cerebrovascular disease was not examined in this study.

6.4 Indicators of the socioeconomic status

It is generally recognized that health and well-being are a function of multiple interrelated factors, including biological factors, social factors, life-style behaviors, and use of health services. It is also widely recognized that major advances in health during the twentieth century were primarily a result of improvements in economic and material conditions of life (29, 214). To gain insight into the social conditions that influence health, researchers generally use measures of education, occupation, or family income to define an individual's socioeconomic status, as has been done also in the present study.

The use of neighborhood socioeconomic characteristics, such as median household income or proportion of community living below the poverty level, may provide information about the level of stress on stroke mortality. In the ARIC study, poorer neighborhoods were associated with increased prevalence of coronary heart disease and risk factors (290). Furthermore, the use of a single social indicator to represent all social conditions may be flawed in that different social conditions may operate through a multitude of different mechanisms. Less frequently have studies included multiple measures of SES or multiple social ambience, each of which may independently contribute to mortality and morbidity from cerebrovascular diseases. Adjusting for one individual social factor, such as educational level, may not be adequate to account for disparities in morbidity or mortality.

In the report of Lynch et al (291), both the psychosocial and health risk behaviors of adults were more common among those whose parents were poor when the patients were growing up. Thus, many individual characteristics, such as personality factors, psychosocial attitudes and orientations, as well as health risk behaviors, should be viewed as products of, or responses to, social environments rather than strictly as individual behavioral choices (292). It was suggested by Marmot and Wilkinson (293) that the relationship between smaller inequalities in income and better population health reflects increased psychosocial well-being.

Occupation may be a less valid indicator of SES for women than for men; a circumstance causing misclassification that tends to diminish observed SES gradients. For example, the SES of married women may, in some instances, be better classified as higher because of their husbands' occupation rather than their own (294).

In the present study however, the findings remained very similar, independent of the SES indicator used. This was true for income, education and profession, but there was, unfortunately, no data on the level of the SES of the neighborhood nor on psychosocial factors.

6.4.1 Socioeconomic status and subarachnoid hemorrhage (Study II)

The age-standardized incidence of SAH among both men and women aged 25-44 years was approximately three times higher in the low- than in the high-income group. In older individuals, differences between the income groups were less pronounced. Among survivors of the acute stage, poorer prognosis was observed in patients with low-income than in those with high-income.

It was somewhat surprising that such wide differences among the income groups were observed in Finland, where the income gap is smaller than in most other western countries. Furthermore, almost all acute SAH events are treated in public hospitals, where the costs for the patient are minimal and are not based on the examinations performed or treatments given. Therefore, it is unlikely that the observed socioeconomic

differences in SAH mortality and morbidity are due to any economic constraints in making use of the health care services. Since considerable discrepancy between the income groups were observed initially in the incidence, it is probable that the socioeconomic differences in risk factors of SAH are mainly responsible for the mortality difference. There is evidence that cigarette smoking, a critical modifiable risk factor for SAH, is more common among lower socioeconomic groups (295). The prevalence of two other modifiable risk factors for SAH, high blood pressure and alcohol consumption also differs according to SES. Alcohol abuse seems to contribute especially to a poor outcome after SAH. Young male manual workers are also more prone to various kinds of physical effects from cold weather or other adverse conditions, which may contribute to cold-induced hypertension (296) and precipitate an attack of SAH and ICH (297).

This study has suggested that the key to the reduction of excess SAH deaths is primary prevention by means of health education and health behavior changes. These efforts should be directed especially to young persons of lower socioeconomic groups, since they are the ones who are at the highest risk and could benefit most from intervention. However, the data posited the existence of discrimination in examination and treatment patterns for different socioeconomic groups. In part, these may have depended on the area of residence and the availability of CT-scans during the early FINMONICA period. It is, however, likely that the decisions of physicians also play a role in these SES differences in the examination patterns.

Socioeconomic differences have been observed in many different diseases and in many different countries. The ones observed in the present study in SAH mortality and morbidity are not easy to abolish, but neither are they inevitable. Finland has an ethnically and genetically homogenous population and it is very unlikely that there are major, immutable biological distinctions between the high- and low-income groups. If the SAH mortality and morbidity in the middle- and low-income groups could be lowered to the level of the high-income group, a considerable number of young persons would be saved from death or disability. A potential remedy to reduce SAH mortality

and morbidity markedly exists; i.e., focus more attention on the risk factors and on the diagnosis and treatment of SAH in persons from lower socioeconomic groups.

