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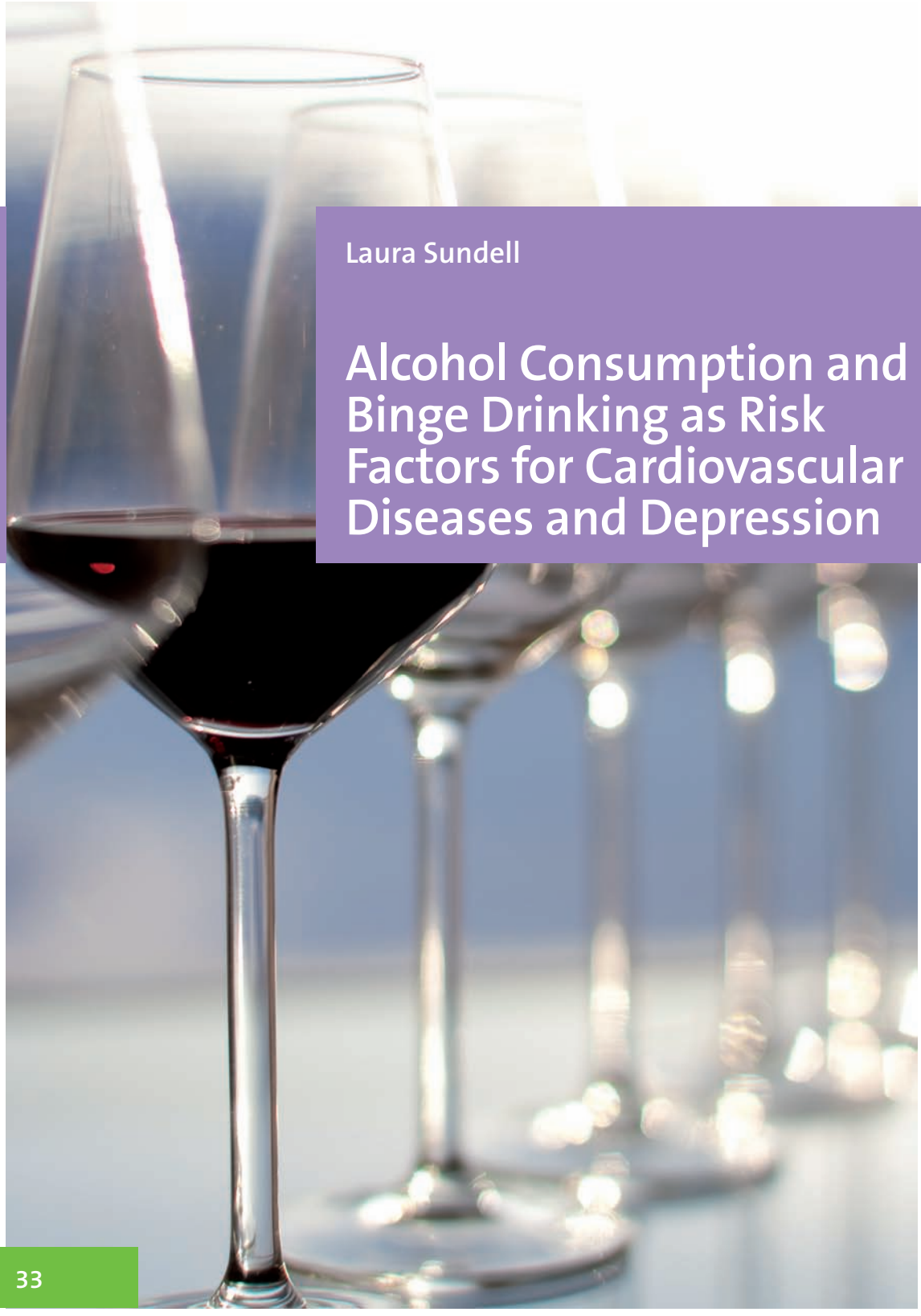

RESEARCH

Laura Sundell

Alcohol Consumption and Binge Drinking as Risk Factors for Cardiovascular Diseases and Depression

Laura Sundell

Alcohol consumption and binge drinking as risk factors for cardiovascular diseases and depression

Academic dissertation

To be presented with the permission of the Faculty of Health Sciences, School of Medicine, of the University of Eastern Finland for public examination in the lecture hall L1 in Canthia building, on 22 May 2010, at 12 noon.

Department of Chronic Disease Prevention
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and

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Abstract

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Research has shown alcohol consumption to be both harmful and beneficial to health.

Heavy alcohol consumption is associated with elevated risk for all-cause mortality compared to moderate drinking. Furthermore, the lower mortality related to moderate drinking is attributed to lower risk for coronary heart disease. Traditionally, alcohol consumption has been assessed in terms of average alcohol consumption with little or no regard for different drinking patterns. Within the past few years, however, studies have shown that drinking patterns may modify the effects of alcohol on health independently of average alcohol consumption.

The aim of this thesis was to investigate the role of binge drinking as a potential risk factor for mortality and morbidity.

All four studies were based on the FINRISK population cohorts recruited in 1987, 1992 and 1997. The data were further linked to the two administrative registers used in Finland: the Finnish Hospital Discharge Register for non-fatal cases and the Causes of Death Register for fatal cases.

Study I demonstrated binge drinking to be a risk factor for all-cause mortality, IHD mortality, mortality due to external causes and alcohol-related diseases independently of average alcohol consumption.

Study II showed ex-drinkers and binge drinkers to experience more depressive symptoms than do lifelong abstainers and subjects with no binge drinking pattern. Furthermore, binge drinking was found to associate with depression independent of average alcohol consumption and other potential confounders, although age and gender altered this association.

Study III found binge drinking to be an independent risk factor for total and ischemic strokes, and Study IV found that binge drinkers had higher fibrinogen levels than did non-binge drinkers. Furthermore, we found that fibrinogen only slightly mediates the increased risk for coronary endpoints related to binge drinking; the underlying mechanism remains unknown.

In summary, this series of studies demonstrated that binge drinking should be considered an independent risk factor for mortality and morbidity due to coronary heart disease and stroke. In addition, binge drinking seemed to associate with depression. These results suggest that alcohol drinking patterns modify the effects of alcohol consumption and should be included in further studies evaluating the effects of alcohol on health.

Keywords: Alcohol drinking, cardiovascular disease, depression, risk factor, epidemiology

Tiivistelmä

Laura Sundell. Alcohol consumption and binge drinking as risk factors for cardiovascular diseases and depression. [Alkoholin kulutus ja runsas kertajuominen sydän- ja verisuonisairauksien sekä masennuksen riskitekijänä]. Terveyden ja hyvinvoinnin laitos (THL), Tutkimus 33, 123 sivua. Helsinki 2010.
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Alkoholin käytöllä tiedetään olevan terveyden kannalta sekä myönteisiä että kielteisiä vaikutuksia.

