Sanna Rantakömi

Alcohol Consumption, Atherosclerosis and Stroke

Epidemiologic Follow-up Study in Middle-aged Finnish Men

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ABSTRACT

Alcohol consumption has been associated with a wide range of medical conditions. A J-shaped relationship between alcohol consumption and the risk of ischaemic stroke has been observed, indicating that moderate alcohol consumption is related to low risk of stroke, whereas heavy alcohol consumption leads to an increase in the risk of stroke. Heavy alcohol consumption has been associated with an increased risk of stroke and stroke mortality.

The aims of this thesis were to more closely investigate (I) the effect of binge drinking on the progression of atherosclerosis, (II) the relation of hangover and alcohol consumption with the risk of stroke, (III) the role of alcohol consumption according to the level of blood pressure and body weight with respect to the risk of stroke, and (IV) the association between the frequency of alcohol consumption and stroke mortality in a population-based sample of Eastern Finnish men.

This prospective follow-up study was part of the FinDrink Study, a larger alcohol epidemiologic project. The subjects were a population-based sample of Eastern Finnish men from the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD). The baseline examinations involved two cohorts of 42- to 60-year-old men, the first of which was examined during 1984-1986 (n=1,166) and the second during 1986-1989 (n=1,516).
Binge drinking was associated with increased atherosclerotic progression at the 11-year follow-up. There was a statistically significant relationship between maximum change and in plaque height among men who drank ≥ 6 drinks per one occasion. The self-report alcohol intake response form covered the preceding 12-month period.

Having at least one hangover per year was associated with increased risk of all strokes combined, and especially with ischaemic stroke. Hypertension and overweight, with the presence of alcohol consumption, were related to an elevated risk of stroke. There was a clear positive relation between the frequency of alcohol intake and stroke mortality. The risk of stroke death was increased among men who consumed alcohol ≥ 2.5 times per week.

In summary, this series of studies demonstrated that binge drinking is associated with increased atherosclerotic progression. Blood pressure, overweight and alcohol drinking may have joint effects on stroke risk. In addition, hangover and the frequency of alcohol consumption are associated with an increased risk of stroke and stroke mortality.

National Library of Medical Classification: WA 105, WA 306, WL 356, WL 357
Medical Subject Headings: Alcohol Drinking; Stroke/epidemiology; Risk Factors; Carotid Artery Diseases/epidemiology; Binge Drinking; Cohort studies; Follow-Up Studies; Male; Finland

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TIIVISTELMÄ:

Alkoholinkäyttö on yhdistetty hyvin moniin eri sairauksiin. Alkoholinkulutuksen ja iskeemisen aivohalvauksen välillä on J-käyrän mukainen yhteys, jonka mukaan kohtuullisesti alkoholia käyttävillä henkilöillä on matalin aivohalvausriski, mutta runsas alkoholinkulutus johtaa kohonneeseen riskiin aivohalvauksen suhteen. Runsaan alkoholinkäytön on nähty olevan yhteydessä sekä kohonneeseen aivohalvauksen että myös aivohalvauskuoleman riskiin.

Tutkimuksen tavoitteena oli selvittää tarkemmin (I) humalahakuisen juomisen vaikutuksia ateroskleroosin kehittymiseen keski-ikäisillä miehillä, (II) krapulan yhteyttä aivohalvauksen riskiin, (III) alkoholinkäytön yhteyttä aivohalvauksen riskiin verenpaineen ja painoindeksin eri tasoilla, sekä (IV) alkoholinkäytön yhteyttä aivohalvauskuolemien riskiin.

Tämä seurantatutkimus on osa laajempaa alkoholiepidemiologista FinDrink Study-projektia. Tutkimusjoukko muodostui Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD)- hankkeen väestöotoksesta, jossa oli mukana kaksi keski-ikäisten miesten kohorttia. Alkututkimukset tehtiin ensimmäiselle kohortille (n=1166) vuosina 1984- 1986 ja toiselle kohortille (n=1516) vuosina 1986- 1989.

Humalahakuinen juominen oli yhteydessä kohonneeseen ateroskleroosin etenemiseen 11 vuoden seurannassa. Tilastollisesti merkitsevä yhteys havaittiin kaulavaltimoiden intima-mediakerroksen maksimipaksuuden muutoksen sekä ateroskleroottisten plakkien korkeuden suhteen niillä miehillä, jotka joivat vähintään 6 alkoholiannosta yhdellä kerralla (I). Jo yhden krapulan vuodessa havaittiin olevan yhteydessä aivohalvauksen kokonaisriskiin sekä erityisesti iskeemisen aivohalvauksen lisääntyneeseen riskiin (II). Koholla oleva verenpaine sekä ylipaino liittyivät aivohalvauksen riskiin nimenomaan alkoholia käyttävillä miehillä (III). Alkoholinkäyttökertojen ja aivohalvauskuolemien välillä oli selkeä yhteys. Aivohalvauskuoleman riski oli kohonnut niillä miehillä, jotka käyttivät alkoholia vähintään 2.5 kertaa viikossa (IV).

Näissä tutkimuksissa havaittiin, että humalahakuinen juominen on yhteydessä ateroskleroosin etenemiseen. Verenpaineella, ylipainolla sekä alkoholinkäytöllä voi olla yhteisvaikutuksia aivohalvausriskin osalta. Lisäksi krapulat ja tiheämmät alkoholinkäyttökerrat liittyvät sekä aivohalvauksien että aivohalvauskuolemien kohonneeseen riskiin.

Luokitus: WA 105, WA 306, WL 356, WL 357
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To My Parents,

With Love

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Kuopio, September 2013.

Sanna Rantakömi

List of the original publications

This dissertation is based on the following original publications:

I Rantakömi SH, Laukkanen JA, Kurl S, Kauhanen J. Binge drinking and the progression of atherosclerosis in middle- aged men: An 11-year follow-up. *Atherosclerosis 205(1):266-71, 2009. DOI: 10.1016/j.atherosclerosis.2008.11.004.*

II Rantakömi SH, Laukkanen JA, Sivenius J, Kauhanen J, Kurl S. Hangover and the risk of stroke in middle-aged men. *Acta Neurol Scand. 127(3):186-91, 2013. DOI: 10.1111/J.1600-0404.2012.01696.x.*

III Rantakömi SH, Laukkanen JA, Sivenius J, Kauhanen J, Kurl S. Alcohol consumption and the risk of stroke among hypertensive and overweight men. *J Neurol. 260(2):534-9, 2013. DOI: 10.1007/s00415-012-6672-6.*

IV Rantakömi SH, Kurl S, Sivenius J, Kauhanen J, Laukkanen JA. The frequency of alcohol consumption is associated with the stroke mortality. *Submitted for publication.*

Contents

Abbreviations

AF	Atrial fibrillation
Apo A	Apoprotein A
Apo B-100	Apoprotein B-100
Apo-E	Apolipoprotein E
Apo-H	Apolipoprotein H
ACE	Angiotensin converting enzyme
APP	Amyloid precursor protein
BMI	Body mass index
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy
CCA	Common carotid artery
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CRP	C-reactive protein
CT	Computer tomography
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
GLM	Generalised linear model
HDL	High-density lipoprotein
HZ	Hazard ratio
ICD	International classification of diseases
IMT	Intima media thickness
KIHD	The Kuopio Ischaemic Heart Disease Risk Factor Study
LDL	Low-density lipoprotein
Lp a	Lipoprotein a
LVD	Left ventricular dysfunction
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MRI	Magnetic resonance imagine
NVAF	Non-valvular atrial fibrillation
NOTCH3	Neurogenic locus notch homolog protein 3
REM	Rapid eye movement
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socioeconomic status
TGF-β	Transforming growth factor β
TIA	Transient ischaemic attack
tPA	Tissue platelet activator
Vo_2 max	Maximal oxygen uptake
vWF	von Willebrand factor
WHO	The World Health Organization
WHR	Waist-to-hip- ratio

1 Introduction

Stroke is the second leading cause of death worldwide after heart disease, accounting for 10% of all deaths, and stroke is one of the leading causes of disability (1,2). It has been estimated that stroke causes 8.9% of all deaths in Finland (3). It has been reported that the number of new first stroke cases in Finland was 11,500 in the year 2000 (4). According to National Institute for Health and Welfare the number of all cerebrovascular diseases (among men and women, aged 35-74 years) in Finland was 16,803 in 2011 (5). It has been shown that there was a continuous decrease in the incidence and mortality of stroke during the 15-year period of 1983-1997 in Finland (6). The reason for the decline is a notable improvement in cardiovascular risk factor levels in Finland (7,8). The prevention of stroke and other cardiovascular diseases (CVDs) has also improved thanks to antithrombotic therapy (9,10). In Western countries, the use of acetylsalicylic acid has increased and it is often recommended for patients who have had symptoms of transient ischaemic attack (TIA) for the prevention of cerebral infarction and also for patients with coronary heart disease (CHD), who are at increased risk of stroke (10). It has been proposed that with increasing life expectancy the burden of stroke is likely to increase worldwide (11,12).

Alcohol consumption may have beneficial or harmful effects. Previous epidemiological studies have shown a J- or U-shaped association between alcohol consumption and different CVDs such as myocardial infarction (13) and ischaemic stroke (14). Haemorrhagic stroke has led to a higher mortality risk than ischaemic stroke (15,16). Heavy alcohol drinking is known to increase the risk of all types of strokes (17-20) and stroke mortality (21). Moderate alcohol consumption seems to be protective for ischaemic stroke, but it may be detrimental or neutral for haemorrhagic stroke (22). Binge drinking (23) and hangover have been shown to increase the risk of ischaemic stroke and cardiovascular mortality (24). It has been shown that drinking more than 40 grams of alcohol during 24 hours prior to stroke may predispose to ischaemic stroke (25).

This study clarified the role of binge drinking as a risk factor for progression of carotid atherosclerosis, the relation of hangover with the risk of stroke, the role of alcohol consumption in the risk of stroke at different levels of blood pressure and body weight, and the association between the frequency of alcohol consumption and stroke mortality.

2 Review of the literature

2.1 ALCOHOL CONSUMPTION: DEFINITIONS AND MEASUREMENTS

2.1.1 A standard alcoholic drink and/or unit

The standard alcoholic drink or the standard unit of alcohol is the basic measure of alcohol consumption. The definition of an alcoholic drink or unit varies between countries, but it is usually presented by using the total amount of 100% ethanol in grams or ounces per one serving. In Finland, a standard alcoholic drink contains 12 grams of pure alcohol. In the United States a standard alcoholic drink contains 14 grams of pure alcohol, in the United Kingdom 8 grams, in Australia 10 grams and in Japan 23.5 grams. The amount of alcohol consumed has usually been reported as grams, milliliters, fluid ounces or as the number of alcoholic drinks (26).

2.1.2 Average alcohol consumption

Alcohol consumption is defined as the average amount of alcohol consumed over a long time that can vary, but it has often been 12 months. Average alcohol consumption is usually assessed with questions on habitual alcohol consumption or short-term recall of actual recent alcohol consumption. The quantity-frequency method includes questions about the frequency of drinking (How often do you drink alcoholic beverages during a certain time period (e.g. 12 months)? and the quantity of drinking (On those days when you drink, how much alcohol do you usually drink?). The quantity question deals with the typical number of drinks consumed per occasion, providing the respondent with some definition of drink on which to base on his or her answer (27). Alcohol consumption is calculated by multiplying the quantity and frequency measurements. The short-term recall method about actual alcohol consumption estimates habitual alcohol consumption over a longer period of time and is based purely on the volume of alcohol consumed (28).

2.1.3 Different drinking patterns

Drinking pattern refers to the way in which an individual consumes alcohol; it describes alcohol drinking and drinking behavior better compared to total amount of alcohol consumption.

In studies of alcohol consumption, the subjects can be categorized as abstainers, light drinkers, moderate drinkers and heavy or heavier drinkers. The following definitions are used of subjects in different categories according to alcohol consumption (29) (one drink is equivalent to 0.5 fluid ounce of alcohol, which is equivalent to 28.4 millilitres according to the International System of Units): an abstainer drinks <0.01 fluid ounces of alcohol per day (<12 drinks in the past 12 months); a light drinker drinks 0.01 to 0.21 fluid ounces of alcohol per day (1-13 drinks per month); moderate drinker drinks 0.22 to 1.00 fluid ounces of alcohol per day (4-14 drinks per week) and a heavy drinker drinks >1.00 fluid ounces of alcohol per day (> 2 drinks per day).

Abstainers can be classified in different ways, and the definition may vary from one study to another study. In the National Health and Nutrition Examination Survey I, respondents had to report consuming <1 drink of beer, wine or liquor in the previous year, to be classified as abstainers (27). The National Longitudinal Alcohol Epidemiologic Survey defines a current drinker as a person who reports consuming 12 or more drinks during the last year, while an abstainer is a person who consumed less than 12 drinks during the last

year. Abstainers can be classified into former drinkers, who have consumed at least 12 drinks in a 12-month period at some time during their lives, but not during the 12 months just before the interview, and lifetime abstainers, who have never consumed at least 12 drinks in a 1-year period (29).

Heavy drinking occasions and binge drinking are defined as drinking patterns, with large amounts of alcohol consumed over a short period of time. Heavy episodic drinking is a synonym for binge drinking. Quantitative definitions of binge drinking based on the number of drinks consumed on one occasion are as follows: >4 drinks per occasion for women, >5 drinks per occasion for men (The United States) (30), >5 drinks per occasion at least once in the past 30 days (The United States), half a bottle of spirits or 2 bottles of wine on the same occasion (Sweden) (21), >6 bottles of beer per session (Finland) (31), regular consumption of >7 alcohol units per session for women/ >10 units for men (The United Kingdom). The criteria for drinking patterns vary between studies, but six or more drinks on one occasions for men is widely used. The National Institute on Alcohol Abuse and Alcoholism in the United States addressed some of these concerns when it redefined binge drinking as "a pattern of drinking alcohol that raises blood alcohol concentration level to 0.08 percent or above. For the typical adult, this pattern corresponds to consuming 5 or more drinks (male) or 4 or more drinks (female), in about 2 hours". Heavy alcohol drinking and binge drinking during weekends are typical drinking patterns in Finland and in the Baltic countries, and these drinking patterns are much more common among men than women (32).

2.1.4 Hangover

Hangover is defined by the group of unpleasant mental and physical symptoms that occur after a bout of heavy drinking. Physical symptoms of a hangover include headache, fatigue, increased sensitivity to light and sound, redness of eyes, muscle aches, and thirst. Sympathetic nervous system activity increases in hangover and typical signs are an increased systolic blood pressure (SBP), tachycardia, tremor and sweating. Mental symptoms include dizziness, vertigo, cognitive and mood disturbances, and especially depression, anxiety and irritability (33). There is a variation in symptoms of hangover, and all above-mentioned symptoms do not capture the overall experience for the patient, which remains more or less subjective and varies from person to person and from one drinking episode to another (34). Different hangover symptoms scales (the Hangover Symptoms Scale, the Acute Hangover Scale and the Alcohol Hangover Severity Scale) seem to be appropriate for application in hangover research, but use of one-item hangover scale system is not recommended (35-38). The Hangover Symptoms Scale is used in survey research and the Acute Hangover Scale is used experimental research (37). The Alcohol Hangover Severity Scale is reliable and valid scale when assessing hangover severity and it is useful in surveys and in experimental studies (38). There are many explanatory hypotheses of hangover involving several factors, which are based basically on the potential direct effects of alcohol consumption or on its withdrawal effects.

Hangover as an acute alcohol withdrawal

According to one hypothesis, hangover is the first phase of acute alcohol withdrawal (33,39), and this hypothesis is based on the symptoms of hangover and withdrawal, such as headache, nausea, vomiting, tiredness, anxiety, sweat, cognitive impairment and general discomfort. However, most data believe that hangover and alcohol withdrawal are two different phenomena. There are three clinical stages of alcohol withdrawal: minor, major and *delirium tremens* (40). Only the minor alcohol withdrawal symptoms, which happen within 24 hours after cessation of alcohol intake and manifest as mild autonomic hyperactivity, since hangover appears a few hours after alcohol consumption and lasts for a maximum 24 hours, can explain hangover. Major alcohol withdrawal stage and *delirium tremens* go on during 1-5 days after abstinence and their symptoms, such as hallucinations

and seizures, are not frequent in hangover (39). Even alcohol administration could reverse the symptoms of hangover and withdrawal (33), which could only mean that they have something in common as for biological mechanism, but it does not mean that they are the same phenomenon. The haemodynamic and hormonal changes during alcohol withdrawal differ from changes in hangover (39). The syndrome of abstinence or alcohol withdrawal requires previous and continuous consumption of large doses of alcohol for a long time, whereas hangover occurs after a single alcohol administration and in non-habitual alcohol consumers (41).

Also data in relation to the central nervous system activity presents hangover and alcohol withdrawal as two different phenomena. The electroencephalographic rhythm slows down during hangover and there is a decrease in auditory threshold sensitivity during auditory evoked potentials (42,43). There is a decrease in cerebral activity during hangover, whereas hyperexcitability of the central nervous system takes place during alcohol withdrawal (41).

The role of acetaldehyde

Alcohol is metabolised in two different chemical reactions. Alcohol is transformed into acetaldehyde by alcohol dehydrogenase enzyme, after which aldehyde dehydrogenase metabolises acetaldehyde. Acetaldehyde produces aversive effects (flush syndrome), such as facial blushing, sweatiness, tachycardia, nausea and vomiting at high concentrations of alcohol consumption (33). Some studies have suggested that acetaldehyde could be involved in hangover because some symptoms of hangover, such as nausea, sweatiness and tachycardia, and the adverse state induced by an excess of acetaldehyde are similar (33,39). This linkage of acetaldehyde to hangover should be considered with care, because in these studies it was necessary to obtain an excess of acetaldehyde to show the flush syndrome, in amounts that are not common after acute alcohol consumption, basically in the Caucasian population (44,45). Acetaldehyde is not present in the blood system, nor is accumulated in the organism during hangover, even though an excess of acetaldehyde seems to contribute to the physiological autonomous symptoms of hangover (46).

Cerebral metabolisation of alcohol is possible (45), and that is why the possible central nervous system effects of acetaldehyde should be considered carefully. There are genetic polymorphisms, which are associated with aldehyde dehydrogenase enzyme. After alcohol intake, a dysfunctional allelic variant of aldehyde dehydrogenase can cause accumulation of high levels of plasma acetaldehyde (44,45). It has been shown that abstainers and infrequent drinkers are more frequent in some Oriental populations (47). Greater vulnerability to hangover is seen in Oriental subjects, and it is possible that high levels of acetaldehyde are associated with the origin of hangover (48). Thus, it is possible that the protective factor against alcoholism seen with an inactive variant of aldehyde dehydrogenase may be related to the adverse experience of hangover.