6.4.2 Socioeconomic status and intracerebral hemorrhage (Study III)

When examining the relationship of socioeconomic factors to the subtypes of strokes, it is necessary to consider whether the examinations performed, and accordingly the diagnostic accuracy, depend, on SES. As described in the Methods section, the use of diagnostic examinations in events classified as ICH in the FINMONICA Stroke Register was very high. Therefore, it is unlikely that there were false positives in any of the income groups. Interestingly, however, among patients classified as having suffered an IS, the use of diagnostic examinations was lower, and dependent on the income category. Thus, we cannot exclude the possibility that there are some false negatives; i.e., ICH events erroneously classified as ISs. Since the use of diagnostic examinations was lower in the low-income group with IS, it is possible that there are somewhat more false negative ICH events in the low-income group than in the high-income group. The resulting bias, if any, is likely to be small and tends to reduce the incidence and mortality differences between the income groups. Hence, the real SES differences in the incidence and mortality of ICH may in fact be even larger than the ones reported in the present study. On the other hand, the different use of diagnostic examinations may exaggerate the case-fatality differences slightly, if milder cases of ICH are diagnosed in the high- more often than in the low-income group.

The incidence of cardiovascular disease events depends mainly on the levels of risk factors, whereas the case-fatality and prognosis depend both on the severity of the event and treatment received. Known risk factors for ICH include high blood pressure, arteriosclerosis, smoking, drug and alcohol abuse. Risk factor levels in the FINMONICA areas have been examined in population-based surveys and marked differences between the SES groups have been demonstrated (33, 37, 298). For example, in 1987, blue-collar men had higher serum cholesterol (6.20 vs. 6.14 mmol/L) and higher prevalence of smoking (47% vs. 33%) than white collar men. No difference was observed in diastolic blood pressure (88.3 vs. 88.2 mmHg)(33). Blue collar women had more adverse levels of serum cholesterol (6.02 vs. 5.80 mmol/L), prevalence of

smoking (22% vs. 15%), and diastolic blood pressure (84.1 vs. 82.0 mmHg)(33). Similar differences by SES in risk factors and prevalence of atherosclerosis have been reported from other countries as well. In an American study, comparing RRs of incident ICH between African Americans and European Americans, the RR associated with African American ethnicity came down from 1.9 to 1.6 when educational attainment and systolic blood pressure were taken into account (299). Further adjustment for additional cerebrovascular disease risk factors did not change this estimate appreciably. To our knowledge, no other such studies have been carried out specifically for ICH at the moment. However, since we observed considerable SES differences in the incidence and relatively small differences in case-fatality, it seems likely that the risk factor differences have played a major role in the etiology of SES differences in ICH mortality in Finland. We did observe, however, some disparities in case-fatality and prognosis as well, suggesting that discrimination in treatment may also have contributed to the mortality differences by SES.

6.4.3 Socioeconomic status and ischemic stroke (Study IV)

Earlier studies have shown increased stroke mortality rates for lower SES groups both in Finland and elsewhere (30, 300). Kunst et al (27) described higher stroke mortality rates in men with manual occupations compared with men with non-manual occupations in 11 European countries and in the United States. Finland was one of the countries with the largest SES differences in stroke mortality rates. In keeping with our findings, recent studies from northern Sweden (36) and from the Netherlands (40) have reported an association between low SES and the incidence of stroke. The case-fatality was analyzed in the Swedish study only, and its relationship to SES did not reach statistical significance, although the category of "employed and self-employed professionals" had the lowest case-fatality (36). In a study carried out among white men in the United States(232, 233), SES, expressed as the median family income of the zip code of residence, was significantly associated with death from IS. Our study is in agreement with this previous literature but provides a more precise assessment of the relationship between SES and IS by presenting population-based data on the incidence, case-fatality, and prognosis of validated first IS events.

The Multiple Risk Factor Intervention Trial in the USA (232, 233) is one of the few studies, which have differentiated between hemorrhagic and non-hemorrhagic types of stroke. In that study, SES, expressed as the median family income for the zip code of residence, was not significantly associated with intracranial hemorrhage, but with non-hemorrhagic stroke only. Evaluation of the socioeconomic status in this way may, however, lead to misclassification, which usually tends to reduce the differences.