Alkoholin runsaan kulutuksen tiedetään olevan yhteydessä lisääntyneeseen kokonaiskuolleisuuteen kun taas kohtuukäytön tiedetään vähentävän sepelvaltimotauti-riskiä. Alkoholin kulutusta on perinteisesti tutkittu määrittämällä alkoholin käyttömääriä jolloin erilaiset juomatavat ovat jääneet huomiotta. Viime vuosina on kuitenkin huomattu, että alkoholin juomatapa vaikuttaa terveyteen juodun alkoholin kokonaismäärästä riippumatta.

Tämän tutkimuksen tarkoituksena oli selvittää kerralla runsaasti juomisen merkitystä kuolleisuuden ja sairastavuuden riskitekijänä.

Kaikki neljä osajulkaisua pohjautuivat FINRISKI-väestötutkimusaineistoihin vuosilta 1987,1992 ja 1997. Aineisto yhdistettiin sairaalapoistorekisteriin ja kuolinsyyrekisteriin.

Tutkimuksessa 1, alkoholin runsaan kertajuomisen havaittiin olevan kokonaiskuolleisuuden, sepelvaltimotautikuolleisuuden, ulkoisten kuolinsyiden sekä alkoholiperäisten kuolinsyiden riskitekijä juodun alkoholin kokonaismäärästä riippumatta.

Tutkimuksessa 2, alkoholin käytön lopettaneilla ja kerralla runsaasti juovilla havaittiin olevan enemmän masennusoireita kuin ikänsä raittiina olleilla ja niillä jotka eivät nauttineet alkoholia runsaasti kerralla. Edelleen huomattiin, että alkoholin runsas kertajuominen oli yhteydessä masennukseen juodun alkoholin kokonaismäärästä ja muista sekoittavista tekijöistä riippumatta.

Tutkimuksessa 3, alkoholin runsaan kertajuomisen havaittiin olevan aivohalvausten ja iskeemisten aivohalvausten riskitekijä juodun alkoholin kokonaismäärästä riippumatta.

Tutkimuksessa 4 havaitsimme että runsaasti alkoholia kerralla juovilla on korkeammat fibrinogeeni-pitoisuudet verrattuna niihin jotka eivät juo runsaasti kerralla. Lisäksi havaitsimme että runsaaseen kertajuomiseen liittyvä

lisääntynyt sydäntapahtumien riski välittyy vähäisessä määrin fibrinogeenin välityksellä. Selittävä mekanismi on kuitenkin vielä tuntematon.

Tiivistetysti tutkimuksemme osoittivat, että alkoholin runsas kertakulutus lisää sepelvaltimotautitapahtumista ja aivohalvauksista johtuvaa kuolleisuutta ja sairastavuutta juodun alkoholin kokonaismäärästä riippumatta. Lisäksi havaitsimme että alkoholin kulutus oli yhteydessä masennukseen. Nämä tulokset osoittivat että alkoholin juomatapa muokkaa alkoholin vaikutuksia ja tämän takia tulevaisuuden alkoholin terveysvaikutuksia käsittelevissä tutkimuksissa pitäisi huomioida alkoholin eri juomatavat.

Avainsanat: Alkoholin kulutus, sydän- ja verisuonisairaus, masennus, riskitekijä, epidemiologia

Sammandrag

Laura Sundell. Alcohol consumption and binge drinking as risk factors for cardiovascular diseases and depression. Institutet för hälsa och välfärd. Forskning 33, 123 sidor. Helsinki, Finland 2010.
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Man känner till att alkohol inverkar både positivt och negativt på hälsan.

Stor konsumtion av alkohol sammanhänger med ökad totaldödlighet medan måttlig konsumtion minskar risken för att insjukna i kransartärsjukdom. Alkoholkonsumtionen har traditionellt undersökts genom definition av mängden konsumerad alkohol, men dryckesvanorna har inte beaktats. Under de senaste åren har man dock observerat att dryckesvanorna inverkar på hälsan oavsett den totala mängden konsumerad alkohol.

Syftet med denna studie var att kartlägga hur större engångsintag av alkohol inverkar på dödligheten och risken att insjukna.

De fyra delpublikationerna baserar sig på materialet i FINRISKI-undersökningarna från åren 1987, 1992 och 1997. Materialet kombinerades med uppgifterna i vårdanmälningsregistret och dödsorsaksregistret.

I undersökning 1 konstaterades större engångsintag av alkohol utgöra en riskfaktor avseende den totala dödligheten samt dödligheten i kransartärsjukdom, till följd av yttre orsaker och till följd av alkoholrelaterade orsaker oavsett den totala mängden konsumerad alkohol.

I undersökning 2 konstaterades att personer som helt slutat använda alkohol och personer som intar större mängd alkohol på en gång har mer depressionssymtom än helt nyktra personer och personer som inte intar större mängd alkohol på en gång. Vidare konstaterades att större engångsintag av alkohol sammanhänger med depression oavsett den totala mängden konsumerad alkohol och andra faktorer.

I undersökning 3 konstaterades att större engångsintag av alkohol utgör en riskfaktor avseende stroke och ischemisk stroke oavsett den totala mängden konsumerad alkohol.

I undersökning 4 konstaterades att personer som intar större mängd alkohol på en gång har högre fibrinogenhalt i blodet än personer som inte gör det. Därtill konstaterades att den ökade risk för hjärtstörningar som sammanhäng-

er med stort engångsintag av alkohol i någon mån är relaterad till fibrinogen. Den underliggande mekanismen är tillsvidare okänd.

Sammanfattningsvis visar studierna att stort engångsintag av alkohol ökar dödligheten och insjuknandet i kransartärsjukdom och stroke oavsett den totala mängden konsumerad alkohol. Därtill konstaterades ett samband mellan alkoholkonsumtion och depression. Resultaten visar att dryckesvanorna inverkar på alkoholens effekter och därför borde vanorna beaktas i framtida studier gällande alkoholens inverkan på hälsan.

Nyckelord: Alkoholkonsumtion, kardiovaskulär sjukdom, depression, riskfaktor, epidemiologi

Abbreviations

ANOVA	Analysis of variance
AUDIT	Alcohol Use Disorders Identification Test
BDI	Beck Depression Inventory
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular diseases
HDL	High density lipoprotein
HR	Hazard ratio
ICD	International Classification of Diseases
ICH	Intracerebral haemorrhage
IDL	Intermediate density lipoprotein
IHD	Ischemic heart disease
LDL	Low density lipoprotein
MI	Myocardial infarction
MONICA	Multinational **moni**toring of trends and determinants in **ca**rdiovascular disease
NIAAA	National Institute on Alcohol Abuse and Alcoholism
OR	Odds ratio
RR	Relative risk
SAH	Subarachnoid haemorrhage
VLDL	Very low density lipoprotein
WHO	World Health Organisation

List of original publications

I Laatikainen T, Manninen L, Poikolainen K, Vartiainen E. Increased mortality related to heavy alcohol intake pattern. J Epidemiol Community Health. 2003, 57 (5):379-84.