Hangover as a direct effect of alcohol

Many symptoms of hangover could be explained by different alcohol effects of physiologic systems (33,39). All the alcohol-induced effects are observed after the intake of high doses of alcohol, even though these effects show inter- and intra-individual variability and are modulated by several factors, like individual physiology and nutrition. The main alcohol effects, related to hangover are electrolytic imbalance, hypoglycaemia, gastric irritation, vasodilatation, cytoquine production and sleep alterations. These effects could explain dizziness, vomiting and diarrhoea which are some of the symptoms reported during hangover, and they may be related to some alcohol-induced effects, like electrolytic imbalance or gastric irritation. In the state of electrolytic imbalance, alcohol induces a transient diuretic effect after acute alcohol administration, and as the alcohol concentration disappears, dehydration persists and increases the amount of antidiuretic hormone in the plasma (49) causing the retention of liquids during hangover. An increase in the serum

levels of aldosterone and renin has been observed during hangover, but only the levels of the antidiuretic hormone correlate with hangover severity. In gastric irritation, these effects occur only at high ethanol concentrations, and are mostly affected by the type of alcohol consumed (50).

The vasodilatation effects of alcohol, increases in serotonin, histamine and prostaglandine levels (51), production of cytoquine or a profound deficit in ionised magnesium (52) may lead to headache associated with hangover. The increase in cytoquine production induced by alcohol is due to an increase in tromboxan B2 levels and it explains headache, but also some other symptoms like tiredness, nausea and diarrhoea (53). During hangover there is an increase in different cytoquine levels, such as interleukin-10, interleukin-12, and interferon-gamma (54). A relationship has been shown between cytoquine and memory impairments (55,56). High cytoquine levels are positively related to the scores in a subjective hangover scale (57). Alcohol intake also causes sleep alterations, and high alcohol consumption causes hypnosis and decreases the latency of onset sleep (58). The effects on sleep mean a shorter duration and poor quality of sleep, and may explain the tiredness and cognitive impairment during hangover (56).

Alcohol-induced hypoglycaemia is related to hangover. The intake of high amounts of alcohol causes a decrease in the hepatic gluconeogenesis that seldom induces hypoglycaemia if glycogen stores are normal (59). When glycogen stores run out as in the case of chronic alcoholics, subjects on a low-carbonate diet or in fasting people missing a meal while drinking, alcohol consumption leads to a hypoglycaemic state (59). Alcohol can also induce a reactive hypoglycaemia (60). After a carbohydrate-rich meal combined with alcohol, the insulin response to rising blood glucose levels can increase and lead to hypoglycaemia 2-3 hours after a meal (60). The decrease in glucose affects cerebral functioning, leading to weakness, tiredness and changes in mood observed during hangover. Alcohol is often mixed with low-calorie soft-drinks or meals, and hypoglycaemia induced by alcohol is dependent on the nature of carbohydrates and the individual characteristics of the subject (61).

Hangover as a consequence of the congener effects of alcoholic beverages

The symptoms of hangover are largely caused by the toxic effect induced by several products that are present in alcohol beverages known as congeners (62). Methanol, histamine, amines, amides, acetones and polyphenols are the most common congeners of alcoholic beverages. They are produced during alcoholic fermentation or added during the alcohol production, and contribute to the organoleptic properties of alcohol beverages. It has been shown that alcoholic beverages, such as red wine, whisky, tequila and cognac, which contain high amounts of congeners, increase the frequency and intensity of hangover, whereas rum, gin and vodka do not contain as many of those additives (63). It has been observed that 33% of subjects who consumed 1.5g/kg of bourbon whisky, experienced hangover, compared to only 3% of subjects consuming the same amount of vodka (64). A previous study agrees with these findings, reporting that the severity of hangover is greater with beverages containing larger amounts of alcohol (65).

It is proposed that hangover is produced by formaldehyde and formic acid. Both are metabolites of methanol and more toxic than acetaldehyde (66). The metabolism of methanol correlates with the imitation of hangover symptoms (67). Alcoholic beverages that have higher levels of methanol induce more hangovers. The administration of lower doses of ethanol, which competes for the metabolic enzymes of methanol, thus slows the metabolism of methanol, and it can be used as treatment for hangover (62). It has been found that changes in methanol concentration correlate well with changes in the score on a subjective scale of hangover symptoms (68). There are also results in opposition to the methanol theory. Methanol has a short average life, as it has disappeared from the organs when the symptoms of hangover begin. Some alcoholic beverages (wine and certain liquors) generate low levels of methanol, which is why their pharmacological effects are

almost non-existent (69). The other congeners, such as ethyl formate, ethylic acetate and isopentanol, may also have an effect on the symptoms of hangover (65).

2.2 ATHEROSCLEROSIS

2.2.1 Pathogenesis

Atherosclerosis is a generalised chronic disease which can be manifested as cerebrovascular diseases (strokes), CHD, or peripheral vascular disease. There are two on-going processes in the blood vessels in atherosclerosis, a degenerative and regenerative one, which at first affect the intima (the innermost layer of the artery) and later the media (the middle layer of the artery) at the bifurcations of the major arteries. Atherosclerotic lesions contain the following different components: cholesterol (cholesterol esters); cells, which are basically smooth muscles cells, macrophages and other different cell types; and connective tissue which consists of collagen, elastin and glycosaminoglycans (70,71). Table 1 shows the progression of atherosclerotic lesions.

Table 1. The progression of human atherosclerotic lesions (Modified version from Stary et al., 1994)(73)

Nomenclature and main histology in atherosclerotic lesions
Type I initial lesion isolated macrophages, foam cells
Type II fatty streak lesion mainly intracellular, lipid accumulation
Type III intermediate lesion Type II changes and small extracellular lipid pools
Type IV atheroma lesion Type II changes and core of extracellular lipid
Type V fibroatheroma lesion lipid core and fibrotic layer, or multiple lipid cores and fibrotic layers, or mainly calcific or fibrotic
Type VI complicated lesion surface defect, haematoma-haemorrhage, thrombus

There are different theories involved in the early atherosclerosis: the lipid theory, the hemodynamic theory, the fibrin incrustration theory, the nonspecific mesenchymal hypothesis and the response to injury hypothesis (72). According to the lipid theory, the early lesions in the atherosclerosis process are fatty streak lesions. These lesions are characterised by the accumulation of intracellular cholesterol esters within the macrophages-foam cells (73). The accumulation of low-density lipoprotein (LDL) cholesterol in the intima layer may be the result of the increased plasma LDL concentrations (74), alteration of the permeability of the arterial intima to LDL-cholesterol (75), increased retention of LDL-cholesterol in the intima (76) and impeded transport of LDL-cholesterol from intima to the media layer (74).

Based on the hemodynamic theory, hydrostatic and shear forces are responsible for the development of the lesions. Hypertension predisposes to the development of atheroma and the lesions have a predilection for the branching sites of the arterial system where turbulent or relatively stagnant flow with oscillating or low shear stress is usually detected. Altered haemodynamics (low and oscillating shear stress) may delay the clearance of blood and its components, allowing prolonged contact of potentially toxic substances with the intima layer, which could in turn potentiate endothelial injury. In addition, altered haemodynamics may modify the endothelial permeability to LDL-cholesterol, facilitating its transport to the intima (77,78).

According to the fibrin incrustation theory, fibrinogen is converted into fibrin on the luminal surface of the arteries and a thrombus is formed, which in turn becomes organised and tissue-like. The layered appearance of the atheroma is explainable on the basis of smooth muscle hyperplasia and connective tissue deposition (72).

The degenerative part in atherosclerosis is the accumulation of cholesterol whereas the regenerative part is the proliferation of smooth muscle cells and the subsequent connective tissue production by these cells. The main components of this tissue in these settings are proteoglycans, which have been considered to be the trapping agents of the infiltrating LDL-cholesterol and collagen (79). Different physical (shear stress) or chemical (vasoactive agents) stimuli to the arterial wall induce a migration of smooth muscle cells (mesenchymal cells) from the media to intima, which subsequently proliferate and produce connective tissue (80). The sequence of events described in this theory resembles the healing process.

Based on the response to injury in calcified arteries hypothesis, different physical and chemical stimuli to the arterial wall induce endothelial revealing with subsequent platelet adherence to the uncovered area. Platelets release a growth factor which in turn induces the migration of the smooth muscle cells from the media to the intima. These cells proliferate and produce connective tissue.

2.2.2 Risk factors

The well-documented risk factors for atherosclerosis are age, sex, lipid abnormalities, smoking, hypertension, diabetes mellitus, physical inactivity, alcohol consumption, obesity and haemostatic factors (72). The prevalence of atherosclerosis increases with age. Men are more prone to atherosclerosis than women; this is explicable by the protective role of the female hormones. Because of the protective role of female hormones, atherosclerotic changes in blood vessels appear later for women. High levels of LDL-cholesterol predispose to atherosclerosis while high levels of high-density lipoprotein (HDL) cholesterol have a protective role. The association between smoking and CHD is well established but the mechanism is not clear. It has been suggested that smoking causes reduction of HDL-cholesterol levels and fibrinogenaemia. Hypertension produces a continuous trauma to the endothelium and predisposes to early-stage atherogenesis. In advanced atherosclerosis, it might contribute to plaque growth. Hypertension is associated with a 2- to 3-fold increase in the incidence of strokes and myocardial infarctions as compared to normotension. Myocardial infarctions constitute the major cause of death in diabetics. In diabetics, the coexistence of hyperlipidaemia, hypertension and smoking might contribute to atherogenesis and its complications (81). Physical activity exerts a beneficial influence on the risk factors for atherosclerosis by decreasing blood pressure, weight, and pulse rate by increasing HDL-cholesterol levels and lowering LDL-cholesterol levels, decreasing platelet aggregability, increasing insulin sensitivity and improving glucose tolerance (82). Heavy alcohol intake increases the mortality from cardiovascular events, whereas moderate intake appears to exert a protective effect against CHD as compared to total abstinence (83-85). The moderate alcohol benefit is due to an increase of the HDL-cholesterol levels (86,87). The presence of many confounding determinants complicates the relationship between obesity and cardiovascular events. Smoking tends to be associated with a reduced body weight, whereas hypertension, lipid abnormalities and

insulin resistance are associated with increased weight (88). Many haemostatic factors, like fibrinogen, von Willebrand factor and factor VII have been associated with an increased risk for cardiovascular events. Other important factors are increased platelet count and platelet aggregability.

2.3 STROKE

2.3.1 Definition of stroke and stroke subtypes

The World Health Organization (WHO) defines stroke as "rapidly developing signs of focal or global disturbance of cerebral function, that is lasting longer than 24 hours (unless interrupted by death) with no apparent non-vascular cause" (89).

Stroke can be subdivided into two different types: ischaemic (occlusion of a blood vessel) and haemorrhagic (rupture of a blood vessel). There are two different types of ischaemic stroke: thrombotic stroke and embolic stroke. These types account for approximately 80-85% of strokes (89,90). Intracerebral haemorrhage is the second most common subtype of stroke after ischaemic stroke, accounting for approximately 10% to 20% of all strokes (91).

Thrombotic strokes are the most common type and occur when a blood clot (thrombus) blocks the blood flow to parts of the brain. A thrombus may form in an artery that is affected by atherosclerosis. Thrombotic strokes generally happen at night or early in the morning. TIA may happen before athrombotic stroke. Thrombotic stroke is subdivided into lacunar and non-lacunar strokes. Lacunar infarcts are small infarcts with a diameter of 20 mm and they occur in the deep cerebral white matter, in basal ganglia, or in pons (92). Lacunar infarcts are presumed to result from the occlusion of a single small perforating artery supplying the subcortical areas of the brain (92). Embolic strokes happen when a piece of a clot (embolus) breaks loose and is carried by the bloodstream to the brain, where the larger arteries branch off into smaller vessels. The blood clot reaches a point where it can travel no further but plugs a small cerebral artery and cuts off the blood supply to the brain. Most emboli are caused by atrial fibrillation (AF), where the two small upper chambers of the heart quiver causing the blood to pool and form clots (93).

The rupture in a blood vessel within the brain parenchyma leads to intracerebral haemorrhage. Intracerebral haemorrhage can happen as a complication of a pre-existing lesion, such as a vascular malformation or tumour, which is called secondary intracerebral haemorrhage. Intracerebral haemorrhage in the absence of a single clear underlying lesion is called primary intracerebral haemorrhage and it is the most common type of intracerebral haemorrhage. Intracerebral haemorrhage can be sub-typed according to location into deep or lobar intracerebral haemorrhage (94). Deep intracerebral haemorrhage is related to hypertensive vasculopathy while lobar intracerebral haemorrhage is thought to be caused primarily by cerebral amyloid angiopathy. Intracerebral haemorrhage types can be divided based on whether or not the haemorrhage is related to warfarin use (95,96).

2.3.2 Risk factors

Risk factors for stroke can be divided into modifiable and nonmodifiable risk factors. Modifiable risk factors result from lifestyle and the environment, which can be modified with healthcare and treatment. Unmodifiable risk factors are related to hereditary or natural processes and cannot be modified. Unmodifiable risk factors serve as markers for high stroke risk (97) whereas modifiable risk factors are treatable, at least partly, by medical intervention. The INTERSTROKE study showed that roughly 90% of strokes could be explained by 10 risk factors: 1) hypertension, 2) diabetes, 3) cardiac causes, 4) current smoking, 5) abdominal obesity, 6) hyperlipidaemia, 7) physical inactivity, 8) alcohol consumption, 9) psychosocial stress and depression and 10) diet (98).

Hypertension

Hypertension has proved to be associated with an increased risk of all ischaemic stroke subtypes. It is the most important modifiable risk factor for ischaemic stroke (99). Around 25% of the adult population and about 50% of the population aged ≥65 years suffer from arterial hypertension (100). Within this group 60% of all stroke patients have a past medical history of arterial hypertension (101). In the INTERSTROKE study, hypertension accounted for 50% of the risk of stroke (98).

The influence of traditional and nontraditional risk factors on the incidence of ischaemic stroke patients with hypertension varies according to the subtype. Among hypertensive persons the risk factors for lacunar stroke include diabetes, smoking, hypertension, and physical inactivity (102). Elevated stroke risk has been connected with all stages of hypertension and isolated hypertension (103). The risk of stroke seems to have a continuous association with blood pressure down to levels as low as 115/75 mmHg (103). The national guidelines have redefined categories of hypertension so that normal SBP is <120 mmHg and normal diastolic blood pressure (DBP) is <80 mmHg (104). Variation from one blood pressure measurement to another is associated with greater risk of stroke (105).

Arterial hypertension is associated with damage in many target organs and it promotes atherosclerotic macroangiopathy ensuing stroke, peripheral vascular disease and myocardial infarction. It also advances atherosclerotic microangiopathy leading to stroke, vascular dementia, hypertensive retinopathy and nephropathy. It also promotes the pathogenesis of intracerebral haemorrhage and heart failure (93). Both case-control and cohort studies have shown that hypertension is the single most important risk factor for intracerebral haemorrhage (98,106).

The majority of the intracerebral haemorrhages associated with hypertension may occur deep in the brain parenchyma, but also associations with lobar subtype have been found (107). A previous meta-analysis reported that hypertensives had an almost 3.5-fold risk of intracerebral haemorrhage compared with normotensives (106). Another meta-analysis revealed that self-reported hypertension or a measured blood pressure of >160/90 mmHg increased the risk of intracerebral haemorrhage more than 9-fold (98). The increased risk of intracerebral haemorrhage associated with blood pressure is not related only to clinical hypertension; an increase in blood pressure within normal range is also connected to a linear increase in the risk on intracerebral haemorrhage (108).

Coronary Heart Disease

Subjects with presence of CHD have a 2-fold risk of stroke compared to patients who are not suffering from CHD (109). The risk of stroke due to CHD is approximately 12%. Patients with CHD and left ventricular hypertrophy have 3 times the risk of stroke, whereas CHD patients with congestive heart failure have even 4 times the risk of stroke (109). Within 5 years of a myocardial infarction, the rate of stroke is 8.1% (110), and older patients or patients with a cardiac ejection fraction less than 28% are at higher risk of stroke. The Atherosclerosis Risk in Communities study (111) showed that a history of CHD was a risk factor for non-lacunar and cardioembolic stroke, but not lacunar stroke.

Prevalence of a past history of CHD was higher among patients with non-lacunar stroke and cardioembolic stroke than among patients without ischaemic stroke. The risk of stroke and cerebral infarction has been shown to increase gradually together with increasing numbers of carotid plaques and when adjusted for cardiovascular risk factors. The risk of stroke in subjects with severe plaques was 2.4-fold and the risk of cerebral infarction was almost tripled compared with subjects without plaques (112). It has been found that ischaemic stroke patients have significantly higher serum osteoprotegerin levels than control subjects (113). Osteoprotegerin and its ligand are cytokines that regulate osteoclastogenesis. It is possible that they have implications in CHD via vascular calcification.

Left ventricular hypertrophy

Increased left ventricular mass is a risk factor for cardiovascular diseases independently of other cardiovascular risk factors including arterial hypertension (114). Left ventricular hypertrophy (LVH) is also independently associated with the risk of ischaemic stroke (115). Among hypertensive patients, concentric and eccentric hypertrophy was associated with a 2-fold increase in stroke incidence, but concentric remodelling did not increase the risk of stroke (116). An increased risk of thromboembolic events has been associated with low left ventricular ejection fraction (LVEF) (117). It has been shown that every 5-percentage point decrease in LVEF is associated with an 18% increase in stroke risk in the first 5 years after myocardial infarction. The greatest stroke risk is associated with concentric hypertrophy. In the case of concentric remodelling the risk of stroke is only slightly increased (118).

Left ventricular wall thickness was associated with stroke after adjustment for left ventricular mass. Concentric LVH patients have more lacunar (32.7%) and fewer cryptogenic (23.1%) stroke than other stroke subtypes. Eccentric LVH was associated with cardioembolic stroke subtypes (26.5%), whereas concentric remodelling was associated with lacunar stroke (26.2%) (118). Asymptomatic left ventricular dysfunction (LVD) is present in 3-6% (119,120) of the general population and it carries a less than 4-fold increase in risk of developing congestive heart failure and a 60% increase in risk of death (121). The mechanisms of the association between LVH and ischaemic stroke are not clear, but it is possible that LVH may be a marker of subclinical disease or expose to other states involved in stroke aetiology. It is also possible that LDV promotes blood stasis in the left ventricle and left atrium, leading to an increased risk of thrombus formation and embolic stroke (122).