In the present study almost half of the IS patients with a low-income were still in institutionalized care at day 28 after the onset of symptoms. Similar findings were reported from the Netherlands (46), where patients from the lower socioeconomic group experienced more disabilities up to three years after a stroke and more handicaps up to five years after a stroke despite equality in health care.

6.5 Combined effects of chronobiological and socioeconomic factors

In this study, Sunday was the day of the week with the lowest occurrence of IS. This result was confirmed by overall analyses in persons with low income and low education in both genders and all age groups studied. The Sunday “low” incidence finding was actually more consistent than Monday “high” incidence of IS (“high” incidence on Tuesdays among women was also revealed). The weekly differences in the occurrence of IS were most prominent among persons aged 60 to 74 years, with the younger men and women showing smaller and non significant differences. Previous literature has reported that the weekly variation in the onset of cerebral infarction is greater in the younger (12) and in the working population (282) than in the older age groups. We also observed an excess of IS events on Friday among younger women with higher SES, but this may be a chance finding due to the relatively small number of events in the highest income group. Overall, the results on taxable income were consistent with those on education, suggesting that the observed differences in the excess of IS by SES may be due to differences in modifiable rather than non-modifiable risk factors. Unfortunately, we did not have life-style information, which would have been helpful in assessing the possible relationship of Monday excess with drinking and smoking habits during the

weekend, which have been related to the increased incidence of myocardial infarction and IS.

A novel finding of the present study was that patients with lower SES had the fewest IS on Sundays, and tended to have IS events more often on Mondays compared to their wealthier and better educated counterparts, for whom we did not find a significant weekly difference. This only partially confirms the findings of a previous Finnish study, which suggested that weekday variation in the occurrence of IS may be attributable to the short-term life-style changes during the weekend (301). Unexpectedly, the main findings were among older persons whose life-style during the weekend is likely to be more stable and may not be a proper explanation for the observed variation by day of the week. Unfortunately, data on subtypes of IS was not collected, which might have been helpful in understanding the relationship of weekly variation of IS to age, gender and SES. In this regard, however, it should be pointed out that in the present study, income, education and profession could not explain the seasonal variation in the incidence and mortality of cerebrovascular diseases

6.6 Possible explanations for the observations

The biological reasons for the higher occurrence of strokes during winter are poorly grasped, but several possible mechanisms may be suggested (204). Graded and consecutive cardiovascular adjustments accompany exposure to cold (272). The stimulation of the cold receptors of the skin, in particular, induces stimulation of the sympathetic nervous system, as indicated by increased levels of catecholamines in the blood (302). A seasonal variation in norepinephrine and epinephrine excretion with higher levels in winter, has also been reported in men, suggesting an increase in the activity of the sympathoadrenal system (303). Peripheral vasoconstriction is one immediate response, secondary to an ortho-sympathetic stimulation initiated by the cutaneous thermo-and nociceptors activation (303-305). Furthermore, total cholesterol and triglycerides tend to be higher in winter than in summer. It is hypothesized that exposure to winter weather conditions may induce physiological stresses including sympathetic activation, hypercoagulability (23) and infection that increase the incidence or case-fatality of AMI and stroke (306). The winter peaks in acute myocardial

infarction mortality have been correlated with temperature and shown to be greater among those with less physical protection from the cold (191, 268, 277, 307).

Seasonal variations in other factors such as air pollution (193), exposure to sunlight, incidence of influenza, and diet have also been suggested as culprits, but variation in temperature has been considered the most likely reason (204, 308). Acute respiratory illness may also increase stroke incidence (205, 278). Seasonal affective disorder, expressed as winter depression, can increase the risk of cerebrovascular diseases, particularly in the elderly population (309).