II Manninen L, Poikolainen K, Vartiainen E, Laatikainen T. Heavy drinking occasions and depression. Alcohol Alcohol. 2006, 41(3):293-9.

III Sundell L, Salomaa V, Vartiainen E, Poikolainen K, Laatikainen T. Increased stroke risk is related to a binge drinking pattern. Stroke. 2008; 39:3179-3184.

IV Sundell L, Laatikainen T, Vartiainen E, Poikolainen K, Salomaa V. Binge drinking and increased risk for coronary events: the role of fibrinogen as a mediating factor. (Manuscript)

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Contents

1 Introduction

Research has shown alcohol consumption to be both harmful and beneficial to health. Cumulative evidence shows that alcohol consumption is associated with all-cause mortality in a U- or J-shaped manner, depending on the study. Light to moderate alcohol consumption is associated with decreased mortality compared with non-drinkers. The highest mortality has been observed among heavy drinkers (1) .The increased mortality related to heavy alcohol consumption is attributed to certain cancers, cirrhosis, pancreatitis, stroke, external causes of deaths and accidents. In addition, studies have shown depression to associate with heavy alcohol consumption. The lower mortality related to moderate alcohol consumption is due to a lower risk for coronary heart disease (2).

Epidemiological studies have traditionally assessed alcohol consumption in terms of average alcohol consumption and tend to disregard different drinking patterns. However, recent research has shown that alcohol drinking patterns may modify the effects of alcohol beyond just the volume measurements and could lead to different health outcomes (3, 4).Although the effects of different drinking patterns on health remain unclear, some studies have reported that consuming large amounts of alcohol over a short period of time (often described as binge drinking) increases the risk for mortality due to cardiovascular diseases independent of the total amount of alcohol consumed (5). The mechanisms by which binge drinking increases the risk for CVD have not yet been fully investigated, but adverse lipid composition, effects on coagulation and blood pressure are considered potential pathways (6).

This study assessed the role of binge drinking as a risk factor for cardiovascular disease morbidity and depression. Depression was included in this thesis because of its association with CHD (7) and its importance as a public health problem.

2 Review of the literature

2.1 Alcohol consumption: definitions and measurements

Average alcohol consumption

Alcohol consumption is often measured as the average amount of alcohol consumed over a long period of time (e.g., the past 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?) Consumption is calculated by multiplying the quantity and frequency measurements. The short-term recall method asks about the actual alcohol consumption over a specific period, often a week. Average alcohol consumption estimates habitual alcohol consumption over a longer period of time and is based purely on the volume of alcohol consumed (8).

Heavy drinking occasions and binge drinking

Heavy drinking occasions and binge drinking refer to drinking patterns with large amounts of alcohol consumed over a short period of time. The criteria for heavy drinking occasions or binge drinking vary between studies, but six or more drinks on one drinking occasion for men is widely used. Furthermore, the widely used AUDIT questionnaire includes a question on six or more drinks consumed at one time (9). Another common criterion is five or more drinks for men and four or more for women. Information on heavy drinking occasions is usually drawn from quantity questions (On those days when you drink alcohol, how much alcohol you usually drink?). This type of question provides information on the usual amount of alcohol consumed per typical drinking occasion, but fails to distinguish typically light consumption from occasional heavy drinking. For example, one person might drink one alcoholic beverage every day and the other might drink one alcoholic beverage every day plus ten beers on Friday evening, yielding roughly the same quantity per typical drinking occasion.

Heavy episodic drinking

A synonym for binge drinking is heavy episodic drinking. In addition to the definition of six or more drinks consumed on one occasion, a blood alcohol level above 0.8 g/l or 1 g/l has also been used. The NIAAA suggests five or more (four or more for women) drinks in two hours as an appropriate measure for binge drinking because this typically results in a blood alcohol content of 0.8 g/l (10).

2.2 Definition of atherosclerosis and atherosclerotic cardiovascular diseases (CVD)

Atherosclerosis

Atherosclerosis indicates thickened and hardened lesions in the medium-sized and large muscular, elastic arteries. These lesions are rich in lipids and occur within the intima (the inner layer of the artery). Processes involved in the pathogenesis of atherosclerosis include lipid accumulation, disrupted endothelial function, inflammation, smooth muscle cell proliferation in the intima, plaque erosion and thrombus formation (11). Clinical manifestations of atherosclerotic cardiovascular disease (CVD) include coronary heart disease (CHD), stroke and peripheral artery disease (12). Cardiovascular diseases also include non-atherosclerotic cardiovascular diseases, namely rheumatic heart disease and inflammatory heart disease.

Coronary heart disease

Coronary heart disease (CHD) refers to atherosclerotic manifestation in coronary arteries supplying the heart muscle. Coronary heart disease typically manifests as chest pain. Myocardial ischemia results from an imbalance between oxygen demand and supply in the myocardium. Myocardial infarction (MI) most often results from a non-occlusive or occlusive thrombus formation usually in narrowed atherosclerotic arteries (12).

Stroke

Stroke is defined as acute-onset focal loss of cerebral function. Symptoms of stroke persist for at least 24 hours, whereas similar symptoms lasting less than 24 hours indicate transient ischemic attack. Strokes include ischemic strokes and haemorrhages. Haemorrhages include intracerebral (ICH) and subarachnoidal bleedings (SAH). In Western populations, over 80% of all strokes are of ischemic origin. Atherosclerosis of the carotid arteries accounts for over 30% of ischemic strokes (13). Other causes of ischemic stroke include cardiogenic embolisms and small vessel atherosclerosis.

2.3 Alcohol and all-cause mortality

The effects of average alcohol consumption on all-cause mortality have been studied widely. Most prospective studies have noted a J-shaped curve between average alcohol consumption and all-cause mortality, and have found that moderate consumers of alcohol, who consume on average up to four drinks a day for men and up to two drinks a day for women, have lower all-cause mortality than do abstainers. The highest risk for mortality has been found among heavy drinkers (1, 14, 15, 16, 17, 18, 19). A large meta-analysis of 34 prospective studies found that alcohol consumption of up to 42 g/day was associated with lower mortality than among abstainers, and the lowest mortality occurred at 6 g/day (1). The increased risk for mortality related to high average alcohol consumption is attributed to cancers of the oral cavity, pharynx, larynx, oesophagus, colon, rectum, liver and breast, as well as cirrhosis, chronic pancreatitis, stroke, external causes of deaths and accidents. On the other hand, the lower mortality risk associated with light to moderate alcohol consumption is due mainly to the lower risk for coronary heart disease (2).

The selection of non-drinkers (abstainers) as a reference group has been questioned (20). The non-drinking category may include subjects who have quit alcohol consumption due to health problems or problem drinking in the past and are therefore at higher risk of death than are lifelong abstainers; consequently, such subjects may be responsible for the higher mortality among abstainers compared to light to moderate drinkers (a phenomenon known as the sick-quitter hypothesis) (16, 21). Distinguishing ex-drinkers from lifelong abstainers provides more accurate estimates on mortality due to no alcohol consumption at all than does grouping all abstainers together. If ex-drinkers are excluded from the reference group, the protective effect of moderate consumption has been shown to be lower than in those studies that included former drinkers in the reference group (1, 22).