Atrial fibrillation

Chronic AF is a well-known risk factor for stroke (99). The prevalence of AF is approximately 6% among individuals aged >65 years. The prevalence of AF rises with age (97) and it may account for about 25% of strokes among persons aged 80 to 89 years. Advancing age also increases the risk of stroke in patients with AF for a number of reasons, as aging is associated with left atrial enlargement, reduced atrial flow and left atrial thrombus formation (123). In addition, age is a risk factor for atherosclerosis, including complex aortic arch plaque in patients with AF, which is associated with non-cardioembolic stroke in AF (124). One in every six strokes occurs in a patient with AF, and about 10% of all ischaemic strokes are caused by embolism of left atrial appendage thrombi, but a small portion are caused by coexisting intrinsic cerebrovascular diseases among elderly patients, often patients who are suffering from hypertension (125). The risk of stroke is around 20 times higher among AF patients with valvular heart disease and five times higher among AF patients with non-valvular heart disease compared to patients without AF (105). The Framingham Study (126) found that 92% of the patients presented with recently discovered AF at the time of acute stroke, and these rhythm disturbances continued in a paroxysmal or chronic manner. It is possible that in most of cases AF was the primary cardiac event rather than the consequence of stroke. Ischaemic stroke occurring with AF has been shown to be almost twice as likely to be fatal than stroke not associated with AF, and recurrence has proved to be more frequent and functional deficits more severe in survivors (126). Hypertension in patients with AF is associated with reduced atrial appendage flow velocity, spontaneous echo contrast in the left atrium and thrombus formation. A recent study reported that among men with AF, both abstainers and heavy drinkers, seemed to have the highest risk of thromboembolism or death, even the when the adjustment for well known stroke risk factors have used in analyses (127).

Diabetes

Previous meta-analysis of 102 prospective studies has shown diabetes to be a risk factor for intracerebral haemorrhage (106,128). The relative risk (RR) was 1.6 for persons with

diabetes compared to persons who did not suffer from diabetes. Diabetes is also related to a greater risk of ischaemic stroke (RR 2.26) (129), while another study reported the risk of stroke to vary from 1.5 to even 3-fold (130). In the Framingham Study the incidence of non-haemorrhagic stroke was found to be 2.5-3.5 times higher among diabetic compared to non-diabetic subjects (131). Stroke risk associated with diabetes is more common in females, and diabetes is considered a cardiovascular disease equivalent to stroke in women (132).

Most of the studies published on cerebrovascular disease with diabetes focused on patients with type-2 diabetes. Type-2 diabetes covers 75% to 90% of patients with diabetes. In patients with type-2 diabetes, the frequency of TIA has shown to be three times higher than among non-diabetic persons (133), but some studies have shown a reduced occurrence of TIA in diabetic patients (134,135). Diabetic individuals are more prone to irreversible than reversible ischaemic damage, and it is possible hyperglycaemia may induce early preprogrammed cell death (136). Patients who are suffering from diabetes have a higher mortality rate, more severe disability and slower recovery from stroke than non-diabetics persons (137,138). Almost 20-40% of patients diagnosed with acute stroke have been reported hyperglycaemic and some of them to suffer from diabetes, but 25-50% of patients have been reported early unrecognised abnormalities in glucose tolerance.

Increase in blood glucose after stroke may be a direct neurotoxic consequence or may reflect stroke severity with a subsequent systemic stress response (139). Among hyperglycaemic diabetic patients, a greater incidence of medium to large lesions has been reported (140), similarly to larger infarctions in hyperglycaemic patients without diabetes (141). Stroke recurrence has been shown to be higher among diabetic population (15.2%) than among non-diabetics (11.4%) (142). Diabetes also increases the risk of early progression of stroke due to an impairment of cerebral autoregulation (143,144). Elevated levels of insulin resistance were significantly associated with the risk of ischaemic stroke among non-diabetic subjects (145). The metabolic syndrome, glucose dysmetabolism, obesity, hypertension and dyslipidaemia have been linked to greater risk of first and recurrent stroke (146,147).

Cigarette smoking

Smoking is associated with reduced blood vessel distensibility and compliance, elevated fibrinogen levels, increased platelet aggregation, decreased HDL-cholesterol levels and higher haematocrite levels (97). Around 18% of strokes are attributable to active cigarette smoking, but it has been shown that even 25% of all strokes are a direct consequence on cigarette smoking, which independently increases the RR of stroke around 3-fold (92). The risk is increased, dose-dependent and consistent for all pathological subtypes of stroke. The RR for lacunar stroke was twice as great as for non-lacunar stroke in smokers with diabetes (148). Impaired endogenous fibrinolysis and reduced blood flow in the brain attributable to vasoconstriction by smoking are also associated with lacunar stroke development (9). Stroke risk among former smokers has shown to decrease in the course on time after cessation. Smoking cessation lowered the RR to that of non-smokers. The reduction in risk was significant by 2-years following cessation and reached the level of a non-smoker at 5-years following cessation (149). It is remarkable that even passive cigarette smoking toughens progression of atherosclerosis and there is a greater risk of ishaemic stroke (RR 4.8) among cigarette-smoking women with a cigarette-smoking spouse versus those with a non-smoking spouse. Smoking modifies the influence of oral contraceptives on stroke risk, as there is a 7-fold rise in risk among persons who both smoke and use oral contraceptives (150). In heavy smokers (>40 cigarettes per day) RR of stroke was 2-fold compared to that of light smokers (<10 cigarettes per day). The risk of stroke increases with the number of cigarettes smoked.

Persistent vasoconstriction may cause hypertension, and it has been shown that the RR of stroke among hypertensive smokers is five times higher compared to that of normotensive smokers, but 20 times higher compared to that of normotensive non-smokers

(151). Tobacco use has shown to be a risk factor for intracerebral haemorrhage (152,153). Studies have mainly concentrated on cigarette smoking, but findings can also be generalised to pipes and cigars (154). There is a dose-response relationship between the number of cigarettes smoked and the risk of intracerebral haemorrhage. The effect of smoking also extends to former smokers, although the risk on intracerebral haemorrhage is largest for current smokers. The RR of current smokers versus non-smokers ranges from 1.3 to 1.5 (98,106).

Body mass index

Body mass index (BMI) is a measure of obesity based on height and weight. It is not the most informative measure of obesity in relation to risk of stroke and myocardial infarction. Waist-to-hip ratio (WHR) is the ratio of the circumference of the waist to that of the hips. It measures the absolute amount of abdominal visceral fat (155), (156). It has been shown that there is a relationship between body mass, waist circumference, WHR and height and the risk of stroke, and results have shown that compared with women in the lowest quintile of WHR, those in the highest quintile had an age-adjusted increased RR of 3.1 for all strokes. This association was more obvious for ischaemic than haemorrhagic stroke. When compared to women with a waist circumference <70 cm, women with a waist circumference >90 cm had an increased risk for all strokes and ischaemic stroke, but not for haemorrhagic stroke. When adding BMI to the analyses, the statistical associations became stronger for all strokes and for ischaemic stroke, but did not change the RR for haemorrhagic strokes (156). These findings have shown abdominal obesity to be an independent predictor of stroke risk. Abdominal obesity is connected to endothelial dysfunction (an early marker of atherosclerotic disease) and haemorrheologic disorders (hyperviscocity, hyperfibronogenaemia, reduced red cell deformability and erythrocyte aggregability) (157,158). The effects of abdominal adiposity may also be mediated by increased insulin resistance, enhanced platelet activity through increasing lipid peroxidation and inflammation (159). It is remarkable that the risk of intracerebral haemorrhage is increased not only by high BMI but also by low BMI (94).

Asymptomatic Carotid Stenosis

The prevalence of asymptomatic carotid stenosis rises with age. It is estimated that over 50% of individuals aged ≥ 65 years have asymptomatic carotid stenosis. It has been found that the risk of stroke with asymptomatic carotid stenosis to be approximately 1.3% per year among patients with stenosis less or equal to 75%, and approximately 3.3 % per year among patients with stenosis grater than 75% (160). The risk of stroke associated with asymptomatic carotid stenosis has fallen significantly during the past 20 years (161,162).

Dyslipidaemia

Hypercholesterolaemia has shown to be associated with a lower risk of intracerebral haemorrhage in longitudinal studies (154,163). This is in contrast to earlier case-control studies that reported high cholesterol as a risk factor for intracerebral haemorrhage (164). The mechanism is unclear, but low cholesterol is thought to weaken the endothelial wall. In addition to cholesterol, different lipid fractions have also been investigated, and it has been reported that the associations with lipids are mainly driven by low triglyceride levels (165). Abnormalities in several serum lipid indices have been linked to symptomatic vascular disease. These associations are robust with relation to CHD, but conflicting in regard to stroke (97). Recent studies have shown an association of elevated serum triglycerides, total cholesterol, LDL-cholesterol, and non-HDL-cholesterol with ischaemic stroke risk, especially atherosclerosis and lacunar stroke subtypes. A previous study showed high total cholesterol to be related to high ischaemic stroke risk, with the most robust subtype associations seen with atherosclerotic stroke and lacunar stroke (166). Elevated HDL-cholesterol was shown to be protective for stroke (97).

Lipoprotein a

Lipoprotein a (Lp a) is a LDL-like molecule consisting of apoprotein (apo) B-100 and apo a. Apo a is a member of a family which contains among others the following proteins: plasminogen, tissue platelet activator (tPA), prothrombin, factor XII and macrophage stimulating factor (167). Apo a has structural homology with plasminogen, and it may have a thrombogenic effect by modification, leading to intracellular cholesterol accumulation and foam cell formation. Lp a binding to fibrinogen and fibrin results in the inhibition of plasminogen. Lp a competes with plasminogen for its receptors on endothelial cells, leading to diminished plasmin formation, delaying clot lysis and favouring thrombosis (168). Lp a can also displace plasminogen from the surfaces of macrophages in atherosclerostic plaques, reducing the activation of latent transforming growth factor β (TGF-β). In the absence of TGF-β cytokines might induce smooth muscle cell proliferation and the transformation of these cells to a more atherogenic phenotype (169). Elevated serum concentrations of Lp a have correlated strongly with increased risk of premature cardiovascular disease (170), and these findings have been confirmed among ischaemic stroke patients (171), hypercholesterolaemic male subjects with early signs of atherosclerosis (172), heterozygous family history patients and individuals with asymptomatic carotid atherosclerosis (173). Lp a is an independent risk factor for ischaemic stroke subtypes in white people (174,175), Japanese (176,177) and Chinese (178) populations. Elevated serum Lp a levels and apo E4 genotype have shown to be prominent lipid predictors for ischaemic stroke (179). A previous study reported a positive association between silent multiple lacunar strokes among asymptomatic, high-risk, Japanese patients (44-93 years) and a hypercoagulable state, endothelial damage and significantly raised Lp a concentrations (180). Lp a, homocysteine and fibrinogen are suggested to interact together, promoting atherosclerosis and increasing the risk of vascular events (181).

Inflammatory markers

Inflammation is a part of pathogenesis of atherosclerosis and ischaemic stroke, and inflammatory markers may aid in identifying the persons at risk. Elevated leukocyte count has been associated with cardiovascular and cerebrovascular diseases. White blood cell-derived macrophages and other phagocytes may be involved in vascular injury and atherosclerotic progression (182,183). Associations between white blood cell count and incidence of CHD and stroke, and mortality from CVD have been shown among African Americans (184). A previous study has reported that the incidence of ischaemic cerebrovascular disease is almost 1.5- fold higher in patients with white blood cell count in the upper tertile as leukocytes lead to ischaemic cerebrovascular disease by an effect on chronic atherosclerosis or by inducing acute thrombosis, by increasing the chances of plaque rupture (185).

C-reactive protein (CRP) is an acute phase plasma protein produced by the liver. The levels of CRP rise during inflammatory processes in response to the endothelial cells and T-cells. CRP may assist in complement binding to foreign and damaged cells and it enhances phagocytosis by macrophages, which express a receptor for CRP. It is also believed to be a part of innate immunity. CRP predicts the progression of disease and adverse events in coronary, cerebrovascular and peripheral circulation in healthy subjects, and in patients with atherosclerosis CRP has been shown to exacerbate ischaemic necrosis in a complement-dependent way (186,187). One study reported significantly higher levels of CRP in patients with cardioembolic stroke (5.44 mg/l) than in patients with atherothrombotic large vessel disease (3.36 mg/l) and lacunar stroke (2.64 mg/l) (188). CRP levels have been shown to be significantly higher for all ischaemic stroke subtypes compared with control subjects in the acute phase and at 3-month follow-up. Analysis by aetiological subtype according to the Trial of Org 10.172 in Acute Stroke treatment criteria showed associations for all subtypes during the acute phase. A previous follow-up showed

that there was a strong association between CRP and large vessel disease, but not for small vessel disease, cardioembolic stroke and cryptogenic stroke (189).

von Willebrand factor

von Willebrand factor (vWF) is a plasma glycoprotein. It is a mediator of platelet adhesion during endothelium insult. vWF is released as multimers, resulting in platelet aggregation and formation of thrombus (190). The activity and concentration of vWF is influenced among others by blood group, inflammation, and proteolysis by disintegrin and metalloprotease with thrombospondin. Previous studies have shown that elevated levels of vWF antigen are a risk factor for arterial thrombosis (191,192). There are conflicting results available on vWF and cerebrovascular disease (192,193). It has been assessed by sequential measurements of a number of endothelial markers and adhesion markers in the acute and subacute phases of 52 patients with ischaemic stroke subtypes (194). Plasma vWF levels were significantly higher in stroke patients than in control subjects. During the subacute phase, plasma vWF activities were significantly higher than those in controls. Analysis of vWF plasma levels within different stroke subtypes showed that vWF activities were significantly higher in the acute phase of atherothrombotic, lacunar, and embolic infarction than in controls. During the acute and subacute phases of ischaemic stroke subtypes, an increase in vWF indicates that endothelial cell activation and/ or injury may happen during the acute phase and continue until the subacute phase (194).

Fibrinogen

Fibrinogen is a glycoprotein hexamer containing two sets of three different chains (α, β, γ). Fibrinogen is synthesised by liver hepatocytes and megakaryocytes. In its natural form, fibrinogen forms bridges between platelets and it is mainly responsible for vertebrate blood clotting (195). Carriers of the A allele of the fibrinogen- 455G/A polymorphism have increased plasma fibrinogen levels. A significant association between ischaemic stroke patients with the A1 genotype and multiple lacunar infarcts was shown in a recent study (196). It is possible that increased viscosity and higher quantity of substrate resulting from elevated plasma fibrinogen concentration may promote coagulation and formation of for small-vessel thrombotic occlusion, thus affecting the phenotype of the cerebral infarction (196). This points to a non-thrombotic mechanism underlying the occlusion of small vessels.

Factor VIII

Factor VIII is a clotting factor. The lack of normal factor VIII causes haemophilia A, which is an inherited bleeding disorder. In one population-based case-controlled study (197) a 5-fold increased risk of venous thrombosis associated with a dose-dependent activity above 150 IU/ dl was noted compared with levels below 100 IU/ dl (197). An elevated level of factor VIII may represent a prothrombotic tendency. Some studies support an association between elevated factor VIII activity and increased risk of stroke (192,198). Elevated factor VIII levels are associated with stroke caused by large vessel disease (199), but not with carotid intima media thickness (IMT) (192). Factor VIII may have a direct effect on the occurrence of thrombotic events at sites of arterial wall damage (200). Factor VIII shows familial clustering, but there is no evidence on molecular basis of elevated levels within the factor VIII gene (201).

Oxidative stress

In oxidative stress, there is an imbalance between free-radical production and the ability of the organism to neutralise the effects of free-radicals. Oxidative stress is involved in aging and in the pathogenesis of stroke, atherosclerosis, cancer, and Alzheimer's disease (202). The brain is prone to free-radical damage because it is rich in polyunsaturated fatty acids, which are vulnerable to free-radical-induced peroxidation, and because it contains a large amount of iron, which stimulates free-radical generation (203).

Medication

The use on anticoagulants is considered a risk factor for intracerebral haemorrhage (95). Warfarin is an anticoagulant which is used to prevent cardioembolism resulting from AF. The increased risk of intracerebral haemorrhage related with anticoagulants, and especially with warfarin (204,205), is also seen with other coumarin derivatives (205). The use of aspirin may also increase the risk of intracerebral haemorrhage (206). A recent study reported no association between aspirin medication and a risk of intracerebral haemorrhage, but low-dose aspirin treatment has reported to be protective on the risk of subarachnoid haemorrhage (204). It is reported that the use of anticoagulants has shown better results in the prevention of cardioembolic stroke, but this is not the case in relation to lacunar recurrence (207). Regardless of the risk of intracerebral haemorrhage, the benefits of warfarin and aspirin outweigh the potential risks associated with their use. A recent meta-analysis showed that there was a RR reduction of 62% in both ischaemic and haemorrhagic stroke when adjusted dose of warfarin was compared with placebo, and warfarin has also has proved to be more effective than aspirin (125). An increased risk of intracerebral haemorrhage is associated with direct thrombin inhibitors (208).

Genetic factors

Many single-gene disorders leading to intracerebral haemorrhage have been found in family studies, such as familial cerebral amyloid angiopathy and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (209). Cerebral amyloid angiopathy refers to the accumulation of β-amyloid in the media and adventitia of mostly cortical blood vessels, which can lead to leakage of blood through the blood vessel wall (210). These intracerebral haemorrhage changes due to cerebral amyloid angiopathy occur in the cortical brain regions, referred to as lobar intracerebral haemorrhage. The frequency of cerebral amyloid angiopathy increases with age. Almost 50% of all persons older than 90 years have signs of cerebral amyloid angopathy. Nearly 50% of intracerebral haemorrhages in the lobar region are related to amyloid angiopathy (211). In the case of familial cerebral amyloid angiopathy, there are mutations in the APP gene, and in the case of CADASIL, there are mutations in the NOTCH3 (neurogenic locus notch homolog protein 3) gene (209). The apo E gene has shown to be strong genetic risk factor for intracerebral haemorrhage. It is considered a strong risk factor for cerebral amyloid angiopathy, and is thought through this aetiology to be related with intracerebral haemorrhage (210). However, apo E has also been shown to influence blood vessels through other mechanisms. Many other candidate genes have been implicated, such as ACE (angiotensin converting enzyme), ApoH (apoliprotein H), factor VII, factor XIII, interleukin- 6 (209), and erythrocyte complement receptor 1 (212).

Physical activity and cardiorespiratory fitness

Physical activity (both leisure-time and occupational physical activity) is connected with lower stroke risk whereas sedentary behaviour is related to higher stroke risk. Increased regular physical activity is associated with reductions in fibrinogen, homocysteine, and platelet activity and elevations in HDL-cholesterol and plasma tissue plasminogen activator activity (97), and these changes can explain the beneficial effects of physical activity on lowered risk of stroke. A recent meta-analysis reported that a high level of leisure-time physical activity has beneficial effects on cardiovascular health by reducing the overall risk of stroke and CHD by 20% to 30% (213). It has also been shown in earlier studies that high level of leisure-time physical activity (vigorous physical activity >3 hours per week) is associated with a reduced risk of total stroke and different subtypes of stroke (ischaemic stroke, subarachnoid haemorrhagic and intracerebral haemorrhagic) (214,215). Moderate level of leisure-time physical activity has been shown to be associated with a reduced risk of ischaemic stroke as well as intracerebral haemorrhage, and daily commuting physical

activity has been linked to a reduced risk of ischaemic stroke (214). The Northern Manhattan Study showed that moderate-to-heavy intensity physical activity was associated with a reduced risk of ischaemic stroke, the reduction being as high as 35% (216). Physical activity may be protective against intracerebral haemorrhage, but some studies have not shown crucial evidence for that (98,217). A meta-analysis of 23 studies that examined the relationship of physical activity with risk of stroke noted that highly active subjects experienced a 27% lower risk of stroke incidence or mortality versus low-active subjects (215). It has been shown that moderate level of occupational physical activity may reduce CVD by 10% to 20 % (213), and active occupational activity was also associated with a lower risk of total and ischaemic stroke, but only when both women and men were combined in the study (214). A recent study reported that self-reported low physical activity is shown to be associated with increased risk of incident stroke and regular physical activity is associated with a decreased risk of TIA and incident stroke (≥4 times per week) (218).