The etiology for observed weekly periodicity with the higher occurrence of IS on Mondays is not clear. Gnechi-Ruscione et al (310) found that the onset of acute myocardial infarction is unevenly distributed over the week with increased incidence of events on Monday, which might be due to the shift from a period of non-scheduled to scheduled activity. On the other hand, cardiological studies have found no evidence of weekly variation of life-threatening ventricular arrhythmias and sudden deaths on Mondays have been considered to be mainly due to ischemic heart disease (311). A recent analysis of the MONICA myocardial infarction register data suggested that the Monday excess in coronary heart disease might simply be an artifact of registration (312). However, the FINMONICA Stroke Register team exerted considerable effort in registering the date of the event of the stroke onset according to the first presentation of symptoms rather than according to hospital admission. For this reason, it is not likely that findings of the study were classified erroneously regarding day of onset.

The mechanisms by which social conditions impact on stroke risk and stroke mortality are still unclear. For example, lower educational attainment may cause miscommunication between patient and physician, leading to poorer compliance with antihypertensives medications, resulting in uncontrolled hypertension and increased stroke risk. Lower income may result in inadequate living conditions, increased stress, and greater distance to health care resources. Finally, disparities in mortality may exist because of the inequalities in the distribution of resources in the community.

There is evidence that psychosocial risk factors increase the risk of cardiovascular diseases (313-316). It has been suggested that biologically plausible mechanisms are likely to mediate associations between psychosocial risk factors and classical (conventional) risk factors of cardiovascular diseases (315, 317). Current evidence from clinical trials of behavioral and pharmacological treatments targeting psychosocial factors support the need for increased research to develop, implement, and test behavioral and pharmacological interventions aimed at reducing the impact of psychosocial factors on the development and prognosis of cardiovascular diseases (317).

6.7 Public health significance of the study

The attention received by the 'inequalities in health' as a health policy problem at the national and international level has been documented by a variety of rather heterogeneous activities in recent years. In Finland, the reduction of socioeconomic differences in health has been one of the main goals of the health policy as expressed in the "Health for all by the year 2000 Program" (318). Recent limited data suggest, however, that this goal may not have been reached. In Europe, a revision of the concept was recently adopted through the targets of the program "The Health 21 Strategy" (214). This program has a more realistic approach and quite deliberately calls for the realization of equal opportunities in health for all citizens rather than for the abolition of socioeconomic differences in health, which was probably an unrealistic expectation.

In rich countries, well-educated people are the first to adopt messages about a healthy life-style and they are more inclined to change their health behavior (319). Consequently a social profile emerges; i.e., people with a high level of education have more leisure-time physical activity; are leaner; have lower levels of blood pressure, cholesterol, and fibrinogen; are less often smokers; and less prone to DM (320) Even in developed countries, those with a low level of education and/or engaged in manual labor are clearly at higher risk for cerebrovascular diseases than the highly educated or professionally employed (34, 36, 40). The accepted wisdom assumes that universal health care systems decrease health-care disparities through improved access to care. There is also an expectation that, given the equal availability to health care across

income, educational, and occupational demarcations, differentials in the incidence and mortality from cerebrovascular disease would be minimized (321). But as has been pointed out (in this study), considerable discrepancies related to SES have been observed in the patterns of diagnostic and treatment practices for IS. Similar differences were found in acute coronary events (322). Partially, they were due to the area of residence, because individuals in rural areas tend to have lower incomes and longer distances to specialized centers, which can offer more sophisticated diagnostic services. However, essentially similar SES differences were observed only when inhabitants of urban areas were included in the analysis. Undoubtedly, the differences in the diagnostic and treatment practice patterns have contributed to the differences in case-fatality and prognosis. Interestingly, in this connection, 28 days after the onset of the event, more patients with a low SES than those with a high SES were still in institutionalized care and/or in need of help in the activities of daily living. If this extensive need of care could be reduced, it would substantially reduce the burden of IS on the health care system as well as on the families of these patients. For example, in Study IV it was observed that the population-attributable risk of the incidence of first IS due to low socioeconomic status was 36% for both genders. For death from the first IS, it was 56% for both genders.

Taken together, Studies II, III and IV reinforced conclusions that the key to the reduction of excess incidence and deaths caused by cerebrovascular diseases among individuals with low SES is primary prevention by means of health education and lifestyle changes. Better control of hypertension, avoidance of smoking and excessive alcohol consumption are undeniably useful in the prevention of cerebrovascular events among persons with low SES, and at the same time, those measures will reduce the risk of other cardiovascular diseases as well. It should be noted that psychosocial factors such as mental stress and depression coexist with classical risk factors and can trigger a cerebrovascular event (323).