Almost all studies evaluating the effects of average alcohol consumption on all-cause mortality are based on estimates of alcohol consumption obtained with quantity-frequency questionnaires, which tend to disregard patterns of drinking. For example, with the same average alcohol consumption per week, one could drink 2 drinks per day with no variation and the other could drink 14 drinks in a single day. Recent research has shown that alcohol drinking patterns may modify the effects of alcohol beyond the volume measurements and lead to different health outcomes (3, 4, 23).

Table 1 lists the prospective cohort studies on all-cause mortality that have taken into consideration the drinking pattern in addition to the volume measurements.

For the same average alcohol consumption, a habit of infrequent drinking has been associated with higher mortality than one of frequent drinking (24, 25). Fur-

Table 1 Summary of prospective studies on alcohol drinking patterns and all-cause mortality

Reference	Study population	n men/women age	Outcome follow-up time	Drinking pattern definition	Adjustment for average alcohol consumption
Tolstrup et al. 2004	Denmark, population-based cohort study	N = 56 535 26 909 men 29626 women Age 55-65 y	Total mortality, 6.8 years	Frequent vs. non-frequent drinkers (at least twice per week vs. rarely)	Yes. Based on quantity-frequency questionnaire
Rehm et al. 2001	USA, population-based cohort study	N = 5072 2037 men 3035 women Age > 18 y	Total mortality, 11.3 years	Heavy drinking occasions vs. no heavy drinking occasions (8 drinks/ occasion or getting drunk at least monthly)	Yes. Based on quantity-frequency questionnaire
Malayutina et al. 2002	Russia, population-based cohort study	N = 6502 men Age 25-64 y	Total mortality, 9.5 years (separate analyses for CVD/CHD/external-cause mortality)	Binge drinking vs. moderate drinking (binge drinking definition: > 160 g alcohol per typical drinking occasion)	Yes. Analysed separately by quantity categories and frequency categories
Kauhanen et al. 1997	Finland, population-based cohort study	N = 1641 men Age 42-60 y	Total mortality, 7.7 years (separate analyses for CVD/external-cause mortality and fatal MI)	Binge drinking vs. moderate consumption (Binge drinking definition: 6 or more beer/occasion)	Yes. Based on quantity frequency questionnaire
Baglietto et al. 2006	Australia, population-based cohort study	N = 41 528 men and women Age 27-75 y	Total mortality, 10.5 years	Average alcohol consumed in 1-3 d vs. same amount consumed in 4-6 d.	Yes. Based on quantity-frequency questionnaire and diary
Mukamal et al. 2005	USA, cohort of subjects hospitalised due to acute MI	N = 1919 men and women	Total mortality and cardiovascular disease mortality after acute MI	Binge drinking vs. non-binge drinking	Analysed separately by volume categories (light, heavy)

thermore, with the same average alcohol consumption, heavy drinking occasions have been associated with higher mortality than alcohol consumption without heavy drinking occasions (5, 26). An American cohort study of subjects hospitalised due to acute MI showed a double risk for all-cause mortality and CVD mortality among binge drinkers than among abstainers and non-binge drinkers (27). A Russian study found that occasional binge drinking showed no association with increased mortality, whereas frequent binge drinking increased the risk (28). Despite the variety of ways to measure drinking patterns, infrequent drinking, occasional heavy drinking and habitual drinking with binges have all been associated with higher mortality than habitual light to moderate alcohol consumption without episodes of heavy drinking.

Reference category	Further adjustments	Results
Very light drinkers (less than one, but more than zero drinks per week)	Diseases before baseline, education, smoking, BMI, diet	Higher mortality risk related to non-frequent consumption pattern with the same average consumption. HR 1.25 (CI: 0.70-2.24) for non-frequent, > 20 drinks per wk among men. HR 2.19 (CI: 1.15-4.17) for non-frequent > 20 drinks per week among women.
Lifetime abstainers	Income, marital status, smoking	RR 1.62 (CI : 0.86-3.07) men RR 1.08 (CI : 0.15-7.93) women for occasional heavy drinkers with low average consumption. J-shaped curve for average alcohol consumption. Higher mortality among occasional heavy drinkers, RR not significant.
Moderate drinkers (< 80 g per typical drinking occasion)	Age, education, blood pressure, smoking, BMI, total cholesterol	Episodic binge drinking was not associated with increased mortality whereas frequent binge drinking increased mortality. RR 1.05 (CI: 0.80-1.36) for binge drinking with occasional binge episodes. RR 1.61 (CI: 1.04-2.50) for binge drinkers with frequent binge episodes.
Less than 3 bottles of beer on a typical drinking occasion	Smoking, leisure time physical activity, occupational status, marital status, social contacts, depression, previous diseases, systolic blood pressure, LDL, HDL, fibrinogen, BMI	Higher mortality risk related to the binge drinking habit. RR 2.05 (CI: 1.01-4.14) for binge drinkers compared to that for non-binge drinkers.
Alcohol consumption in 7 days/week	Age, sex, country of birth, education, smoking, physical activity, household size, previous medical conditions, fruit and vegetable intake, total energy intake, saturated fat, BMI.	With the same average alcohol consumption, the number of drinking days was inversely associated with mortality in men. HR 0.96 (CI: 0.92-1.00) per additional drinking day for men. For women, the minimum mortality rate at 4 drinking days/week and maximum at 7 days/week. (HR at 4 versus 7 drinking days: 0.65; 95% CI 0.47-0.90).
Separate analyses for abstainers and non-binge drinkers as a reference category	Age, sex, BMI, marital status, race, income, education, physical activity, smoking, medical history, thrombolytic therapy and medications	Higher all-cause and cardiovascular mortality after acute MI among binge drinkers than among non-binge drinkers and abstainers.

2.4 Alcohol and coronary heart disease

Several studies have assessed the effects of average alcohol consumption on coronary heart disease mortality. Most cohort studies have shown an inverse (29) or shallow U-shaped (30, 31) relationship between average alcohol consumption and coronary heart disease mortality. Moderate alcohol consumers have been found to have lower coronary heart disease mortality than abstainers (30, 31). Lower mortality has been observed with an average alcohol consumption of one to three drinks a day (32). One case-control study showed that those subjects who consumed alcohol regularly and had consumed alcohol in the 24 hours before myocardial infarction had lower risk for MI than did those who had consumed no alcohol in the 24 hours prior to MI (33).

Though the vast majority of studies have found moderate regular alcohol consumption to protect against coronary heart disease, a few exceptions exist. The Nurses' Health Study found no protective effect of light to moderate alcohol consumption on CHD among subjects with low folate intake (34). One cohort study evaluating the effects of alcohol consumption on CHD among Russians found no protective effect of moderate consumption (35).