Cardiorespiratory fitness can be measured directly by using maximum oxygen capacity measurement during exercise testing, and it provides a quantitative measure of physical activity. It has been shown that low cardiorespiratory fitness is associated with an increased risk for stroke, and maximum oxygen capacity has been shown to be a strong predictor of stroke (219).

Renal disease

Poor kidney function has proved to be a risk factor for stroke, including intracerebral haemorrhage (220), and in addition to patients with kidney disease, the risk also exists in the general population, but not all studies have found associations between kidney disease markers and intracerebral haemorrhage (221). Reduced glomerular filtration rate was associated with a 40% increased risk of stroke (221). Microalbuminuria has shown to be associated with a two-fold risk of stroke (221).

Depression

It has been reported that depression and psychosocial stress are important risk factors for stroke, but the mechanism for this association is not clear (98). The use of some antidepressants, such as tricyclic antidepressants and selective serotonin reuptake inhibitors, has been shown to be associated with increased risk of stroke (222). The use of antidepressant was associated with a doubled risk of haemorrhagic and fatal stroke.

Diet

Dietary factors have been implicated in intracerebral haemorrhage, although it is still unclear which dieatary constituents drive the association (152,206). Low plasma levels of vitamin A, C, E, and carotenoids have been shown among stroke patients compared with healthy controls (223,224). It has also been reported among hypertensive and overweight men that low plasma levels of vitamin C increase the risk for any stroke (225). A protective effect of natural and synthetic antioxidants has been demonstrated in animal models of stroke. After permanent ischaemia or ischaemia followed by reperfusion in rats and in primates, dietary supplements of vitamin C and E have been shown to reduce infarct size and neurological impairment (226,227).

Age

Age is one of the most significant risk factor for stroke. About 95% of strokes occur in people who are 45-years or older. Two-thirds of strokes occur among those who are older than 65 years. It is remarkable that stoke can occur at any age, even in foetal stages (228). Stroke mortality risk also increases with age. It has been shown that cardioembolic stroke, simultaneous aetiologies and microangiopathy were all associated with the highest mean age.

Cardioembolic stroke is the most common cause among those over 70 years and macroangiopathy among those aged 45-70 years, while combined different aetiologies have been reported among those who are younger than 45 years (185). It is thought that cardioembolic stroke due to an increase of AF parallel to aging (229,230). In the Northern Manhattan Stroke Study 55% of ischaemic strokes were cryptogenic among population aged 20-44 years. The proportion of lacunar strokes was 18%, intracranial atherosclerosis 9%, cardioembolic strokes 6% and extracranial atherosclerosis 6%. Cardioembolic strokes were much more common in the group ≥45 years and a decrease in incidence was seen in cryptogenic strokes (231). In the study of patients aged 15-45 years, undetermined aetiology of stroke was the reason in 23% of the cases, whereas small vessel disease was the cause in 20% of cases, large artery atherosclerosis in 7%, cardioembolic stroke in 18% and other determined aetiology in 22% of the cases (232). Stroke aetiology has been more variable among young cohorts.

Sex

Men have a greater risk of stroke than women, and this is especially true of middle-aged to old men. Among the very elderly or young men this excess risk does not exist. Men have an almost 19% greater chance of a stroke than women, and among men who are under 65 years the risk is even greater compared with equivalent risk for women (233). The overall stroke mortality rate is higher among men than women, but little is known about sex differences in mortality rates from different stroke subtypes. In a large study of 633,229 stroke patients in the United States, the risk of ischaemic stroke death was higher for white women than for white men. Among other ethnic groups of women the risk was lower than or similar to that of men. There is variation in ratio of men to women mortality rates according to age for all stroke subtypes. Among women there was a lower risk of ischaemic stroke than men at ages <65 years. In the age group >65 years, women had a higher risk than men (234). It has been shown that sex distribution differs significantly between different aetiologic subtypes of stroke (185). The highest proportion in men was in the macroangiopathic stroke group, being 66.2%, and correspondingly, the lowest proportion was in the cardioembolic stroke, being 49.9%. In the Atherosclerosis Risk in Communities study (111) the RR for all ischaemic stroke subtypes among men was higher than among women.

Race

The incidence of stroke and stroke mortality varies between ethnic groups, and this may be due to genetic or non-genetic differences. Stroke is more common among black than among white people. It has been shown that white people had a significantly greater proportion of cardioembolic stroke than Hispanics or black people even though the incidence of cardioembolic stroke was lowest in white people, whereas among Hispanics and black people, there was a significantly greater proportion of intracranial atherosclerotic stroke than among white people and also the incidence rate was higher among them. There were no significant differences between different ethnic groups according to lacunar, extracranial atherosclerotic and cryptogenic stroke, but the proportion of lacunar stroke was slightly higher among Hispanics (22%), and black people (21%) compared to white people (16%) (235). The high incidence of non-lacunar and cardioembolic strokes among black people may be explained by the high prevalence of smoking, hypertension and diabetes (111). The increased risk of lacunar strokes among black people remained significant after further adjusting for traditional and non-traditional factors (111).

2.3.3 Stroke mortality

Stroke is the second most common cause of death in the world (1). According to the WHO, it accounts for 9 million first-ever strokes every year and 30.7 millions stroke survivors were recorded in 2004 (236). About a quarter of the patients with incident stroke will die

within a month, about a third of them by 6 months, and half of them by one year (237). Stroke prognosis is even worse for those with intracerebral or subarachnoid haemorrhage, the 1-month mortality for them being about 50%. It has been reported that stroke causes 8.9% of all deaths in Finland (3). During the years 1983-1997, there was a continuous decrease in the incidence and mortality of stroke in Finland (6). One reason for the decline is the fact that cardiovascular risk factor levels have clearly improved in Finland (7,8).

A major cause of early mortality is neurological deterioration with contributions from other causes, such as infections secondary disease to aspiration. Later, deaths are caused by cardiac disease or different complications consequent on stroke (237). The best predictors of stroke recovery at 3 months are the initial neurological deficit, age, high blood glucose, body temperature and previous stroke (238). After TIA or minor stroke, the risk of further stroke is higher than was earlier expected, reaching even 30% within the first months in some subgroups (239). Death after stroke is significantly associated with old age, male sex, stroke severity and stroke type and history of previous stroke (240). The association with haemorrhagic stroke is related to the high mortality in patients with haemorrhagic stroke, being 3-4 times greater than that of patients with ischaemic stroke within the first weeks after stroke. After 2-3 months, the mortality rates of patients with haemorrhagic and ischaemic strokes are equal (153). It has been reported recently in the United Kingdom that over 33% of individuals die in the first month after haemorrhagic stroke and the cause of death is more likely intracerebral haemorrhage than subarachnoid haemorrhage (241). In Japanese study stroke mortality within 30 days after the onset has been reported to be the highest in subarachnoid haemorrhage patients (28.4%), followed by cerebral haemorrhage (15.2%) and mortality is the lowest in cerebral infarction (5.2%) (242).

2.4 ALCOHOL CONSUMPTION AND ATHEROSCLEROSIS

Intima-media thickness (IMT) of the carotid arteries has been shown to be a marker of generalised atherosclerosis (243). Carotid IMT has been associated with atherogenic risk factor profile (244-246) and increased risk of CHD and stroke (247,248).

Previous studies show that binge drinking increases the risk of hypertension and the risk of CHD, although no effect on the risk of other cardiovascular diseases has been observed (249,250). A modest association between alcohol consumption with common carotid artery (CCA) IMT and carotid plaques has been observed in men, whereas no significant relationship in women was observed in a previous study (251). It has been shown that alcohol drinking patterns play a role in the progression of atherosclerosis (252) and men with a heavy acute style of alcohol drinking had greater progression of carotid atherosclerosis as compared to men with a more evenly distributed drinking habit (252). Another study showed that carotid atherosclerosis was less prevalent among those who drank up to 6 drinks per week, but the association was stronger when the consumption exceeded 14 drinks per week (253). These findings in carotid arteries were seen in women and men who were 65 years or older (253). Also the Bruneck Study showed that carotid IMT seemed to be highest among the heaviest drinkers (254). In their study a J- or U-shaped association was present in both early and advanced atherogenesis. A recent study reported a differential effect of daily-moderate versus weekend-binge alcohol consumption on atherosclerotic plaque development in mice and highlighted the importance of patterns of alcohol drinking (255).

On the other hand, occasional drinking (alcohol consumption more infrequently than once a week) had no effect on the incidence and progression of atherosclerosis (254). It is possible that the adverse and beneficial effects of regular alcohol consumption on arterial disease are mediated by a dose-dependent promotion or deceleration of atherogenesis (254). Another study has shown that heavy drinkers are more prone to develop carotid

atherosclerosis than abstainers, and this alcohol-related risk was observed to be more significant when atherosclerosis in carotid artery was more diffuse and severe (256).

Atherosclerotic changes associated with alcohol consumption and binge drinking pattern are not only seen in older people. The CARDIA Study found that even moderate alcohol consumption could have proatherogenic effects among young adults (257). The association was found between binge drinking and atherosclerosis of coronary arteries, which was measured by coronary artery calcification (257). Another study has also reported that alcohol consumption is associated with carotid IMT in young adults (258).

2.5 ALCOHOL CONSUMPTION, INCIDENT STROKE AND STROKE MORTALITY

Most studies have suggested a J- or U-shaped association between alcohol consumption and ischaemic stroke, with a protective effect among light or moderate drinkers and an elevated risk of stroke among those with heavy alcohol consumption (20-22,259-267). There is strong evidence that chronic alcoholism and heavy drinking are risk factors for all stroke subtypes (17,22,259,268-270). A recent study has been reported that chronic alcohol drinking (≥300 grams per week) is associated with the higher severity of the neurological deficit (271). Table 2 presents a summary of studies on the association of alcohol consumption and stroke incidence.

Light-to-moderate alcohol consumption has been linked to elevated HDL-cholesterol and endogenous tissue plasminogen activator levels. Some studies estimating the impact of alcohol consumption on ischaemic stroke risk have not reported consistent results. Most studies report a protective effect of light-to-moderate drinking (1-2 drinks per day) on the risk of ischaemic stroke including data from the Nurses' Health Study and the Northern Manhattan Stroke Study. No significant association between moderate alcohol consumption and ischaemic stroke was found in the overall population, although a protective effect of alcohol has been found among subjects aged 60-69 years (265). Only wine consumption was suggestive of a reduced risk of ischaemic stroke, whereas beer drinking or spirit consumption was not (265). A previous study has also found that a small amount of alcohol can have a beneficial effect on the risk of stroke, excluding intracerebral haemorrhage and subarachnoid haemorrhage (272). It has been shown that even though light-to-moderate drinking is not generally associated with an increased risk of ischaemic stroke, drinking pattern or beverage type can affect this relation. In that study they found that drinking more than 2 drinks per day was associated with a higher risk for ischaemic stroke (273). The association did not exist with lower alcohol consumption, and only consumption of red wine had an inverse relation with ischaemic stroke. Light alcohol drinking had no effect on the risk of subarachnoid haemorrhage, but there was a slight decrease in the risk of intracerebral haemorrhage and cerebral infarction (17). Light-to-moderate alcohol consumption has been shown to reduce the overall risk of stroke and ischaemic stroke in men. The reduced risk was observed with alcohol consumption up to one drink per day (one to seven drinks per week) (264).

Some epidemiological studies have found an increased risk of ischaemic stroke with recent moderate and heavy drinking (268,274). Heavy alcohol consumption is associated with elevated blood pressure, enhanced coagulability, cardiac arrhythmias, and decrease in cerebral blood flow (97). The risk of haemorrhagic stroke is associated with increasing alcohol consumption in a dose-dependent manner. There are many studies showing that high alcohol intake is associated with an increased risk of intracerebral haemorrhage (98,106,152). This association can be explained by platelet dysfunction, coagulation disturbances, or endothelial damage. For ischaemic stroke, moderate alcohol consumption has been reported to be protective, but the risk of intracerebral haemorrhage is increased,

suggesting a linear manner and a dose-response relationship between alcohol intake and intracerebral haemorrhage (152). A prospective study of Japanese men aged 40-69 years showed that heavy alcohol drinking (alcohol consumption ≥300 grams ethanol/week) was associated with increased risk of stroke and especially haemorrhagic stroke (275). A study showed that heavy drinking was associated with increased risk of both ischaemic and haemorrhagic strokes among women (270). Previous cohort studies reported an adverse effect of heavy alcohol consumption on the risk of haemorrhagic stroke (19,261,266,276,277) and a beneficial effect of light-to-moderate alcohol consumption on CHD (278-280). In a cohort study of Japanese men, heavy drinking (≥69 grams of ethanol/day) was associated with an elevated risk of subarachnoid haemorrhage (281). The Honolulu Heart Program has shown an association between alcohol and haemorrhagic stroke. The risk of haemorrhagic stroke was more than doubled for light drinkers and nearly tripled for heavy drinkers compared with non-drinkers. The effect of alcohol was even greater on haemorrhagic strokes than subarachnoid strokes, there being a 3- to 4-fold increased risk for moderate and heavy drinkers compared with non-drinkers (276). Among heavy alcohol drinkers (≥35 drinks/ week) the risk for stroke incidence was 22% greater than among non-drinkers (18). A J-shaped relationship between alcohol consumption and the risk of ischaemic stroke has been observed, while heavy alcohol consumption has led to an increase in the risk of stroke (21). Another study has shown the association between alcohol consumption and risk of stroke to be U-shaped. The risk was even 20% lower among those who consumed 1-6 drinks per week compared to abstainers (282). They also found that apo E genotype may modify this association, and it is possible that apo E4-positive persons may have an increased risk of ischaemic stroke even with moderate alcohol consumption (282).

It is well known that hypertension and obesity are risk factors for stroke (101). It has been shown that high alcohol consumption may lead to a dose-related increase in blood pressure (283) which is related to an increased risk of stroke, but the inter-relationship between alcohol consumption, hypertension and the risk of stroke may be complicated (284). A previous study has shown an increased risk of cerebral haemorrhage among heavy drinkers, whereas light drinking reduced the risk of cerebral infarction (285).

Some prospective studies have shown that BMI may increase the risk of stroke (286-289). It has been suggested that this association can be modified by other risk factors, and especially by hypertension (286-289). An elevated BMI was associated with an increase in the risk of ischaemic stroke in the Physician Health Study (290) whereas abdominal obesity, rather than general obesity, was associated with the risk of stroke in the Northern Manhattan Stroke Study (159).

Previous studies on the relation between alcohol consumption and stroke mortality have shown contradictory findings that may be due to the different stroke types that were defined as fatal outcome events. Table 3 presents a summary of studies on the association of alcohol consumption and stroke mortality. Moderate drinkers have been reported to have lower total mortality compared with lifetime infrequent drinkers, but higher mortality has been found among regular heavy drinkers and also among former drinkers (291). Higher cerebrovascular disease mortality was found among women who were never, former and heavy drinkers than among women who were infrequent drinkers (291). Among heavy alcohol drinkers (≥35 drinks per week) the risk for stroke mortality was 30% greater than among non-drinkers (18). Another study found a similarly higher risk for stroke mortality among heavy drinkers when alcohol consumption was at least 29 drinks per week (18). Light-to-moderate drinking (≤28 drinks per week) was associated with a reduction in death from CHD, but it had no effect on death from stroke (263). No significant increase or decrease in the risk of stroke has been reported among light-to-moderate drinkers, but there was a non-significant suggestion of a reduced risk of fatal stroke among light drinkers (monthly to 2-4 drinks per week) (292). One study also found an increase in risks of total mortality and stroke mortality when alcohol consumption was 15-21 units per week (293). Some other studies have also found an increased risk of death from stroke

among individuals who consume very high amounts of alcohol (15,293). Conversely, one study found the highest risk of death from stroke in non-drinkers with a flat relation with increasing amounts of alcohol consumed (153). The lowest crude rates for death from all causes, myocardial infarction and stroke have been reported among moderate drinkers, and it has also been found that abstainers or those who rarely drink have the highest mortality rate for stroke compared to moderate drinkers (294). A study based on fatal and non-fatal stroke outcomes found a non-significant increased risk in lifetime abstainers compared with occasional drinkers, but the risk of stroke was considerably increased among the heaviest category of drinkers (295).

It has been reported that almost one-third of older persons with one of the following chronic diseases; stroke, heart failure, Alzheimer´s disease and other causes of dementia, chronic obstructive pulmonary disease, depression and diabetes; drink alcohol (296). And almost 7% of these persons are reported to be at high risk and more than 50% of them drink in heavily in a single session (296). Different drinking patterns have seldom been taken into account although a significant association between ischaemic stroke mortality and drinking habits has been observed (21,31). Drinking habits were associated only with deaths from ischaemic stroke (21), and these findings have been seen among middle-aged and elderly men who were infrequent drinkers, reported binge-drinking on rare occasions. A previous study found that high level of alcohol consumption was related to death from cerebrovascular disease, but only among women (297).

Table 2. Summary of studies of association alcohol consumption and stroke incidence

Authors	Study population	Number of subjects and stroke cases	Men %	Women %	Age, years	Study follow-up, years	Outcome	Assessment of alcohol consumption	Findings
Donahue et al. 1986 (276)	Honolulu Heart Program	8,006 290	100	0	45-69	12	Stroke	Non-drinker, light drinker, moderate drinker, heavy drinker	The risk of haemorrhagic stroke more than doubled for light drinkers (RR 2.3; 95% CI 1.20-4.30) and almost tripled for heavy drinkers (RR 2.9; 95% CI 1.4-8.0), when compared to non-drinkers.
Woo et al. 1990 (298)	Elderly Chinese cohort	427 7	40	60	≥60	2.5	Stroke	Drinker versus teetotaller	Alcohol drinkers had an increased RR 1.9 (95% CI 0.01-11.6) but it was not statistically significant.
Iso et al. 1995 (261)	Rural Japanese cohorts	2,890 178	100	0	40-69	10.5	CHD and stroke	Never drinker, ex-drinker, current drinker	Heavy drinking was associated with increased risk of haemorrhagic stroke (HR 3.4; 95% CI 1.2-9.2). Light-to- moderate drinking was associated with protection against non-haemorrhagic stroke.
Kiyohara et al. 1995 (285)	Hisayama Study	1,621 304	43.6	56.4	≥40	26	Stroke	Non-drinker, light drinker (<34 grams/ day), heavy drinker (≥34 grams/day)	Heavy alcohol consumption is associated with increased risk of cerebral haemorrhage (RR 3.13; 95% CI 1.08-9.10), whereas light drinking reduces the risk of cerebral infarction.