It is probably idealistic to expect that the socioeconomic differences in mortality and morbidity from cerebrovascular diseases can be totally eliminated. Distinctions observed in the present study were, however, very large, and a substantial narrowing of

the gap should be possible. In principle, this could be achieved in two ways. First, the incidence differences can be influenced by focusing more attention on the primary prevention of cerebrovascular diseases and other related diseases; e.g., cardiovascular disease in those with low SES. It should be obvious that those persons who already have long standing high blood pressure and coronary heart disease are at increased risk for cerebrovascular disease, and therefore the patients with a low SES should receive adequate treatment and secondary prevention measures without hesitation. Second, differences in case-fatality and prognosis can be reduced by ensuring that the low SES patients with cerebrovascular disease receive diagnostic, treatment, and rehabilitation services that are equal to those of their wealthier counterparts.

7 SUMMARY AND CONCLUSIONS

Cerebrovascular diseases not only have high prevalence, but also impose a heavy burden of disabling illness and create high expenses for the community as well as the individual. Identification and reduction of the risk factors for cerebrovascular diseases offer some possibilities for prevention and therefore arouse substantial public health interest. The existence of socioeconomic differences in morbidity and mortality in European countries has been pointed out by various studies, initially as a comparison between countries (30, 44). There is solid evidence that classical risk factors can explain a large part of the differences in cardiovascular mortality among people with different SES (27, 33-36, 322).

On the one hand, Study I reported a significantly higher incidence of IS and ICH in winter than in summer in the FINMONICA areas. On the other hand, the incidence of SAH did not vary significantly by season. The greater incidence of IS in winter was particularly prominent among men aged 25 to 64 years but less prominent in elderly men and in women generally. The 28-day case-fatality of IS showed significant seasonal variation only in women ($p = 0.001$), with the lowest proportion of fatal events in summer.

Study II analyzed the relationship of SES with the mortality and morbidity of SAH. The age-standardized incidence of SAH among men and women aged 25-44 years was approximately three times higher in the low-income group than in the high-income group. In older individuals, differences among the income groups were less pronounced. Among survivors of the acute stage, a poorer prognosis was observed in patients with low- than in those with high-income.

Study III examined the association of SES with the incidence, mortality and case-fatality of ICH. The age-standardized incidence and mortality of ICH among persons aged 25-74 years were significantly higher in the low- than in the high-income group in both genders. Among men aged 25-59 years, the adjusted OR of ICH death within one year after the onset of the event was twice as high in the low- as in the high-income

group (OR = 2.12, 95% CI 1.02 - 4.40). Observed differences in case-fatality were, by contrast, rather small.

In study IV, the incidence and mortality, as well as case-fatality, of IS were all inversely related to income. Furthermore, 28 days after the onset of symptoms, a greater proportion of patients with low-income than of those with high-income was still in institutionalized care and/or in need of help for the activities of daily living. Population-attributable risk of the incidence of first IS due to low socioeconomic status was 36% for both genders, whereas for death from first IS, it was 56% for both genders.

Study V showed a clear variation in the incidence of SAH, ICH and IS by day of the week. Observed variation depended strongly on age and gender. In the analysis by gender and age group, IS demonstrated a difference by day of the week only in the age group 60-74, both in men and women ($p < 0.001$ and $p = 0.02$ respectively). In contrast, variation by day of the week in the incidence of SAH and ICH events was pronounced in men below the age of 59 years. In addition, findings in Study V suggested that the incidence of IS is much higher on Mondays in persons with low SES.

In conclusion, the present study showed that the occurrence of cerebrovascular diseases varies significantly by season and by day of the week in Finland. Furthermore, marked socioeconomic differences were found in the incidence and mortality of cerebrovascular diseases with decidedly higher rates in persons with low socioeconomic status. The key to the reduction of excess deaths from cerebrovascular diseases among individuals with low SES is primary prevention by means of health education and life-style changes. Therefore, persons with low SES should be given high priority in the prevention of cerebrovascular diseases and cardiovascular diseases in general. Observed excess in socioeconomic differences does not seem to vary by season, but does, to some extent, by day of the week. A reduction of this excess could markedly decrease the burden of cerebrovascular diseases on society, and thus ensure an important public health improvement.

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