The effects of alcohol consumption on coronary heart disease are suspected to vary according to the drinking pattern (3, 23 ,36). Studies on alcoholism (37), problem drinking (38) and inebriation (39) have shown higher mortality from coronary heart disease and from all cardiovascular diseases (40) for subjects with these conditions than for those with no problem-drinking behaviour. Recent drunkenness and heavy alcohol consumption have been shown to predispose to sudden coronary death (41, 42). Furthermore, IHD-mortality and morbidity was found to be more prevalent among patients hospitalized with alcohol intoxication compared to those with other alcohol related diseases, suggesting previous rapid drinking with consequent serious intoxication, a known risk factor for cardiac arrhythmias (43).

Epidemiological studies assessing the effects of drinking patterns in terms of drinking frequencies have reported the following findings. The British Regional Heart Study found that daily light drinkers had the lowest rate of major ischemic heart disease events, whereas the highest attack rate was among occasional drinkers (44). A large American cohort study reported lower rates of myocardial infarction among men who consumed alcohol on most days during the week than among those who consumed alcohol less than once a week. The amount of alcohol consumed did not alter the association (45). A pattern of infrequent drinking was associated with increased CHD mortality in a Danish cohort also (46). An Australian case-control study found a lower risk for major coronary event among moderate regular drinkers than among abstainers. The risk for coronary events was higher among those who

drank one to two drinks rarely or engaged in binge drinking behaviour (> 13 drinks a day) (4).

Those studies that have assessed the impact of heavy drinking occasions (binge drinking) on CHD endpoints have found the following findings. A Finnish cohort study showed higher mortality from fatal MI among binge drinkers than among non-binge drinkers with the same average alcohol consumption (5). A higher risk for CHD among binge drinkers was also observed in a Canadian cohort, even though no adjustment was made for their average alcohol consumption (47). A Russian cohort study reported that binge drinking at least once a month led to higher risk for CHD mortality than did moderate alcohol consumption without binges (28). A recent meta-analysis that included most of the published data on alcohol drinking patterns and CHD showed a protective effect of regular alcohol drinking on CHD risk, but a higher risk for binge and irregular drinkers (48).Even if most published studies have found a higher risk for coronary endpoints in binge drinkers, at least one exception exists: one Swedish case-study nested with a population cohort found no association between heavy drinking occasions and MI (49). (Prospective studies are summarised in Table 2).

Table 2 Summary of prospective studies on alcohol drinking pattern and coronary heart disease

Reference	Study population	n men/women age	Outcome, follow-up time	Drinking pattern definition
Shaper et al. 1987	Britain, population-based cohort study	N = 7729 men aged 40-59 y	MI (fatal or non-fatal) or sudden cardiac death, 6.2 years	None, occasional, weekend and daily drinkers
Kauhanen et al. 1997	Finland, population-based cohort study	N = 1641 men aged 42-60 y	MI (fatal and non-fatal analysed separately), 5.6 years	Binge drinking vs. moderate drinking
Murray et al. 2002	Canada, population-based cohort study	N = 1154 men and women aged 18-64 y	Physician visit, hospitalisation or death due to CHD, 8 years	Binge drinking vs. non-binge drinking (≤ 8 drinks at one sitting)
Malayutina et al. 2002	Russia, population-based cohort study	N = 6502 men aged 25-64 y	Coronary heart disease mortality, 9.5 years	Binge drinking vs moderate drinking
Tolstrup et al. 2006	Denmark, population-based cohort study	N = 53 500 men and women aged 50-65 y	Incidence of CHD, 5.7 years	Frequent/ non-frequent drinking (at least 1 time/wk vs. rarely)
Mukamal et al. 2003	USA, population of Health Professionals	N = 51 529 male	Myocardial infarction, 12 years	Frequent > 3 times/wk, non-frequent less than once per wk

Adjustment for average alcohol consumption	Reference category	Further adjustments	Results
Analysed separately according to light, moderate and heavy average drinking categories		Age, smoking, social class	Lowest attack rate among daily light drinkers. The highest rate among occasional drinkers.
Yes. Based on quantity-frequency questionnaire	Less than 3 bottles of beer on a typical drinking occasion	Smoking, leisure time physical activity, occupational status, marital status, social contacts, depression, previous diseases, systolic blood pressure, LDL, HDL, fibrinogen, BMI	Higher mortality for fatal MI among binge drinkers. No difference in acute MI incidence.
No	No binge drinking behaviour (≤ 8 drinks at one sitting)	Age, education, marital status, smoking	Higher CHD mortality and morbidity among binge drinkers than among non-binge drinkers.
Yes. Analyzed separately by quantity categories and frequency categories.	Moderate drinkers	Age, education, blood pressure, smoking, BMI, total cholesterol	Higher CHD mortality among binge drinkers (at least one binging episode per month) than among moderate drinkers. Adjusted model non significant.
Analysed separately according to quantity and frequency categories	Infrequent drinking (less than once/wk)	Education, smoking, leisure time physical activity, BMI, diet	Infrequent drinking was associated with higher CHD incidence than was frequent drinking.
Analysed separately according to quantity and frequency categories	Infrequent < 1 drinking day/wk	Age, smoking, BMI, diabetes, hypertension, cholesterol, parental history of MI, use of aspirin, physical activity, intake of energy, intake of vitamins, fats and fibre	Frequent alcohol consumption associated with lower rates of MI than did the consumption of alcohol < 1/wk. The amount of alcohol consumed did not alter the association.

2.4.1 Alcohol and stroke

Heavy alcohol consumption has been shown to increase risk for both ischemic and hemorrhagic strokes (50, 51). The relationship between alcohol consumption and haemorrhagic stroke, including both intracerebral (ICH) and subarachnoid (SAH) haemorrhages, has proved to be linear, with the highest risk being among heavy drinkers (50, 52, 53, 54, 55).

Many cohort studies have found that average alcohol consumption is related to ischemic strokes in a J-shaped manner. Studies have shown that light to moderate alcohol consumption provides greater protection against ischemic stroke than does abstention (50, 56, 57, 58, 59, 60, 61, 62). A meta-analysis summarising over 35 cohort and case-control studies found a protective effect against ischemic stroke for an average alcohol consumption of 12-24 g/day (RR 0.72 CI 0.57-0.91) (50). However, other cohort studies have found no protective effect of moderate consumption against ischemic stroke (63, 64, 65, 66), suggesting that the protective effect of moderate consumption against ischemic stroke remains somewhat uncertain.

The first evidence that acute alcohol intoxication predisposes to SAH (67) and ischemic stroke (68) came from Finnish case-control studies by Hillbom and Kaste. They showed that alcohol intoxication preceded hospital admission due to SAH or ICH in a significant proportion of cases. Later, the same research group found that moderate or heavy alcohol consumption during the 24 hours prior to hospital admission or heavy alcohol consumption during the previous week increased the risk for ICH, whereas recent light drinking failed to increase the risk for stroke (69). Furthermore, moderate to heavy alcohol consumption during the 24 hours prior to disease onset proved to be a risk factor for ischemic stroke as well (70).