Table 2 to be continued

Truelsen et al. 1998 (272)	Copenhagen City Heart Study	13,329 833	45.5	54.5	45-84	16	Stroke	Never/ hardly ever, monthly, weekly, daily	Intake of wine on a monthly (RR 0.83; 95% CI 0.69-0.98), weekly (RR 0.59; 95% CI 0.45-0.77) or daily basis (RR 0.70; 95% CI 0.46-1.00) was associated with a lower risk of stroke compared with no wine intake. With beer or spirits there was no association between intake and risk of stroke.
Leppälä et al. 1999 (17)	Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort	26,556 960	100	0	50-69	6.1	Stroke	Non-drinker, light (≤ 24 grams/day), moderate (25-60 grams/day),heavy drinking (>60 grams/ day)	The risk of subarachnoid haemorrhage increased linearly with increasing alcohol consumption, but the association between alcohol consumption and the risk of intracerebral haemorrhage was U-shaped (light drinking RR 0.83; 95% CI 0.46-1.50; moderate RR 0.64; 95% CI 0.31-1.35) and heavy drinking RR 1.77; 95% CI 0.73-4.31).
Berger et al. 1999 (264)	Physicians´ Health Study	22,071 679	100	0	40-84	12.2	Stroke	<1 drink/ week, 1 drink/ week, 2-4 drinks/ week, 5 or 6 drinks/ week, ≥1 drink/ day	Light to moderate alcohol consumption reduces the overall risk of stroke (RR 0.79; 95% CI 0.66-0.94) and of ischaemic stroke (RR 0.77; 95% CI 0.63-0.94) in men. The benefit is seen with 1 drink/ week. Greater consumption does not increase benefit.
Jousilahti et al. 2000 (299)	Finnish Cohort	14,874 470	48.4	51.6	25-64	12	Stroke	Drinks consumed per week: 1-3, 4-6 and ≥7 drinks/week	An increased risk of stroke was seen when the amount of drinks increased (RR 1.24; 95% CI 1.03-1.50) for men, RR 1.33; 95% CI 1.06-1.65) for women in multivariable model for all strokes.

Table 2 to be continued

Sankai et al. 2000 (281)	Six Japanese communities	12,372 71	40.2	59.8	40-69	9.4	Stroke	Lifetime teetotaller, former drinker, current drinker (division: <9 grams/ day and (heavy drinker) ≥69 grams/ day)	Among heavy-drinking men, there was an increased risk of subarachnoid haemorrhage (RR 4.3; 95% CI 1.1-16.8), but among women with heavy drinking, no increased risk was found.
Djousse et al.2002 (265)	Framingham Study	9,171 441	42.2	57.8	≥50	10	Stroke	Never drinker, former drinker (0.1-11 and ≥12 grams/day of ethanol), current drinker (0.1-11,12-23 and ≥24 grams/day of ethanol)	Total alcohol consumption was not significantly associated with ischaemic stroke. A protective effect of alcohol intake was seen among subjects aged 60-69 years (HR 0.3; 95% CI 0.2-0.7).
Klatsky et al. 2002 (277)	Keiser Permanente Medical Care Program Cohort	128,934 431	44	56	30-70	18	Stroke	Lifelong abstainer, ex-drinker, <1 drink/ month, >1 drinks/month, <1drink/ day, 1-2 drinks /day, 3-5 drinks/day, >6 drinks/day	Only heavy drinking is weakly related to increased risk of haemorrhagic stroke.
Mukamal et al. 2005 (273)	Cardiovascular Health Study	4,410 434	36.1	63.9	≥65	9.2	Stroke	None, former, <1 drink, 1-6 drinks, 7-13 drinks, ≥14 drinks	Alcohol consumption of 1-6 drinks per week is associated with a 20% lower risk compared to abstention. Alcohol consumption and risk of ischaemic stroke was U-shaped: RR 0.75; 95% CI 0.53-1.06.
Elkind et al. 2006 (300)	Northern Manhattan Study	3,176 190	37.2	62.8	≥40	5.9	Stroke	<1 drink/ month, >1 drink/ month to ≤2 drinks/ day, >2 drinks and <5 drinks/ day, ≥5 drinks/day	Moderate alcohol consumption was associated with decreased risk of ischaemic stroke (RR 0.67; 95% CI 0.46-0.99).

Table 2 to be continued

Chiuve et al. 2008 (301)	Nurses´Health Study	71,243 1,559	0	100	34-59	20	Stroke	0, 0.1-4.9, 5-14.9, 15-29.9. ≥30 grams/day; moderate drinking for women: 5-15 grams/day	There was a J-shaped association for both ischaemic (RR 1.41; 95& CI 1.07-1.88) and haemorrhagic stroke (RR 1.40; 95% CI 0.86-2.28) with increased risk with high amounts of alcohol (≥30 grams/day).
Chiuve et al. 2008 (301)	Health Professionals Follow-up Study	43,685 994	100	0	40-75	18	Stroke	0, 0.1-4.9, 5-14.9, 15-29.9,≥30 grams/ day; moderate drinking for men: 5-30 grams/day	There was a J-shaped association for both ischaemic (RR 1.39; 95% CI 1.08-1.79) and haemorrhagic stroke (RR 0.99; 95% CI 0.58-1.71) with increased risk with high amounts of alcohol (≥ 30 grams/ day).
Ikehara et al. 2009 (275)	Japan Public health Center-Based Prospective Study	19,356 629	100	0	40-69	9.9	CHD and stroke	Never, past, current drinker; frequency of alcohol drinking: 1-3 days/ month (occasional), 1-2 days/week, 3-4 days/ week or almost every day	Heavy alcohol consumption was associated with increased risk of total stroke (HR 1.70; 95% CI 1.10-2.61) and haemorrhagic stroke (HR 2.09; 95% 1.03-4.27) in the low social support group.
Jiminez et al. 2012 (302)	Nurses´Health Study	83,578 2,171	0	100	30-55	26	Stroke	0, >-4.9, 5-14.9, 15-29.9, 30-45 grams/day	Low-to-moderate alcohol consumption was associated with a lower risk of total stroke (HR 0.83; 95% CI 0.75-0.92 (<5 grams/day), HR 0.79; 95% CI 0.70-0.90 (5-14.9 grams/day), HR 0.87; 95% CI 0.72-1.05 (15-29.9 grams/day), HR 1.06; 95% CI 0.86-1.30 (30-45 grams/day)
Makita et al. 2012 (303)	The Iwate-Kenpoku Cohort Study	8,059 186	100	0	40-80	5.5	Myocardial infarction and ischaemic stroke	None or occasional/day, ≤ 25 grams/day, > 25 grams/ day	No protective role of alcohol consumption was seen on ischaemic stroke subjects (HR 1.25; 95% CI 0.88-1.75 (≤ 25 grams/day) and HR 1.26; 95% CI 0.87-1.83).

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; RR, relative risk

Table 3. Summary of studies of association alcohol consumption and stroke mortality

Authors	Study population	Number of subjects and stroke cases	Men %	Women %	Age, years	Study follow-up, years	Outcome	Assessment of alcohol consumption	Findings
Blackwelder et al. 1980 (304)	Honolulu Heart Program	7,888 55	100	0	not reported	8	CHD and stroke mortality	Low and high level of alcohol	Even at low level of alcohol consumption (1 to 10 ml of ethanol/ day) the risk of death from stroke was higher than among non-drinkers.
Hansagi et al. 1995 (21)	Swedish Twin Register	15,077 769	47	53	≥42	20	Stroke mortality	Occasionally in the week, a couple of times a month, occasionally in the month, a few times in the year, more rarely/ never	An elevated risk of death due to ischaemic stroke was seen among men who were infrequent drinkers (RR 2.0; 95% CI 1.3-3.2), binging seldom (RR 1.6; 95% CI 1.1-2.5) and who occasionally felt intoxicated (RR 1.8; 95% CI 1.1-2.8). For women ex-drinkers had the highest risk of death from ischaemic stroke (RR 3.3; 95% CI 1.5-7.2), but the risk decreased with low drinking level (RR 0.6; 95% CI 0.5-0.8).
Thun et al. 1997 (262)	Cancer Prevention Study II	489,626 2,379	51.3	48.7	30-104	9	CHD, CVD, and stroke mortality	None, less than daily, 1 drink/ day, 2-3 drinks per day, ≥4 drinks/day	Moderate alcohol consumption reduced overall mortality. For stroke mortality RRs for women were 0.9; 95% CI 0.7-1.1 in group 2-3 drinks per day and 0.9; 95% CI 0.7-1.2 in group ≥4 drinks per day. For men the highest RR 0.8; 95% CI 0.6-0.9 was those who consumed 2-3 drinks per day.

Table 3 to be continued

Yuan et al. 1997 (263)	Four Communities in Shanghai	18,244 269	100	0	45-64	6.7	CHD and stroke mortality	Light to moderate drinking (28 or fewer drinks/ week), heavy drinking (29 or more drinks/ week)	Light to moderate drinking did not protected against risk of death from stroke. Heavy drinking was associated with a significantly increased risk of stroke (RR 1.7; 95% CI 1.04-2.25)
Maskarinec et al. 1998 (297)	Multiethnic cohort, Hawaii	27,678 433	50.5	49.5	>30	˜20	CHD and stroke mortality	Alcohol intake: (drinks/week) for males: 0,1-7, 8-14, 15-28, 29-42, 43-70, >70; for females: 0,1-7, 8-14, 15-35, >35	Persons with moderate alcohol intake had a lower risk of dying than non-drinkers, whereas among those with high alcohol consumption the risk of death from cerebrovascular diseases was increased, but only in women (HR 1.29; 95% CI 1.08-1.53).
Gaziano et al. 2000 (292)	Physicians´ Health Study	89,299 150	100	0	40-84	5.5	CVD and stroke mortality	Rare/never, 1-3 times/month, 1 time/ week, 2-4/ week, 5-6/week, 1/day, ≥2/day	No significant increase or decrease according to stroke was not seen in any category; there were non-significant signs of reduced risk of fatal stroke among light drinkers- monthly (RR 0.95; 95% CI 0.49-1.83) to 2-4 drinks per week (RR 0.59; 95% CI 0.30-1.15).
Jakovljevic et al. 2004 (294)	Institute for Chronic Diseases and Gerontology	286 7	50.7	49.3	30-60	20	Myocardial infarction and stroke mortality	None- or rare drinker, moderate drinker (1-2 drinks/day), heavy drinker (≥3 drinks/day)	Moderate alcohol drinkers had lower mortality rate compared to non-drinkers.

Table 3 to be continued

Hart et al. 2008 (305)	Midspan Collaborative Cohort Study	6,000 113	100	0	35-64	29	CHD and stroke mortality	Alcohol units/week: none, 1-7, 8-14, 15-21, 22-34, ≥35	Alcohol consumption of 15-21 units per week (RR 1.62; 95% CI 1.15-2.28) was associated with increased risk of stroke. When alcohol consumption was ≥35 units per week RR was 1.81 (95% CI 1.23-2.68).
Mogensen et al. 2012 (240)	The Copenhages Stroke Study	988 310	44	56	69-82	10	Stroke, heart/arterial disease, non-vascular disease	Daily alcohol consumption (yes/no)	Alcohol consumption was not predictive of any one cause of death after stroke.
Romelsjö et al. 2012 (306)	Swedish Cohort	49,111 6,352	100	0	47	35	Cardiovascular mortality (myocardial infarction and stroke)	0.1-10, 10-30, 30-60, >60 grams/day	For binge drinkers HR was 1.79: 95% CI 0.55-5.79.
Yang et al. 2012 (307)	Chinese Cohort	220,000 4,644	100	0	40-79	15	Overall and cause-specific mortality	<140, 140-279, 280-419, 420-699, ≥700 grams/week	The risk of stroke mortality was positively associated with alcohol drinking and especially with heavy drinking (HR 1.55; 95% CI 1.37-1.75).

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; RR, relative risk

3 Aims of the study

The aim of this thesis was to investigate the role of alcohol consumption as a risk factor for the progression of atherosclerosis and the risk of stroke and stroke mortality among men from Eastern Finland.

The specific aims were as follows:

1. To investigate the effect of binge drinking on the progression of atherosclerosis (I).

2. To study the relation of hangover and alcohol consumption with the risk of stroke (II).

3. To investigate the significance of alcohol consumption according to the level of blood pressure and body weight with respect to the risk of stroke (III).

4. To examine the association between the frequency of alcohol consumption and stroke mortality (IV).

4 Methods

4.1 STUDY POPULATION

4.1.1 The Kuopio Ischaemic Heart Disease Risk Factor Study

The studies were carried out among the participants of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD). The KIHD is a prospective, population-based study designed to investigate risk factors for CVDs, atherosclerosis and other related outcomes among middle-aged men in Eastern Finland (308). The study population is a representative, randomly selected sample of men from the city of Kuopio and surrounding rural communities. Of 3,433 men 42, 48, 54, or 60 years old, 198 were not included because of death (84), serious disease (65), or migration from the area (43) or unknown address (6). Of 3,235 eligible men, 367 refused to participate and 186 were not contacted and the remainder, 2,682 (83% of those eligible men) agreed to participate in the study (308,309). The baseline examinations were performed in two different cohorts as follows: the first cohort was examined during March 1984- December 1986 (n= 1,166) and the second cohort during August 1986- December 1989 (n= 1,516). In the first cohort all men were 54 years old and in the second cohort they were 42, 48, 54, and 60 years old. The men who underwent ultrasound examination of carotid arteries were from the second cohort (Study I). That cohort was selected for ultrasound examination because of different age groups and it could be more representative than only one age group in the first cohort. The study protocol was approved by the Research Ethics Committee of the University of Kuopio. All participants gave a written informed consent to participate in the study. Table 4 presents the description of the KIHD population at baseline and different follow-up examinations. Table 5 presents the description on the study population and main variables.

Table 4. The description of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) population at baseline and at 4-, 11-, and 20-year follow-up examinations (number of eligible men)

Baseline	**4-year follow-up**	**11-year follow-up**	**20-year follow-up**
1984-1989	**1991-1993**	**1998-2001**	**2005-2008**
Participants	Participants	Participants	Participants
Cohort 1 and 2	Cohort 2	Cohort 2	Cohort 1 and 2
2682	1038	854	1241

Table 5. The description of the study population and main variables

Study	n	Baseline population	Follow-up time, years	Main outcomes
I	751	Carotid artery ultrasound at baseline and 4-year follow-up	11.0	Maximum IMT, mean IMT and plaque height
II	2,466	With no stroke	15.7	206 strokes, 167 ischaemic strokes
III	2,599	With no stroke	14.9	224 strokes, 181 ischaemic strokes
IV	2,609	With no stroke	20.2	66 stroke deaths

Abbreviations: IMT, intima media thickness

4.2 DATA COLLECTION

The survey included three self-administered questionnaires that were mailed to the participants prior to their health examination. The participants were then invited to the study centre for a clinical examination. The participants underwent a health examination that included an interview conducted by a research nurse. At the interview some of the items in the questionnaires, including drug use, were ascertained. During the clinical examination blood samples were taken and physical tests performed. One of the self-administered questionnaires included questions about participants´ demographic characteristics, socioeconomic background, childhood circumstances, working history, major life events, leisure time activities, family life, health behaviour, such as physical activity, smoking and alcohol consumption, current health status and drug use. The other two questionnaires included questions on participants´ psychosocial well-being.

4.3 MEASUREMENT OF ALCOHOL CONSUMPTION

4.3.1 Alcohol consumption

Assessment of alcohol consumption was carried out by using the Nordic alcohol consumption inventory, which is a well-structured quantity and frequency method (310). Mainly the same questions were asked at baseline and at follow-up examinations. The questions dealt with the average frequency of any alcohol consumption, average frequency of consumption of specific beverages and the average quantity of specific beverages that were usually consumed at one time. The self-report alcohol intake response form covered the preceding 12-month period.

Types of alcoholic drinks varied slightly at different follow-up examinations because of changes in the use of different alcoholic drinks and drinking culture. Different types of wines were more common in latter follow-up examinations, but at baseline beverage types were divided into beer or cider, mild wine, fortified wine and hard liquor. The usual frequency and dose of alcohol intake (measured in glasses or in bottles) were recorded for each type of beverage (beer, wine, fortified wine, spirits) with a structured response form

assessing total alcohol consumption and timing or pattern of drinking (number of drinks per one occasion).

The average total alcohol intake (grams of ethanol per week) was calculated on the basis of the known ethanol content of various beverages. One alcoholic unit is equivalent to an average of 12 grams of 100% ethanol. A bottle of ordinary beer (0.33 l) in Finland contains 12 grams of ethanol while a bottle of strong beer contains 14 grams of ethanol, which is also the ethanol content in one portion of liquor (252). Average alcohol consumption per week was calculated by multiplying the average beverage-specific quantity and frequency consumed, and then multiplying the sum by the alcoholic content that was specific for different beverages. All calculated amounts were then summed together and presented as grams of alcohol per week.

Frequent drinking was defined during the period of past 12 months as consumption of any amount of alcohol at least 2 times per week on average. Frequent drinking was based on a question about average frequency of alcohol consumption. Response options were as follows: once a month or more seldom, 2-3 times per month, about once a week, 4-5 times a week and daily.

4.3.2 Binge drinking

Binge drinking was defined as consuming six or more alcoholic units of beverage on one occasion. The groups of drinking were as follows: Group (1) consumed <6 portions and Group (2) consumed ≥6 portions of any alcohol on one occasion (Study I). The self-report alcohol intake response form covered the preceding 12-month period. Six or more units are considered the threshold for risky drinking according to the National Institute of Health and Welfare in Finland. The same definition is also used for heavy episodic drinking or binge drinking in the Nordic countries (311).

4.3.3 Hangover

Frequency of hangovers was assessed using the following structured question: "How often did you experience hangover during the past 12 months?" The response alternatives were: never, once a year, 2-3 times a year, 4-5 times a year, about once every 2 months, about monthly, 2-3 times a month, about once a week, at least twice a week (Kauhanen, Epidemiology, 1997) (Study II).

4.4 ASSESSMENT OF OTHER VARIABLES

4.4.1 Blood pressure

Blood pressure was measured with a random-zero sphygmomanometer, after 5 and 10 minutes of rest in a seated position in a quiet room, and reported as the mean of 6 measurements (3 supine, 1 standing, 2 sitting) of SBP and DBP.

4.4.2 Body mass index

Body mass index was computed as the ratio of weight in kilograms divided by the square of height in metres (kg/m^2).

4.4.3 Biochemical measurements

Diabetes was defined on the basis of self-reported diabetes or a fasting blood glucose value of 6.7 mmol/ l or more. Blood glucose was measured with the glucose dehydrogenase method. The serum cholesterol content lipoprotein fractions HDL and LDL and serum triglyceride fractions are separated from fresh serum by combined ultracentrifugation and precipitation (312). Lipoprotein fraction cholesterol and triglycerides were measured enzymatically; detailed descriptions of them were presented in a previous study (312).

Serum CRP was measured with an immunometric assay as reported previously (313). Treatment for hypertension or hyperlipidaemia was evaluated by a review of medications.

4.4.4 Coronary heart disease and atrial fibrillation

The diagnostic classification of coronary events was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80%) and history of CHD. Symptomatic CHD was defined as a history of myocardial infarction (on the basis of standard criteria including characteristic symptoms with either typical electrocardiogram criteria or elevations of cardiac enzymes), angina pectoris on effort or the use of nitroglycerine for chest pain once a week or more frequently (314). Family history of CHD was defined as positive when the father, mother, sister or brother of a subject had myocardial infarction, angina pectoris or CHD (315). AF was coded according to the ICD, 9th revision ICD-9 codes 390-459 and ICD-10 codes I00-99. Heart failure was defined as a diagnosis of heart failure based on clinical symptoms and findings.

4.4.5 Maximal oxygen uptake and energy expenditure

Maximal oxygen uptake was a measure of cardiorespiratory fitness during exercise (315). Energy expenditure (in kcal/week) for each physical activity was calculated by multiplying the metabolic index of the activity (in metabolic equivalent x hour/week) by body weight in kilograms (314,315).

4.4.6 Smoking

Smoking was estimated by a questionnaire, and the classification was "never smokers", "former smokers" and "current smokers" (measured in cigarette packs per day in years of smoking). Current smoking as a covariate was defined as lifelong exposure to smoking and it was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination. Lifelong cumulative smoking exposure was defined as the product of years smoked and the number of tobacco products smoked daily at the time of examination.

4.4.7 Socioeconomic status

We assessed socioeconomic status (SES) using a summary index that combined measures of income, education, occupation, material standard of living, and housing conditions, all of which were assessed with the self-administered questionnaire. Minimum value on SES was 0 and maximum 25. A high value on the SES index indicated low SES (316).

4.5 ULTRA-SOUND SCANNING OF CAROTID ARTERIES

The ultrasonographic scanning of carotid arteries was performed with the subject lying in supine position. Images were focused on the posterior (far) wall. High-resolution B-mode ultrasonography was used to examine a 1.0- to 1.5- cm section at the distal end of the left and right common carotid artery (CCA) proximal to the carotid bifurcation, as explained in detail by Salonen et al. (317,318) (Figure 1). The site of the most advanced atherosclerotic lesion and the projection showing the greatest distance between the lumen-intima interface and the media-adventitia interface was located in both right and left CCAs.

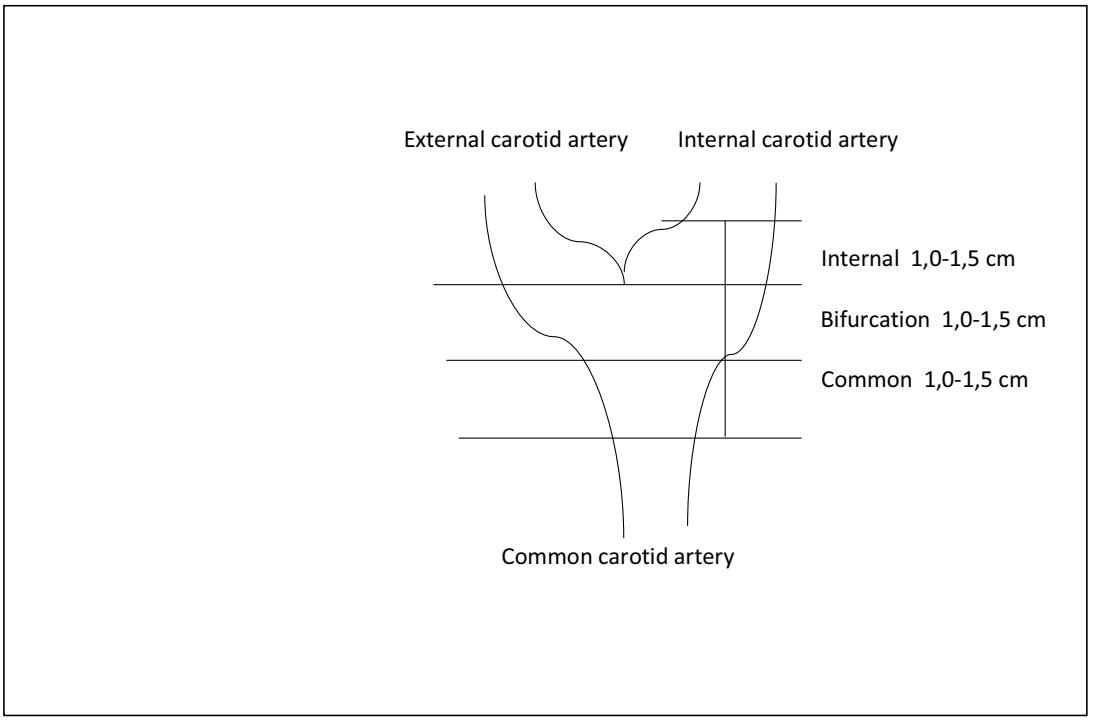

Figure 1. Schematic diagram for sites measuring changes in carotid artery.

Ultrasonographic scanning was conducted with the ATL UM4 duplex ultrasound system with a 10-MHz sector transducer (Advanced Technology Laboratories) at baseline. The 11-year follow-up examinations (Study I) were conducted by using Esaote AU4 equipped with a 10-MHz annular array probe (LA13A). Wedge phantom studies of the system at baseline, calibrated against an RMI 414B tissue phantom, and demonstrated measurements precision of ±0.03 mm (317,319). The short-term reproducibility of ultrasonographic assessment of the severity of carotid atherosclerosis was high, as indicated by the 90% agreement between the original and blindly done re-assessment in a random subsample by the same observer (318).

Baseline scanning and 11-year follow-up scanning were recorded by using a videotape recorder. Video frames of the B-mode scanning were digitised and IMT was assessed at baseline with Prosound software and at 11-year follow-up with Prowin software, which connects an edge-detection algorithm specially designed for use with ultrasound scanning and allowed tracking and recording of the lumen-intima and media-adventitia interfaces (320). On average, 100 estimates of the distance between these interfaces were recorded over the 1.0- to 1.5- cm section of each CCA. The IMT for the posterior wall was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line (317).

4.6 ASCERTAINMENT OF STROKE AND STROKE MORTALITY

4.6.1 Collection and classification of stroke data (II-III)

Incident strokes between 1984 and 1992 were ascertained through the Finnish part of the WHO MONICA (Multinational Monitoring of Trends and determinants in Cardiovascular Diseases) (FINMONICA) stroke register (312). Information on stroke incidence from 1993 to 2003 (Study II) and from 1993 to 2004 (Study III) was obtained by computerised linkage to the Finnish national hospital discharge registry and death certificate registers. Diagnostic information was collected from hospitals and classified by one neurologist (J.S.) with diagnostic criteria which were identical to the FINMONICA criteria (312,321). Hospital documents, death certificates, autopsy reports and medico-legal reports were the sources of information on stroke. The diagnosis of stroke was based on sudden onset of clinical signs or focal or global disturbance of cerebral function lasting over 24 hours (except in the case of sudden death or if interrupted by surgical intervention) with no apparent cause other than vascular origin. Each suspected stroke (ICD-9, codes 430-439 and ICD-10 codes I60-I68 and G45-G46) was classified into a definite stroke, no stroke, or an unclassified event. The FINMONICA stroke register data were annually rechecked with the data obtained from the computerised national hospital discharge and death registers. Each definite stroke was classified into an ischaemic stroke (ICD-9 codes 433-434, ICD-10 code I63) or a haemorrhagic stroke (ICD-9 codes 430-431, ICD-10 codes I60-I61). If a subject had multiple non-fatal strokes during the follow-up time, the first stroke was considered as the end point. By 1993, computed tomography (CT) was performed in 90% of the cases; by 1997, CT, MRI, and autopsy was done in 100% of the cases (312).

4.6.2 Collection and classification of stroke mortality data (IV)

Strokes between 1984 and 1992 were ascertained through the Finnish part of the WHO MONICA (Multinational Monitoring of Trends and determinants in Cardiovascular Diseases) (FINMONICA) stroke register (312). Information on strokes between 1993 and 2010 was obtained by computerised linkage to the Finnish national hospital discharge registry and death certificate registers. Further diagnostic information was collected from hospitals and classified by one neurologist (J.S.) using diagnostic criteria identical to the FINMONICA criteria (312,321). The FINMONICA stroke register data were annually rechecked with the data obtained. All deaths from stroke were classified according to ICD-10 using codes I60-I61 and I63.

4.7 STUDY DESIGNS

4.7.1 Study I

We examined the association between binge drinking pattern and the progression of atherosclerosis. A total of 751 men participated in this study. The average follow-up time was 11.0 years. The outcome measures included the maximum IMT, the mean IMT and plaque height change. The maximum IMT was defined as the average of the maximum IMT of the right and left CCA. The mean IMT was defined as the mean of the ~100 IMT readings from each CCA. Plaque height was defined as the difference between maximum and minimum IMT recordings and averaged over the right and left CCA. These measures represented potentially dissimilar aspects of atherosclerosis progression. It was thought that maximum IMT gives an estimation of how deeply intima-media thickening intrudes into the lumen in this part of the CCA. Mean IMT was seen to be an overall measure of the process of atherosclerosis, whereas plaque height was seen as sensitive to the roughness of the arterial wall by representing the range of IMT. The arithmetic differences between the baseline and the 11-year follow-up values for each of the three measures were calculated and they describe the progression of atherosclerosis.

4.7.2 Study II

We investigated the relation of hangover and alcohol consumption with the risk of stroke. A total of 2,466 men participated in this study. The average follow-up time was 15.7 years. The individuals with strokes prior to the baseline investigation were excluded. Analyses were carried out separately for all strokes and for ischaemic strokes.

4.7.3 Study III

We investigated the role of alcohol consumption according to the level of blood pressure and body weight with respect to the risk of stroke. A total of 2,599 men participated in this study. The average follow-up time was 14.9 years. The individuals with strokes prior to the baseline investigation were excluded. Analyses were carried out separately for all strokes and for ischaemic strokes.

4.7.4 Study IV

We examined the association between the frequency of alcohol consumption and stroke mortality in a population-based sample of Eastern Finnish men. A total of 2,609 men participated in this study. The average follow-up time was 20.2 years. The individuals with strokes prior to the baseline investigation were excluded.

4.8 STATISTICAL METHODS

In the statistical analyses the descriptive data were presented as mean and standard deviation for continuous data and percentages for categorical data. The correlations between risk factors used were analysed using Pearson´s correlation test. The level of significance was $p < 0.05$ in all analyses. Statistical analyses were performed by using the SPSS version 14.0 for Windows (SPSS, Inc., Chicago, Illinois) (Studies I, II and III) and the SPSS 19.0 IBM software (Study IV).

4.8.1 Study I

The association between binge drinking and the progression of IMT was assessed by estimating the mean change in maximum thickness and in mean thickness and also in plaque height for dissimilar levels of usual drinking dose of different types of alcohol. Analyses of drinking pattern were performed with adjustment for the total consumption of any alcohol. Analyses were performed in three different ways. First, in Model 1, mean change in the maximum thickness of IMT was estimated, with adjustment for age, baseline IMT measure, total average consumption of alcohol and zooming depth left and right. According to mean change in maximum IMT analyses were also performed without baseline IMT adjustment. In Model 2, further adjustments with SBP and DBPs, HDL- and LDL-cholesterol, BMI, smoking, cholesterol-lowering medication and antihypertension medication were added to Model 1. In Model 3, further adjustments including CRP, triglyceride, diabetes and maximal oxygen uptake were added to Model 2. All statistical analyses were performed by using general linear model (GLM) univariate procedure.

4.8.2 Study II

The association of alcohol consumption with strokes was analysed with a Cox proportional hazards regression model. Model 1 was adjusted for age only. Model 2 was further adjusted for current smoking, serum HDL-cholesterol, serum LDL-cholesterol, BMI, SBP, myocardial ischaemia during exercise, symptomatic CHD and CHD in family, CRP, diabetes and total alcohol consumption. Model 3 was further adjusted for AF and heart failure. All of these models are based on the previously established risk factors and significant risk factors in

our cohort. All of these models were analysed separately for all strokes and for ischaemic strokes. Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariate models. The fit of the proportional hazard models was examined by plotting the hazard functions in different categories of risk factors over time. The results indicated that the application of the models was appropriate.

4.8.3 Study III

The association of alcohol consumption with strokes was analysed with a Cox proportional hazards regression model. The models were analysed separately for any strokes and for ischaemic strokes. Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariate models. The fit of the proportional hazard models was examined by plotting the hazard functions in different categories of risk factors over time. The results indicated that the application of the models was appropriate. RRs of associations between alcohol consumption and the risks of stroke among men with hypertension were carried out with adjustment for age, year of examination, SES, serum LDL-cholesterol, BMI, smoking and energy expenditure of physical activity (kcal/ day). RRs of associations between alcohol consumption and the risks of stroke among overweight men were performed after adjustment for age, year of examination, SES, serum LDL-cholesterol, smoking and energy expenditure of physical activity (kcal/ day). Analyses according to blood pressure were performed at blood pressure levels <140/ 90 mmHg and ≥140/ 90 mmHg. The evaluation of BMI was made according to median (26.4 kg/ m^2) in two categories: <26.4 kg/ m^2 and ≥26.4 kg/ m^2.

4.8.4 Study IV

The association of alcohol consumption with stroke mortality was analysed with a Cox proportional hazards regression model. Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariable models. The fit of the proportional hazard models was examined by plotting the hazard functions in different categories of risk factors over time. The results indicated that the application of the models was appropriate. The frequency of alcohol consumption was classified as follows: <0.5, 0.5-2.5 and >2.5 times per week. RRs of associations between the frequency of alcohol consumption and the risks of death from stroke in Model 1 were carried out with adjustment for age and year of examination. Model 2 was adjusted for age, year of examination, SBP, smoking, BMI, diabetes, and SES. Model 3 was adjusted for age, year of examination, SBP, smoking, BMI, diabetes, SES, and total alcohol consumption.

5 Results

5.1 BINGE DRINKING AND THE PROGRESSION OF ATHEROSCLEROSIS

5.1.1 Binge drinking and progression of maximum IMT

Table 6. Characteristics of the study population according to baseline health status (mean (SD) or prevalence (%))

	Binge <6 (n=583)	**Binge ≥ 6 (n=168)**
Characteristics	**mean (SD)**	**mean (SD)**
Age, years	51.7 (6.7)	49.7 (6.8)
BMI, kg/m^2	26.4 (3.0)	27.4 (3.4)
Weight, kg	79.6 (10.8)	83.8 (11.9)
Mean of maximum IMT in right and left CCA, mm	0.9 (0.2)	0.9 (0.2)
Mean of mean IMT in right and left CCA, mm	0.8 (0.2)	0.7 (0.1)
Plaque height, mm	0.2 (0.2)	0.3 (0.3)
Serum LDL-cholesterol, mmol/l	3.9 (0.9)	3.9 (0.9)
Serum HDL-cholesterol, mmol/l	1.3 (0.3)	1.3 (0.3)
Serum triglycerides, mmol/l	1.4 (0.8)	1.4 (1.0)
Systolic blood pressure, mmHg	131.2 (14.8)	131.7 (16.5)
Diastolic blood pressure, mmHg	87.1 (9.7)	88.5 (9.6)
Serum CRP, mg/l	2.3 (4.8)	2.4 (3.2)
Serum gamma-GT U/I	26.0 (18.7)	33.3 (34.0)
Serum Hb, g/l	147.4 (9.2)	148.3 (9.0)
Diabetes (%)	3.3	3.6
Treatment for hypertension (%)	17.7	17.3
Treatment for high cholesterol (%)	0.9	0.6
Total alcohol consumption, g/week	54.2 (71.6)	171.0 (166.2)
Smoking (cigarette pack/day x years of smoking)	5.9 (12.9)	10.7 (15.4)
Maximal oxygen uptake (Vo_2 max), ml/kg/min	32.2 (7.8)	31.7 (7.0)

Abbreviations: BMI, body mass index; CCA, common carotid artery; CRP, C-reactive protein; HDL, high density lipoprotein; IMT, intima media thickness; LDL, low density lipoprotein; SD, standard deviation; Vo_2 max, maximal oxygen uptake

Table 6 presents the baseline characteristics of the study population in Study I. During the 11-year follow-up, maximum progression of atherosclerosis in carotid arteries in Model 1, adjusted for age, baseline IMT, total average consumption of alcohol and zooming depth left and right, was 0.395 mm for those who drank ≥6 drinks per one occasion and 0.324 mm for those with less than 6 drinks per occasion (Figure 2). Men with greater alcohol consumption had increased risk for atherosclerotic progression at 11 years compared to those who drank less than 6 drinks per one occasion (p = 0.008) (Figure 2). After further adjustment for SBP, DBP, HDL- and LDL-cholesterol, BMI, smoking, cholesterol-lowering medication and antihypertension medication (Model 2) the change was 0.388 mm among those who drank ≥6 drinks per occasion and 0.331 mm among those who drank less than 6 drinks per occasion.

In Model 3, after further adjustment for CRP, triglyceride, diabetes and maximal oxygen uptake, the change was 0.387 mm for those who drank ≥6 drinks, while for those who drank less than 6 drinks the change was 0.332 mm. After adjusting for other covariates, the results remained statistically significant (in Model 2, p = 0.031 and in Model 3, p = 0.037) (Figure 2), indicating clearly that men with greater alcohol consumption had increased risk for atherosclerotic progression at 11 years compared to those who drank less than 6 drinks per one occasion. The analyses were also adjusted without baseline IMT adjustment. Adjusting without baseline IMT changed the results only little. The value for those who drank ≥6 drinks was 0.388 mm only in Model 3. The values were otherwise equal to the values of analyses made with baseline IMT adjustment. The results remained statistically significant in every model as follows: p = 0.008 for Model 1, p = 0.029 for Model 2 and p = 0.034 for Model 3. After additionally adjusting for SES into the Model 3, the association between binge drinking and the mean change in maximum IMT changed only a little (p=0.043). The mean rate of IMT thickening during the first four years was 0.066 mm in maximum IMT and during the next seven years 0.011 mm for the cohort of 751 men.