The long-term effects of different drinking patterns on stroke risk beyond acute alcohol intoxication have been investigated in only a few cohort or case-control studies. A Swedish cohort study found that the risk for ischemic stroke was higher among men who sometimes felt intoxicated, had a pattern of infrequent drinking or engaged in occasional binge drinking than did lifelong abstainers (64). A Finnish case-control study found that regular light to moderate alcohol consumption protected against ischemic stroke, whereas a pattern of sporadic or irregular drinking attenuated the benefit (57). A recent Korean cohort study found higher total stroke mortality among male binge drinkers who drank daily than among non-drinkers (71).

2.5 Mechanisms linking alcohol to cardiovascular diseases

2.5.1 Alcohol and elevation of blood pressure

High blood pressure is a well-known risk factor for coronary heart disease and is considered a major risk factor for all strokes (72, 73). A large meta-analysis summarising over 61 prospective studies showed that during middle and old age, blood pressure is strongly and directly related to stroke, CHD and other vascular deaths with no threshold above blood pressure values of 115/75 mmHg (74).

Alcohol consumption has been shown to increase blood pressure (38, 75, 76, 77), and long-term average alcohol consumption has been found to increase blood pressure in a dose-response manner. The Framingham Study found that an increase in alcohol consumption increases blood pressure, whereas a decrease in consumption was associated with a decrease in blood pressure (78). A trial in 46 healthy men showed a clear decrease in blood pressure after the cessation of alcohol consumption and an increase in blood pressure again when habitual drinking patterns resumed (79).

Consuming large amounts of alcohol in one occasion has been shown to raise blood pressure more than the consumption of the same amount of alcohol over a longer period of time (80). The Intersalt Study showed higher blood pressure values among those heavy drinkers with greater variation in daily consumption compared with those having more stable consumption pattern (77). A Finnish study found that weekend binge drinkers had higher systolic blood pressure than did teetotallers, whereas no difference was observed in diastolic blood pressure (81). Furthermore, alcohol ingestion in study settings increased blood pressure in otherwise normotensive subjects (82). Moreover, alcohol withdrawal has been associated with higher blood pressure in alcoholic patients with normalised blood pressure values after a detoxification period (83).

2.5.2 Alcohol and arrhythmias

Alcohol is known to have arrhythmogenic properties, causing both supraventricular (84) and ventricular arrhythmias (85). Arrhythmias are typically triggered after heavy drinking episodes and during withdrawal. The most common arrhythmias observed after alcohol consumption are supraventricular arrhythmias, including atrial fibrillation (85, 86). The term "holiday heart" refers to supraventricular arrhythmias developed after heavy alcohol consumption and which often cease after abstention (86). Atrial fibrillation is a well-known risk factor for ischemic stroke of embolic origin (87, 88).

A Finnish case-control study showed that recent heavy alcohol consumption (> 151 g/week) during the past week prior to the onset of stroke was a risk factor for ischemic stroke. Furthermore, the consumption of > 40 g alcohol within the preceding 24 hours was a risk factor for ischemic stroke due to cardiogenic embolus and to large-artery atherosclerosis (89).

Heavy chronic alcohol use is considered a major risk factor for dilated cardiomyopathy (90, 91), and ventricular arrhythmias triggered after heavy alcohol consumption are often observed in subjects with cardiomyopathy and ventricular dysfunction. However, ventricular arrhythmias are also observed after heavy alcohol drinking in subjects without heart failure (85, 86). Ventricular arrhythmia, which may end as ventricular fibrillation, is the main mechanism by which heavy alcohol drinking predisposes to sudden death.

2.5.3 Alcohol, lipids and atherosclerosis

Elevated total, LDL cholesterol and low HDL cholesterol are associated with increased risk for coronary heart disease (92, 93) and ischemic stroke (94, 95, 96). In addition, apolipoprotein B (ApoB) and the ApoB:ApoA-1 ratio has been associated with CVD risk (97, 98). Atherogenic lipid particles include VLDL, IDL, LDL and lipoprotein a (Lp(a)), where LDL is considered the main atherogenic particle. HDL cholesterol plays an anti-atherogenic role by acting as a reverse cholesterol transport that carries excess cholesterol from tissues to the liver, thus decreasing the amount of circulating cholesterol.

Alcohol consumption has also been shown to increase HDL levels (99, 100, 101, 102, 103, 104). Average alcohol consumption of up to 21 drinks per week was associated with increased HDL levels, although the drinking pattern was not taken into account (104). A meta-analysis of 42 experimental studies found increased concentrations of HDL cholesterol, apolipoprotein A1 and triglycerides after moderate

alcohol consumption (on average 30 g of alcohol per day) (105). Furthermore, heavy alcohol consumption has been shown to increase triglyceride concentrations (106). An angiographic study found a J-shaped association between average alcohol consumption and carotid atherosclerosis in which the protective effect on atherosclerosis progression was mediated though lowered LDL cholesterol levels related to moderate regular alcohol consumption (107).

Some studies estimate that approximately half of the anti-atherogenic effect related to moderate alcohol consumption is mediated by an elevated HDL concentration. The Multiple Risk Factor Intervention Trial showed that about 45% of the beneficial effect related to alcohol consumption on the risk for CHD was mediated by elevated HLD cholesterol levels (104). The findings from the Honolulu Heart Study and the Lipid Research Clinics Follow-up Study showed a similar protective effect of HDL cholesterol in the relationship between alcohol consumption and CHD (108, 109). The effect of alcohol consumption on CVD mortality in one cohort proved to be independent of the LDL cholesterol pathway (109). However, another cohort showed that a low LDL level accounts for some of the protective effect related to alcohol consumption (108). A large cohort study of middle-aged women (the Female Health Professional Study) showed that the reduced risk for CVD related to moderate alcohol consumption was mediated primarily by effects on lipids (29%), followed by effects on glucose metabolism (25%), inflammatory/haemostatic factors (5%) and blood pressure when these mediating factors accounted for 86% of the lower risk for CVD.(110) A case-control study of 340 men and women who had suffered a myocardial infarction found that the protective effect of moderate alcohol consumption was mediated in large part by elevated HDL cholesterol levels, whereas the other lipoprotein fractions (total cholesterol, LDL, VLDL, triglycerides) had no effect on the relationship (103). In addition to beneficial changes in HDL concentrations among light to moderate drinkers, also low lipoprotein a (Lp(a)) levels are associated with moderate alcohol consumption (111).

Although moderate regular alcohol consumption has been associated with elevated HDL cholesterol levels and lower cardiovascular mortality, a pattern of irregular drinking and binge drinking have been associated with adverse lipoprotein composition and accelerated atherosclerosis (6). This latter relationship, however, has seen little investigation.