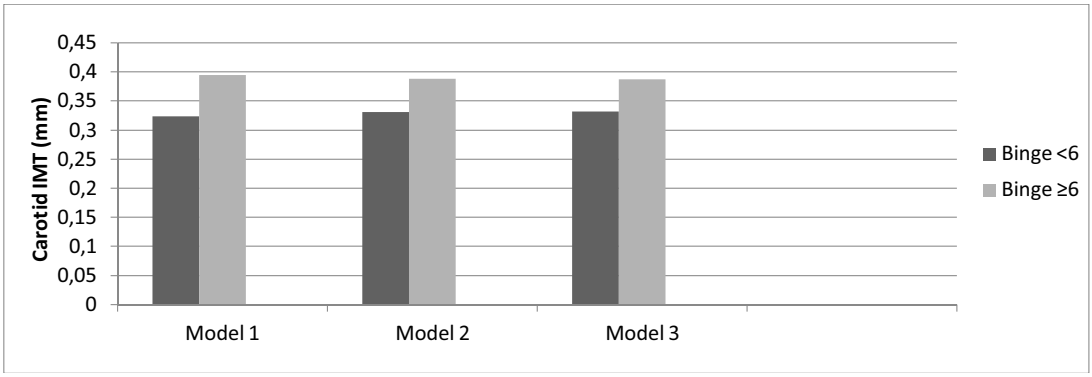

Figure 2. Mean 11-year change in the maximum IMT in middle-aged Finnish men by drinking pattern (mean change in maximum IMT, mm)

Model 1: Adjusted for age, average load of alcohol consumption, zoom depth and baseline intima media thickness (IMT).

Model 2: Adjusted for Model 1 and high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP), medication for hypertension and hyperlipidaemia, body mass index (BMI) and smoking.

Model 3: Adjusted for Model 2 and C-reactive protein (CRP), triglycerides, diabetes and maximal oxygen uptake (Vo_2 max).

5.1.2 Binge drinking and change in plaque height

The results were consistent with maximum IMT findings when we used plaque height as an outcome. The 11-year progression of plaque height in Model 1 was greatest in those subjects who consumed ≥6 drinks after adjustment for age, baseline IMT measure, total average consumption of alcohol and zooming depth left and right. The progression of plaque height was 0.257 mm for those with alcohol consumption ≥6 drinks and 0.182 mm for those with less than 6 drinks per one session (p = 0.002) (Table 7). In Model 2 plaque height was 0.249 mm for those who consumed more alcohol and 0.190 mm for those who consumed less alcohol; in Model 3, the corresponding figures were 0.248 mm and 0.192 mm. After adjusting for other covariates, the results still remained statistically significant (in Model 2, p = 0.012 and in Model 3, p = 0.017) (Table 7). After additionally adjusting for SES into Model 3, the association between binge drinking and the change in plaque height changed only marginally (p=0.014).

Table 7. 11-year progression of plaque height progression in middle-aged Finnish men by drinking pattern (change in plaque height IMT, mm)

	n	Model 1	p-value	Model 2	p-value	Model 3	p-value
Binge <6	583	0.182	-	0.190	-	0.192	-
Binge ≥6	168	0.257	0.002	0.249	0.012	0.248	0.017

Model 1: Adjusted for age, average load of alcohol consumption, zoom depth and baseline intima media thickness (IMT).

Model 2: Adjusted for Model 1 and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP), medication for hypertension and hyperlipidemia, body mass index (BMI) and smoking.

Model 3: Adjusted for Model 2 and C-reactive protein (CRP), triglycerides, diabetes and maximal oxygen uptake (Vo_2 max).

5.1.3 Binge drinking and change in mean IMT

The mean IMT change at 11-years adjusted for age, alcohol consumption, zoom depths and baseline IMT was 0.231 mm for men in the highest category and 0.203 mm for those in the lowest category (p = 0.126); in Models 2 and 3 the values for the highest and the lowest category were 0.228 mm and 0.206 mm, respectively (Table 8). Adjusting for other covariates somewhat diminished the relationship. In Models 2 and 3 the statistical significance changed after adjusting for other covariates (p = 0.211 and p = 0.210). The results according to change in mean IMT without baseline IMT adjustment were almost the same as with IMT adjustment. The results did not change without baseline IMT adjustment. The mean rate of IMT thickening during the first four years was 0.028 mm; and the mean rate of IMT thickening during the next seven years was 0.013 mm for the cohort of 751 men.

Table 8. 11-year progression of mean IMT in middle-aged Finnish men by drinking pattern (change in mean IMT, mm)

	n	Model 1	p-value	Model 2	p-value	Model 3	p-value
Binge <6	583	0.203	-	0.206	-	0.206	-
Binge ≥6	168	0.231	0.126	0.228	0.211	0.228	0.210

Model 1: Adjusted for age, average load of alcohol consumption, zoom depth and baseline intima media thickness (IMT).
Model 2: Adjusted for Model 1 and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP), medication for hypertension and hyperlipidemia, body mass index (BMI) and smoking.
Model 3: Adjusted for Model 2 and C-reactive protein (CRP), triglycerides, diabetes and maximal oxygen uptake (Vo_2 max).

5.2 HANGOVER AND THE RISK OF STROKE

5.2.1 Hangover and stroke risk

After adjustment for age, the RR for any stroke among men with ≥1 hangover per year was 2.33-fold (95% confidence interval (CI), 1.19 to 4.56; p=0.013) compared to men without hangover (Table 9). The corresponding age-adjusted risk for ischaemic stroke was 2.99 (95% CI, 1.52 to 5.86; p=0.001). After adjustment for age, current smoking, HDL-cholesterol, LDL-cholesterol, BMI, SBP, myocardial ischaemia during exercise, symptomatic CHD and CHD in family, CRP, diabetes and total alcohol consumption the RR for any stroke was 1.94 (95% CI, 0.95 to 3.96; p=0.070). Multivariable adjusted RR was 2.58-fold (95% CI, 1.24 to 5.36; p=0.011) for ischaemic stroke among men with hangovers. After additional adjustment of AF and heart failure the risk was 1.86-fold (95% CI, 0.91 to 3.81; p=0.091) for any stroke and 2.45-fold (95% CI, 1.18 to 5.12; p=0.017) for ischaemic stroke as compared to men with no hangovers. The risk of any stroke and ischaemic stroke according to hangover and the absolute risk values are shown in Table 9. The strongest risk factors for any stroke were age ($p < 0.0001$), BMI ($p = 0.032$), CRP ($p = 0.029$), diabetes ($p= 0.001$) and SBP ($p < 0.0001$). The strongest risk factors for ischaemic stroke were age ($p < 0.0001$), BMI ($p = 0.020$), SBP ($p = 0.002$), diabetes ($p < 0.0001$) and hangover ($p = 0.017$).

Table 9. The frequency of hangovers and the risk of any stroke and ischaemic stroke among men in Eastern Finland

Risk of any stroke according to hangover (206 cases)

	Model 1		**Model 2**		**Model 3**		
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	Absolute risk cases per 1,000 follow-up years
Hangover <1	1.00		1.00		1.00		5.2
Hangover ≥ 1	2.33 (1.19-4.56)	0.013	1.94 (0.95-3.96)	0.070	1.86 (0.91-3.81)	0.091	10.1

Risk of ischaemic stroke according to hangover (167 cases)

	Model 1		**Model 2**		**Model 3**		
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	Absolute risk cases per 1,000 follow-up years
Hangover <1	1.00		1.00		1.00		4.1
Hangover ≥1	2.99 (1.52-5.86)	0.001	2.58 (1.24-5.36)	0.011	2.45 (1.18-5.12)	0.017	9.6

Model 1: Relative risks (RRs) are adjusted for age.

Model 2: RRs are adjusted for Model 1, current smoking ((pack-years) denotes the lifelong exposure to smoking, estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination), serum high-density lipoprotein (HDL) cholesterol, serum low-density lipoprotein (LDL) cholesterol, body mass index (BMI), systolic blood pressure (SBP), myocardial ischaemia during exercise, symptomatic coronary heart disease (CHD) and CHD in family, C-reactive protein (CRP), diabetes and total alcohol consumption.

Model 3: RRs are adjusted for Model 1, Model 2, atrial fibrillation (AF) and heart failure.

5.3 ALCOHOL CONSUMPTION AND THE RISK OF STROKE AMONG HYPERTENSIVE AND OVERWEIGHT MEN

5.3.1 The risk of stroke according to the levels of blood pressure

Table 10 presents the associations between hypertension, alcohol consumption and the risk of any stroke. After adjustment for age, year of examination, SES, serum LDL-cholesterol, BMI, smoking and energy expenditure of physical activity (kcal/ day), there was a significantly increased risk for any stroke among alcohol consumers with blood pressure over 140/90 mmHg compared to men with blood pressure under 140/90 mmHg who did not consume alcohol. The risk of any stroke was 1.72-fold (95% CI, 1.12-2.66; p=0.014) and 1.90-fold (95% CI, 1.15-3.13; p=0.012) for ischaemic stroke among hypertensive men who did not consume alcohol. Additionally, among hypertensive men who consumed alcohol RR was 1.86-fold (95% CI, 1.20-2.89; p= 0.005) for any stroke and 2.02-fold (95% CI, 1.21-3.35; p=0.007) for ischaemic stroke. The risk of stroke was not statistically significantly increased among normotensive men who consumed alcohol.

Table 10. Relative risks of stroke according to blood pressure among men in Eastern Finland

	Ischaemic stroke	**p-value**	**Any stroke**	**p-value**
	RR (95% CI)		**RR (95% CI)**	
Normotensive men who did not consume alcohol	1.00		1.00	
Hypertensive men who did not consume alcohol	1.90 (1.15-3.13)	0.012	1.72 (1.12-2.66)	0.014
Alcohol consumers with normal blood pressure	1.74 (0.99-3.07)	0.055	1.40 (0.84-2.31)	0.195
Alcohol consumers with hypertension	2.02 (1.21-3.35)	0.007	1.86 (1.20-2.89)	0.005

Adjusted for age, year of examination, socioeconomic status, serum low-density lipoprotein (LDL) cholesterol, current smoking ((pack-years), lifelong exposure to smoking, estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination) and energy expenditure of physical activity (kcal/ day).

5.3.2 The risk of stroke according to the levels of body weight

Table 11 presents the associations between overweight, alcohol consumption and the risk of any and ischaemic stroke. Elevated BMI was associated with an increased risk for any stroke and for ischaemic stroke. After adjustment for age, year of examination, SES, serum LDL-cholesterol, smoking and energy expenditure (kcal/ day), there was a trend of an increased risk for any and ischaemic stroke across BMI categories. Men with elevated BMI (≥26.4 kg/ m^2) who did not consume alcohol had 1.63-fold (95% CI, 1.11-2.40; p= 0.013) risk for any stroke and 1.33-fold (95% CI, 0.87-2.04, p= 0.199) risk for ischaemic stroke after adjusting for risk factors. The association was strongest for overweight men (≥26.4 kg/ m^2) who consumed alcohol; they had 1.73-fold (95% CI, 1.18-2.54, p=0.005) risk for any stroke and 1.71-fold (95% CI, 1.14-2.57; p=0.010) risk for ischaemic stroke after adjusting for risk

factors. The risk of stroke was not statistically significantly increased among men whose BMI was <26.4 kg/ m^2 and who consumed alcohol. Men with hypertension and binge drinking (over 6 drinks of alcohol) had 1.66-fold (95% CI, 1.07-2.57; p= 0.025) risk for any stroke compared to those who consumed less alcohol. Similarly, men who were overweight and binge drinkers (over 6 drinks of alcohol) had 1.50-fold (95% CI, 0.99-2.28; p= 0.05) risk for any stroke compared to those who consumed less alcohol.

Table 11. Relative risks of stroke according to body mass index among men in Eastern Finland

	Ischaemic stroke	**p-value**	**Any stroke**	**p-value**
	RR (95% CI)		**RR (95% CI)**	
Normotensive men who did not consume alcohol	1.00		1.00	
Hypertensive men who did not consume alcohol	1.33 (0.87-2.04)	0.199	1.63 (1.11-2.40)	0.013
Alcohol consumers with normal blood pressure	1.31 (0.83-2.07)	0.246	1.50 (0.99-2.27)	0.057
Alcohol consumers with hypertension	1.71 (1.14-2.57)	0.010	1.73 (1.18-2.54)	0.005

Adjusted for age, year of examination, socioeconomic status, serum low-density lipoprotein (LDL) cholesterol, current smoking ((pack-years), the lifelong exposure to smoking, estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination) and energy expenditure of physical activity (kcal/ day).

5.4 ALCOHOL CONSUMPTION AND STROKE MORTALITY

Table 12. Characteristics of the study population according to baseline health status (mean (SD) or prevalence (%))

Characteristic	Mean (SD) or % (n=2,609)
Age, years	53.0 (5.2)
BMI, kg/m^2	26.8 (3.6)
Socioeconomic status	12.3 (5.1)
Smoking, cigarettes/ day	5.6 (10.2)
Alcohol consumption, g/ week	76.6 (137.8)
Systolic blood pressure, mmHg	134.1 (17.0)
Diastolic blood pressure, mmHg	88.6 (10.5)
Total cholesterol, mmol/l	5.9 (1.1)
Serum HDL- cholesterol, mmol/l	1.3 (0.3)
Serum LDL- cholesterol, mmol/l	4.0 (1.0)
Triglycerides, mmol/l	1.3 (0.8)
Diabetes, %	5.3

Abbreviations: BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation

5.4.1 Relative risks of stroke mortality

Table 12 presents the baseline characteristics of 2,609 Eastern Finnish men (Study IV). Table 13 presents the RR of death from stroke according to the frequency of alcohol consumption per week. In Model 1, after adjustment for age and year of examination, the RR of death from stroke was 0.68-fold (95% CI, 0.29-1.60; p=0.374) among men who consumed alcohol 0.1-0.5 times per week compared to non-drinkers, whereas among those men who consumed alcohol 0.5-2.5 times per week, the corresponding RR was 1.16 (95% CI, 0.56-2.40; p=0.699). The RR of death from stroke was 2.47-fold (95% CI, 1.15-5.34; p=0.021) among men who consumed alcohol >2.5 times per week compared to men who did not consume alcohol.

The RR of death from stroke was 0.70-fold (95% CI, 0.30-1.66; p=0.419) among men who consumed alcohol 0.1-0.5 times per week compared to non-drinkers, after adjustment for age, year of examination, SBP, smoking, BMI, diabetes, and SES (Model 2). Among those men who consumed alcohol 0.5-2.5 times per week, the corresponding RR was 1.08 (95% CI, 0.51-2.27; p=0.846). The risk of death from stroke was 2.44 (95% CI, 1.11-5.40; p=0.027) among men who consumed alcohol >2.5 times per week as compared to non-drinkers.

In multivariable Model 3, the RR of death from stroke was 0.71-fold (95% CI, 0.30-1.68; p=0.437) among men who consumed alcohol 0.1-0.5 times per week compared to non-drinkers and 1.16 (95% CI, 0.54-2.50; p=0.704) among those who consumed alcohol 0.5-2.5 times per week, after adjustments for age, year of examination, SBP, smoking, BMI,

diabetes, SES, and total alcohol consumption. Even when the total amount of alcohol consumption (grams per week) was taken into account with other covariates, RR was 3.03-fold (95% CI, 1.19-7.72; p=0.020) among men who consumed alcohol >2.5 times per week compared to non-drinkers.

Table 13. Relative risk of stroke mortality by alcohol consumption times per week.

Alcohol consumption times/week		**<0.5**		**0.5-2.5**		**>2.5**	
Mean amount of alcohol grams/week		**14.06**		**82.18**		**248.17**	
	Reference		p-value		p-value		p-value
Model 1							
RR	1.00	0.68	0.374	1.16	0.699	2.47	0.021
95% CI		0.29-1.60		0.56-2.40		1.15-5.34	
Model 2							
RR	1.00	0.70	0.419	1.08	0.846	2.44	0.027
95% CI		0.30-1.66		0.51-2.27		1.11-5.40	
Model 3							
RR	1.00	0.71	0.437	1.16	0.704	3.03	0.020
95% CI		0.30-1.68		0.54-2.50		1.19-7.72	

Model 1: Relative risks (RRs) are adjusted for age and year of examination.
Model 2: RRs are adjusted for age, year of examination, systolic blood pressure (SBP), smoking, body mass index (BMI), diabetes and socioeconomic status (SES).
Model 3: RRs are adjusted for age, year of examination, SBP, smoking, BMI, diabetes, SES and total alcohol consumption.

6 Discussion

Figure 3 describes associations between alcohol consumption and atherosclerosis, hangover and stroke, and alcohol consumption and stroke mortality. This figure is simplified description of all possible associations.

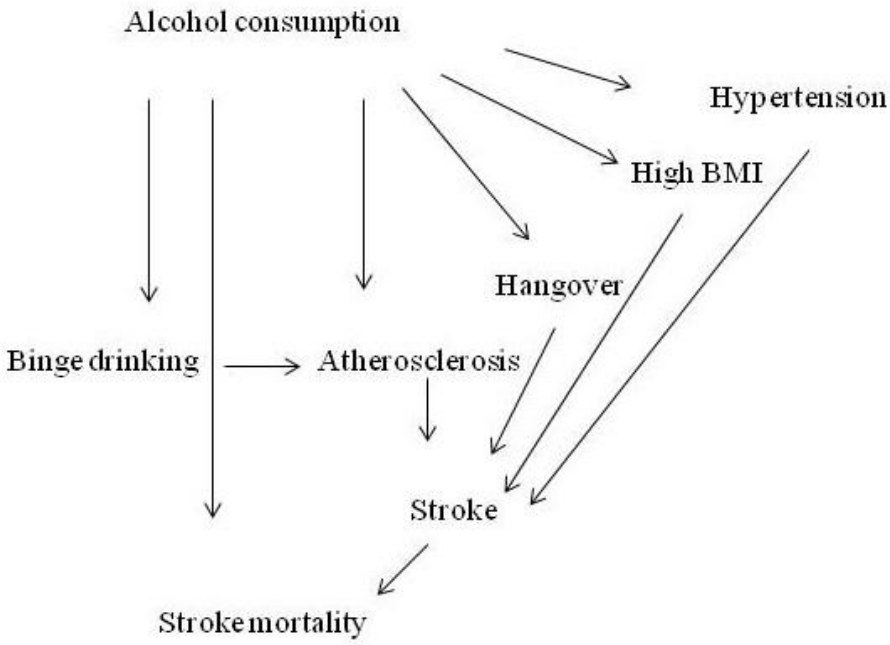

Figure 3. Schematic description about associations between alcohol consumption and atherosclerosis, stroke and stroke mortality

6.1 BINGE DRINKING AND THE PROGRESSION OF ATHEROSCLEROSIS

Binge drinking was associated with increased atherosclerotic progression at 11-year follow-up. Statistically significant relationships between maximal IMT change and plaque height were seen among men who drank ≥6 portions per one occasion.

The current findings are consistent with a previous study showing that the pattern of drinking is related to the progression of atherosclerosis (252). The previous study showed that binge drinking enhanced the progression of carotid atherosclerosis, and the association was independent of the total average of alcohol consumption at 4-year follow-up (252). Heavy drinkers were observed to be more prone to develop carotid atherosclerosis than abstainers, and this association is more significant when atherosclerotic changes in carotid arteries were more diffuse and severe (256). This indicates that the high level of alcohol intake played an important role in the progression of atherogenesis.