One case-control study found that the alcohol consumption pattern of regular drinkers was associated with higher HDL levels than that of occasional drinkers (occasional drinking is defined here as non-daily drinking) (103). An experimental study of ten non-alcoholic men showed elevated LDL levels after three days of heavy drinking (106). Furthermore, another experimental study of 29 alcoholics and 17 healthy

controls found alterations in apolipoprotein B containing lipoprotein concentrations at the end of the drinking period and the changes persisted several days after abstinence (112).

The first evidence of accelerated atherosclerosis related to a pattern of irregular drinking came from an angiographic study by Gruchow et al. They showed that in 526 men with a diagnostic coronary angiography, a pattern of regular drinking was associated with lower occlusion scores than one of either non-drinking or occasional drinking. Men with the most variable drinking patterns had higher coronary occlusion regardless of the total amount of alcohol consumed. Furthermore, they showed that regular drinkers had higher total and HDL cholesterol levels than did non-drinkers and occasional drinkers. The lowest total:HDL cholesterol ratio occurred among regular drinkers with low variability between the amounts consumed per typical drinking session (113).

The Kuopio Ischemic Heart Study (KIHD) found that in a four-year follow-up, a higher progression of carotid atherosclerosis occurred among men with a pattern of binge drinking than among men with a non-binge drinking pattern. The more rapid progression of atherosclerosis observed among binge drinkers was independent of their total average alcohol consumption (114). Later on, the findings from an 11-year follow-up of the KIHD cohort confirmed that binge drinking men suffered more rapid progression of carotid atherosclerosis than did men with no binge drinking pattern (115).

2.5.4 Alcohol and inflammation

Cumulative evidence indicates that inflammation plays a crucial role in the pathogenesis and progression of atherosclerosis (11, 116). Many cohort studies have reported an association of systemic markers of inflammation with CHD (117, 118). A large meta-analysis of prospective cohort studies showed consistent associations between CRP, fibrinogen, albumin and leukocyte count with CHD (119).

Average alcohol consumption and acute phase inflammation markers (CRP, fibrinogen, IL-6) are related in a U- or J-shaped manner (120, 121, 122, 123). The lowest levels of inflammation markers occur among light to moderate drinkers, and higher concentrations among heavy drinkers and non-drinkers. This anti-inflammatory effect of moderate alcohol consumption has been considered a potential mechanism linking moderate alcohol consumption to decreased risk for CVD.

Whether the increased risk for CVD events related to irregular and binge drinking patterns are associated with a pro-inflammatory state remains unclear. Some studies have reported higher levels of inflammation markers among occasional and binge drinkers. One cross-sectional study reported lower CRP levels among moderate drinkers (5-7 drinks/week), whereas occasional drinking (1-3 drinks/month) and non-drinking was associated with higher CRP levels (124). A Russian cross-sectional study reported that after excluding ex-drinkers from the analysis, the association between average alcohol consumption and CRP was linear. The Russian study cohort included mostly binge drinkers with a preference for strong alcohols (125). These findings are in agreement with those of a Finnish study, which found higher CRP levels among alcohol abusers than among controls (abuse was defined as consuming > 280 g alcohol/week) (126).The results of a Finnish cohort study suggest that the higher risk for CVD death during a hangover is mediated in part by the fibrinogen concentration (127).

2.5.5 Alcohol and coagulation

Alcohol influences coagulation in numerous ways. Moderate alcohol consumption has been associated with favourable thrombolytic potential (128, 129). The Framingham Offspring Study found lower levels of fibrinogen, plasma viscosity and coagulation factors among light to moderate drinkers, whereas heavier drinking was associated with impaired fibrinolytic potential (130). A meta-analysis of 42 experimental studies reported consistent associations between moderate alcohol consumption and decreased fibrinogen concentrations (105).

Among chronic heavy alcohol users with no cirrhosis of the liver, the predominant effect is on platelets with both qualitative and quantitative defects. Alcoholics with cirrhosis of the liver have defects with clotting factors in addition to platelet abnormalities. These defects predispose to prolongation of bleeding time and haemorrhagic complications (131).

Platelet defects also occur during the alcohol withdrawal state. The alterations observed during withdrawal include a rise in platelet count and in platelet aggregability. These platelet changes predispose to thrombosis (132). Furthermore, acute alcohol ingestion has been shown to increase platelet aggregation (133) , to decrease fibrinolytic activity (134) and to shorten the bleeding time (135).

2.6 The role of fibrinogen as an inflammation and haemostatic marker

Fibrinogen is an acute phase inflammation marker and a haemostatic protein (136). The mechanisms by which fibrinogen increases the risk for cardiovascular events include the prothrombotic effect (137), effects on endothelial function, platelet aggregation and plaque formation (138). Furthermore, fibrinogen is the major determinant of plasma viscosity, which is an independent risk factor for coronary events (139). Fibrinogen is considered a major risk factor for both myocardial infarction (137, 140) and ischemic stroke (141, 142).

In addition to the observed elevated risk related to high fibrinogen values, fibrinogen is associated with other major cardiovascular risk factors, such as smoking (140, 141) hypertension (140) cholesterol (143) and low socio-economic status (144). It has been estimated that some known cardiovascular risk factors affect through their influence on fibrinogen levels. Strong evidence suggests that smoking is associated with fibrinogen levels, that quitting smoking reduces fibrinogen concentrations, and that some harmful effects related to smoking are mediated through fibrinogen levels (145).

2.7 Alcohol and depression

Both clinical and epidemiological studies have shown that heavy alcohol consumption and alcoholism are associated with depression (146, 147, 148). A large American population study (Epidemiologic Catchment Area Study, ECA) involving over 20 000 subjects found that among those with an alcohol disorder, 37% suffered a comorbid mental disorder. The most common mental disorders co-occurring with alcohol disorders include affective-anxiety and antisocial personality disorder (147).

Even though research has firmly documented the comorbidity of alcoholism and heavy alcohol consumption with depression, the mechanisms of these associations are unclear. Some studies have attributed this co-occurrence to both causality (149) and shared aetiology (150, 151, 152). Furthermore, the question of primary-secondary distinction between alcoholism and depression has not been fully understood. One longitudinal study reported alleviated depression in the short term after alcohol consumption, but worsened symptoms in the long term. Furthermore, depression has been shown to lead to increased alcohol consumption over the short term, but with the opposite long-term effect (153).

Only a few studies have investigated the associations between alcohol drinking patterns and depression. One cross-sectional study found that the quantity of alcohol consumed per drinking occasion was associated with depressive symptoms, whereas the frequency of drinking had only a minor influence (154). A recent prospective Finnish cohort study showed that binge drinking was positively associated with depression five years later, and that the association was independent of the average alcohol consumption (155).

In addition to the well-documented association between heavy alcohol consumption and depression, research has also shown that abstaining from alcohol is related to poorer mental health (156, 157, 158, 159). Better mental health among moderate drinkers than among abstainers has been attributed to the tendency of past problem drinkers to abstain from alcohol. Although the evidence is insufficient, some studies have reported worse mental health among abstainers than among moderate drinkers even though past problem drinkers were excluded from the analysis (158, 159).