It has been shown that there is a greater risk of atherosclerosis when alcohol consumption is high, 14 or more drinks per week, whereas lower consumption has an inverse relationship with the progression of atherosclerosis (253). In a previous study a modest association between alcohol consumption and carotid plaques was observed in men, whereas no significant relationship between IMT and carotid plaques was seen in women (251). Common carotid artery IMT has shown to be associated with risk factors (such as alcohol consumption) for stroke, but bifurcation IMT and carotid plaque have been more directly associated with CHD (322). However, some other studies have shown no relation between alcohol drinking and carotid artery IMT (265,323).

It has been reported that alcohol consumption is associated with early atherogenesis progression and CVD risk and that association follows a J-shaped curve (254,256,324). It has been suggested that drinking more rarely than once a week has no effect on atherogenesis (254). Furthermore, light alcohol consumers who drink alcohol regularly have lower risk of atherosclerosis than heavy drinkers or abstainers (254). A J-shape association has been shown between alcohol consumption and subclinical atherosclerosis in men (325). It has also been suggested that drinking patterns and advanced atherogenesis follow a U-shaped curve (243).

It has been shown that binge drinking is related to the risk of CVD and CVD mortality (249,273). Furthermore, beer binging has also been shown to be related to fatal myocardial infarction and all-cause mortality (31). Among hypertensive men moderate alcohol consumption has been observed to be associated with a decreased risk for myocardial infarction, but not with risk for total death or CVD mortality (326).

The protective effect of moderate alcohol intake against atherosclerosis is partly explained by the effects of ethanol on lipoproteins. Alcohol drinking is associated with increased plasma concentrations of HDL-cholesterol and apo A-I. Almost half of the decrease in CHD risk is suggested to be due to an increase in plasma HDL-cholesterol and about 20% to a reduction in plasma LDL-cholesterol level (86,327,328). The protective role of moderate alcohol intake may partly be explained by interferences with haemostasis and thrombosis. Studies have also shown that ethanol alters the synthesis of prostacyclin, release of thromboxane, platelet aggregation, increases the level of endogenous plasminogen activator, depresses the concentration of LDL-cholesterol and elevates the levels of HDL-cholesterol (329-331). Heavy consumption of alcohol (>60 grams alcohol per day) may promote atherosclerosis, which is explained by platelet aggregation, the activation of the clotting cascade and the promotion of LDL- cholesterol oxidation by acetaldehyde (332).

Binge drinking seems to be associated with an increased risk of atherosclerosis progression in men, and the association is observed to be even stronger than previously reported. When studying the detrimental effects of alcohol and assessing the risk for atherosclerosis, it is important to take into the consideration drinking patterns, not only the average amount of alcohol intake.

6.2 HANGOVER AND THE RISK OF STROKE

An association between hangover and the risk of stroke was observed. At least one hangover a year is associated with an increased risk of ischaemic stroke in men. Hangover increased the risk of stroke even after total alcohol consumption was taken into consideration.

Drinking pattern is associated with the development of atherosclerotic diseases (252). Moderate alcohol consumption has been inversely related to the risk of stroke (300,333-335). Light alcohol consumption may have a protective effect on the vascular system, while heavy alcohol consumption was observed to increase the risk of all types of stroke (17) and

stroke mortality (21). Binge drinking and hangovers are related to an increased risk of ischaemic stroke and cardiovascular mortality (24). Increased cardiac work with normal peripheral resistance that occurs during hangover may be one explanation for that increase (24).

Hangover symptoms are considered to be an outcome of episodic heavy drinking (311). It has been suggested that hangover is a different phenomenon from alcoholic withdrawal, but for heavy drinkers, hangover and withdrawal may appear at the same time, and hangover is associated with the intake of high doses of alcohol (336). A previous study showed that 75% of the persons who had consumed intoxicating doses of alcohol experienced hangover at least once whereas 40% of heavy drinkers reported hangovers monthly or more regularly (336). Hangover has a strong association with binge drinking pattern of alcohol consumption (56) and it has been shown that heavy drinking, including both episodic and binge drinking, may trigger cardiogenic brain embolism (337). It has been suggested that drinking for intoxication may trigger cerebrovascular infarction in young adults (25). Heavy drinking and binge drinking during weekends are typical drinking patterns in Finland and in the Baltic countries, and these drinking patterns are much more common among men than women (32).

The mechanism for reduced risk of ischaemic stroke with light to moderate alcohol consumption may be related to an increase in HDL- cholesterol (87), a decrease in platelet aggregation (338) and low plasma fibrinogen concentration (338). The deleterious risk mechanisms for those who are heavy alcohol consumers include alcohol-induced hypertension, hypercoagulable state, reduced cerebral blood flow and AF. A previous study showed that in patients with non-valvural atrial fibrillation (NVAF), history of stroke was far more frequent than history of myocardial infarction, with alcohol consumption being most frequent in patients with NVAF (339). Another study showed that the prevalence of AF was significantly higher in patients who had died at 5-year follow-up compared to those who survived (340). Although alcohol has some favourable effects on blood lipids and haemostatic factors, it also increases blood pressure (341), which is one of the most important determinants of stroke risk. Binge drinking increases both SBP and DBP during the intoxication period although no significant differences were observed in blood pressure values during the hangover period (341). Heavy drinking on one occasion has been shown to be associated with an increased risk of hypertension (342). Daily alcohol consumption was also associated with lobar haemorrhage (343).

6.3 ALCOHOL CONSUMPTION AND THE RISK OF STROKE AMONG HYPERTENSIVE AND OVERWEIGHT MEN

Our study showed an association between alcohol consumption and the risk of stroke among men with hypertension and overweight. Hypertension and overweight with the presence of alcohol consumption were related to an elevated risk of stroke, whereas normal blood pressure and body weight with alcohol drinking were not associated with an increased risk of stroke. We also observed that the risk of any stroke was increased among hypertensive binge drinkers and men who were both overweight and binge drinkers.

It has been shown that hypertension increases the risk of developing stroke (344). Alcohol drinking pattern may be an important factor in the pathogenesis of alcohol-related hypertension, since a study found a significant increase in blood pressure levels among those who drank on a daily basis as compared to those who drank only on 2-3 days, as in weekend drinking (345). It has been reported that a reduction in alcohol consumption may lower blood pressure corresponding to 18% decrease in the incidence of death from stroke (346). It has been shown that patients with previous stroke had a higher BMI and slightly elevated blood pressure although they did not consume alcohol (347).

Some studies have shown that BMI is a strong risk factor for stroke (289,348). The relationship between alcohol consumption and BMI is complex and may be confounded by other behaviours, such as smoking, dietary intake, and levels of physical activity. Overweight and obese men are shown to be at risk of total, ischaemic and haemorrhagic stroke (289). Low alcohol consumption has been shown to be connected with good dietary habits (349). The role of hypertension as a mediator between obesity and stroke has been shown in the earlier studies (350,351). Therefore, excess weight gain is a key risk factor for increased blood pressure in most patients with essential hypertension.

Obesity raises blood pressure by increasing renal tubular reabsorption, impairing pressure natriuresis and causing volume expansion (352). Patients with stroke are prone to lose weight and that weight loss correlates with poor outcome. The catabolic signalling stimulates tissue degradation and changes in body composition which may have an impact on recovery and survival (353). The relationship between alcohol consumption and cardiovascular risk factors is not clear. Even low alcohol consumption may increase blood pressure. Alcohol consumption also increases serum HDL- cholesterol level, decreases fibrinogen and reduces the activation and aggregation of platelets. It is possible that endothelial dysfunction promotes the macrovascular complications of hypertension, such as myocardial infarction and stroke, because the endothelium regulates vascular tone and structure, but it also exerts anti-inflammatory and antithrombotic effects, which are mediated by nitric oxide (354).

6.4 ALCOHOL CONSUMPTION AND STROKE MORTALITY

An association was observed between frequency of alcohol consumption and stroke mortality. The current study shows a fairly strong association between the frequency of alcohol consumption and stroke mortality, as the risk of stroke death was increased among men who consumed alcohol >2.5 times per week.

Previous studies have shown that the frequency and total alcohol consumption is related to the risk of stroke (22,260,262). An increased risk of mortality from stroke with the amount of alcohol consumed has been found, indicating a J-shaped relation between them (263,267). A cohort study of Scottish men showed a strong positive relation between alcohol consumption and risk of mortality from stroke (260). In that study those men who drank over 35 units of alcohol per week had a two-fold risk of death from stroke compared to the risk of non-drinkers (260). An increased risk of mortality from stroke has been seen with 15-21 units of alcohol (305).

Light to moderate drinking has not been shown to have protective effect against death from stroke (263), while other studies suggested that light alcohol consumption may provide a protective effect on the vascular system, whereas heavy alcohol consumption was observed to increase the risk of all types of stroke (17) and stroke mortality (21). Results from cohort studies have also shown heavy alcohol consumption to be associated with increased mortality from any stroke (263), especially haemorrhagic stroke (355). Furthermore, the Kangwha cohort study showed that binge-drinkers who drank daily had higher stroke mortality risk than non-drinkers (356). Drinking habits are also associated with the risk of death from stroke (21,31).

Some previous studies on alcohol consumption and stroke mortality have shown contradictory findings. This may be due to the slightly different pathophysiology of haemorrhagic stroke and ischaemic stroke (267). Patients with haemorrhagic stroke are generally considered to be at high risk for mortality compared to patients with infarcts due to ischaemic stroke (261,262). There are studies that have found a reduced risk of stroke among moderate drinkers (357) as well as studies indicating either an increased risk (263,357) or no effect on ischaemic stroke among heavy drinkers (358). Light or moderate

alcohol consumption has been shown to have a protective effect against ischaemic stroke (359). However, heavy alcohol consumption was associated with an increased risk of stroke mortality (307).

The association of AF, CHD and diabetes with the risk of ischaemic stroke as well as the risk of death from stroke is well-established in comparative studies, although the role of risk factors such as hypertension, smoking and alcohol consumption has been controversial (240,360,361). Diabetes, AF, intermittent claudication (262), previous myocardial infarction, and stroke (240,262) were shown to be associated with recurrent ischaemic stroke increasing the risk of death from stroke. It has been suggested that smoking and alcohol consumption are more likely related to the risk of haemorrhagic stroke, which increases the risk of death (262). Some studies have shown the risk of haemorrhagic stroke increased together with increasing alcohol consumption (260,263).

The INTERSTROKE study showed that approximately 90% of stroke morbidity could be explained by common risk factors including alcohol consumption (98). A previous study has shown that high alcohol consumption may lead to the dose-related increase in blood pressure (283) that is commonly related to an increased risk of stroke.

On the basis of our study, we found that a high frequency of alcohol consumption (>2.5 times per week) was related to an elevated risk of fatal stroke events even when the amount of alcohol consumption was taken into account with other risk factors. The frequency of drinking might be one of the factors that should be considered in the prevention of fatal stroke.

6.5 METHODOLOGICAL ASPECTS

6.5.1 Study population

The strengths of this study include its prospective population-based design with reliable data on carotid ultrasound at baseline and 11-year follow-up, reliable assessment of causes of stroke and stroke mortality, supplemented with data on health status and risk factors and exclusion of a history of stroke at baseline.

Only men were included in this study. The proportion involved in binge drinking is generally higher among men than among women (362). The study design does not allow generalisation to other ethnic groups or women.

6.5.2 Measurement of alcohol consumption

The measurement of alcohol drinking habits was based on a self-reported questionnaire, which was a limitation of this study. There may thus be a possibility of underreporting and other misclassification by subjects. Despite this, there is no reason to think that reporting bias could be systematically different across various drinking groups (252). On the other hand, it is shown that self-administrated questionnaires seem to be less affected by social desirability and interviewer effects (354). A follow-up study is prone to recall errors because of the relatively long recall period (363).

Since the definition of hangover is not simple, misclassification by subjects may have been possible. As the drinking habits were based on a questionnaire, there may be a possibility of underreporting and other misclassification by subjects. A single validated way to measure hangover would allow comparisons between studies (336). Additionally, the definition of hangover is not simple, as hangover symptoms vary widely and there are many explanatory hypotheses of hangover. One hypothesis is that hangover is the first phase of acute alcohol withdrawal, but there are different stages of alcohol withdrawal such as minor, major and *delirium tremens*, and hangover could only be explained by minor alcohol withdrawal. The minor alcohol withdrawal symptoms appear within 24 h after

cessation of alcohol intake while hangover appears a few hours after alcohol consumption and lasts for a maximum 24 h (336).

6.5.3 Assessment of carotid atherosclerosis with ultrasound

Carotid ultrasound is an easily available, safe, inexpensive, reliable and reproducible non-invasive method measuring the incidence and progression of atherosclerosis. Subclinical atherosclerosis can be best assessed in selected arterial segments by using the B-mode ultrasound (364). The measure of subclinical atherosclerosis with ultrasound is a very useful method for assessing vascular risk together with traditional risk factors (322). It has been shown that traditional risk factors (age, sex, smoking, SBP, DBP, blood pressure-lowering medication and lipid-lowering medication and diabetes) can explain 19.5% of the variance in the total plaque area burden, and adding some other risk factors (such as moderate alcohol consumption and LDL- cholesterol) to the traditional model, contributed an additional 2.4%, explaining 21.9% of the variance in total plaque area burden (365).

6.5.4 Outcome measures

The outcome definitions of stroke and stroke mortality were based on the ICD-9 and ICD-10 diagnoses available in the three administrative registries used in Finland: the National Hospital Discharge Registry, the National Causes of Death Registry and FINMONICA stroke registry. These registries have high coverage and diagnosis accuracy (6,366). Diagnostic information was classified by a neurologist.

6.5.5 Bias and confounding

In the KIHD study the participants filled in comprehensive questionnaires and participated in examinations at the study site. It is possible that those with poorer health may have refused to participate in the study. Thus, it is possible that this might have caused some oversampling of participants who were healthier than the population in general. Those who declined might have had different alcohol drinking patterns as well. Selection bias may have also occurred during the study if those with better health were more likely to continue in the follow-up and those with poorer health were more likely to drop out.

The covariate measures involved varying degree of accuracy, and there is a possibility for unmeasured confounders that were not adjusted for. This brings up the possibility of at least some residual confounding effect remaining in the findings. In the ultrasound measurements there is a possibility of intra- and inter-sonographer and reader variability. Our sonographers and readers were qualified and experienced, so this is not considered a remarkable source of error.

6.5.6 Strengths and limitations of study

The strengths of the study include that we had incident stroke and stroke mortality in the prospective study. We had a reliable data on carotid ultrasound and reliable outcome definitions on stroke and stroke mortality. Carotid ultrasound is a reproducible and non-ivasive method measuring the different changes of atherosclerosis in carotid artery. Our sonographers and readers were very qualified. The outcome definitions of stroke and stroke mortality were based on the ICD-9 and ICD-10 diagnoses available in the following registries used in Finland: the National Hospital Discharge Registry, the National Causes of Death Registry and FINMONICA stroke registry. These registries have high coverage and diagnosis accuracy (366),(6). Diagnostic information was classified by a neurologist.

The following limitations need to be taken into the considerations. This study does not allow generalisation to women and other ethnic groups. We assessed alcohol consumption bu using a self-reported questionnaire and underreporting is possible. Misclassification by subjects is possible, because the definition of hangover is not simple. It is possible that oversampling of healthier participants is possible, because those with poorer health may have refused to participate in the study. The selection bias may also have occurred during

the study and there is a possibility for unmeasured confounders. Alcohol consumption and drinking pattern can also change over the time.

6.6 GENERALISABILITY OF THE FINDINGS

The results of this study can be generalised to those populations that have a similar drinking culture and drinking patterns as in Finland. A study of four Nordic countries has reported that even though Denmark, Sweden, Norway and Finland are culturally quite homogeneous countries, there are differences in the ways alcohol is used. Annual alcohol consumption has, at least until recently, been highest among the Danish population (311). The differences in alcohol consumption between these countries can mainly be explained by difference in the frequency of drinking, and to a lesser degree by the amount of alcohol used per occasion. The estimated quantities drunk by men on a drinking occasion have been larger in Finland and Norway than in Denmark. The frequency of heavy drinking occasions, on the other hand, has been highest in Denmark and lowest in Norway (311). Comparing with other European countries, the highest frequency of drinking has been seen in southern and central European countries and the lowest in northern countries (367). In Northern Europe, the frequency of binge drinking has generally decreased by age, and the quantities consumed to get drunk have decreased by age in Northern Europe as well as in the United Kingdom. In Southern Europe (basically in France) the findings have been the opposite (367).

In the studies included in this thesis, the sample included only men. Thus, one should be cautious about outright generalisation of the results to women. It has been reported, however, that compared to many other parts of Europe, drinking habits between genders are currently much more similar in all Nordic countries. This has been shown in Nordic statistics regarding abstaining, frequency of drinking in general, and the frequency of binge drinking among men and women (367).

7 Conclusions

Based on the findings from these studies, the following conclusions were made:

1. Binge drinking is associated with an increased risk of atherosclerosis progression in men. It is important to take into consideration drinking patterns, not only the average amount of alcohol.

2. Hangover, even once per year, is related to an increased risk of ischaemic stroke in men.

3. Hypertensive and overweight men who consume alcohol are at an increased risk of stroke.

4. There seems to be a fairly strong association between the frequency of alcohol consumption and stroke mortality.

8 Implications for practice and future research

To reduce the risk of stroke, any heavy consumption of alcohol should be avoided. Stroke is one of the most important causes of death, and exposure to alcohol use is projected to increase proportionately with growing wealth (368). Thus, alcohol-attributable stroke burden will continue to increase globally in lack of more effective alcohol policies and control measures (369). Despite some evidence showing moderate alcohol drinking to decrease the risk of stroke (22), the implications of these findings should be examined cautiously. Any advice regarding the consumption of alcohol should be customised to the individual´s risks and potential benefits, because the harmful effects of heavy alcohol consumption often overtake the possible beneficial ones.

In this thesis, alcohol consumption, progression of carotid atherosclerosis and the risk of stroke and stroke mortality were examined in an Eastern Finnish male population. Although it has been reported that drinking habits between genders are quite similar in northern countries (367), it would be interesting to carry out similar studies on alcohol and stroke among women.

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Sanna Rantakömi

Alcohol Consumption, Atherosclerosis and Stroke

Epidemiologic Follow-up Study in Middle-aged Finnish Men

Stroke is the second leading cause of death worldwide after heart disease. It is estimated that 16,803 strokes occur in Finland every year. Alcohol consumption plays a role in the progression of atherosclerosis and it is related to an increased risk of stroke. This study clarified the role of binge drinking as a risk factor for progression of carotid atherosclerosis, the relation of hangover with the risk of stroke, the role of alcohol consumption in the risk of stroke at different levels of blood pressure and body weight, as well as the association between alcohol consumption and stroke mortality.

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