3 Aims of the Study

The aim of this thesis was to investigate the role of the binge drinking pattern as a risk factor for cardiovascular diseases and depression and to study the role of fibrinogen as a mediating factor between CHD morbidity and binge drinking. The more specific aims were as follows:

1. To investigate whether the binge drinking pattern is a risk factor for all-cause mortality, coronary heart disease mortality and morbidity, mortality due to external causes and alcohol-related causes independently of one's average long-term alcohol consumption.

2. To examine the differences in the occurrence of depressive symptoms among ex-drinkers, lifelong teetotallers and subjects with or without a pattern of binge drinking.

3. To investigate the risk for total stroke, ischemic stroke and haemorrhagic stroke in relation to the binge drinking pattern.

4. To examine whether binge drinking associates with high fibrinogen concentrations.

5. To investigate the role of fibrinogen as a mediating factor between increased coronary event morbidity and the binge drinking pattern.

4 Material and methods

4.1 Study population

4.1.1 The National FINRISK Study

The FINRISK samples are independent cross-sectional, random population samples carried out in Finland at five year intervals since 1972. The aim of the FINRISK surveys has been to evaluate cardiovascular risk factors and their changes at the population level.

The first two surveys (in 1972 and 1977) were conducted in the provinces of North Karelia and Kuopio. Over the years, the study has been expanded to include the Turku-Loimaa region in 1982, the Helsinki-Vantaa metropolitan region in 1992 and the province of Oulu in 1997. The survey methods followed the WHO MONICA protocol from 1982 to 1997 (World Health Organization 1988) and the methods were comparable to the methods used in 1972 and 1977 (160).

This study utilised the FINRISK samples recruited in 1987, 1992 and 1997. In each year, a stratified random sample of men and women aged 25-64 years living in the provinces of North Karelia and Kuopio, south western Finland (the Turku-Loimaa region), the capital area (Helsinki-Vantaa) and the province of Oulu was drawn from the Finnish population register. Stratification was carried out according to age, sex and ten-year age group. In 1987, 500 men and women in each age group from the provinces of North Karelia and 250 men and women in each age group from the province of Kuopio and south western Finland comprised the study sample. In 1992, the study sample included 250 men and women in each age group from the provinces of North Karelia and Kuopio, south western Finland and the Helsinki-Vantaa region. In 1997, the study sample included 250 men and women in each age group from all defined areas. The response rate was 81% in 1987, 76% in 1992 and 72% in 1997. In these analyses, those subjects who were randomly selected to participate in the survey more than once were considered eligible only in the first study year.

4.1.2 The FINRISK sub-samples

Psychosocial sub-sample

The study population included participants from the FINRISK-97 sample. A sub-sample included 60% of the original sample and was randomly drawn from the original sample according to sex and ten-year age group, yielding a total of 6000 participants. With 2068 women and 1771 men participating, the total response rate was 64%.

The FINRISK-92 Haemostasis Study

The FINRISK-92 Haemostasis Study included subjects studied in the FINRISK-92 sample. The sub-sample included all the subjects between the ages of 45 and 64 living in the provinces of North Karelia and Kuopio, south western Finland and the Helsinki-Vantaa region who were originally randomly stratified for the FINRISK-92 sample. The total sample of the Haemostasis Study included 3000 subjects. The participation rate was 79.6%, and an adequate blood sample was obtained from 2378 subjects (1133 men and 1245 women).

The Finnish Platelet Aggregation and Inflammation Study (PAIS)

The platelet aggregation and inflammation study (PAIS) was a sub-sample of the FINRISK-97 sample. The sub-sample included 250 men between the ages of 45 and 64 living in the provinces of North Karelia and the Helsinki-Vantaa region, and 500 men between the ages of 65 and 74 from both areas. The total sample size was 2000 men. The participation rate was 79%, and an adequate blood sample was obtained from 1591 men.

4.2 Methods and measurements

4.2.1 Baseline risk factor measurements

The survey included a self-administered questionnaire with questions on health behaviour, socio-economic factors, health status and medical history. The questionnaire was mailed to the participants prior to their health examination. All participants underwent a health examination that included measurements of blood pressure, weight and height. A venous blood sample was also taken at the health examination site.

Blood pressure was measured from the right arm of the participant by a specially trained nurse after 15 minutes of rest in a sitting position. Korotkoff sounds were recorded as the systolic blood pressure, and the fifth phase as the diastolic blood pressure. The measurement was repeated after one minute. This study used the latter blood pressure value, and participants were classified as having hypertension if their blood pressure was ≥ 140/90 at baseline or if they were on antihypertensive medication and had taken their medication within the previous week. Weight and height were measured, and BMI was calculated as weight in kilograms divided by the square of height in metres. Education was assessed with a self-administered question about the total years of full-time education. To control for the effect of birth year on education status, birth year-specific tertiles of total years of education were calculated, yielding three education categories (low, medium, high) for every ten-year age group. Smoking was assessed based on the responses in the self-administered questionnaire and categorised into two groups: smokers and non-smokers. Current smokers included participants who had smoked regularly for at least a year and had smoked daily during the previous month. Other respondents were classified as non-smokers (never smokers, occasional smokers, ex-smokers). A self-administered question enquired about the following chronic infections diagnosed or treated by a physician during the previous year: asthma, chronic obstructive pulmonary disease, chronic bronchitis, rheumatoid arthritis and chronic cystitis.

4.2.2.1 Depressive symptoms: the Beck Depression Inventory (BDI)

The Beck Depression Inventory (BDI) is a frequently used self- administered measure of depressive symptoms (161). The BDI has shown good validity with other psychiatric measures of depression in both psychiatric and non-psychiatric samples (162). This study used the 21-item BDI score. Each item of the BDI includes four or five statements, and the respondents are asked to choose one or more options corresponding most closely with his/her actual condition at that time. If more than one option was chosen, the option indicating more severe depression was selected for the score. The total BDI score varied from 0 to 63. The following cut-off scores are widely used: none or minimal depression < 10, mild to moderate depression 10-18, moderate to severe depression 19-29 and severe depression 30-63 (162, 163). In this study, a BDI score >10 indicates depression.

4.2.2 Laboratory analyses

Cholesterol was measured from fresh serum samples with an enzymatic method (Boehringer Mannheim GmbH Diagnostica). Fibrinogen samples were snap-frozen immediately after venipuncture in a mixture of alcohol and dry ice and stored at -70°C. In 1992, measurements were carried out with the ACL 300R coagulometer from the light scattered by the clot during the prothrombin time assay (IL Test PT-fibrinogen, Instrumentation Laboratories). In 1997, fibrinogen measurements were carried out with the Clauss method by using an IL Test Fibrinogen-C kit and a single lot of IL Test Calibration plasma.

4.2.3 Measurement of average alcohol consumption

Average alcohol consumption was assessed with a self-administered quantity-frequency questionnaire. The questionnaire enquired about the usual quantity and frequency of alcohol consumption during the previous 12 months. The following questions enquired separately about the consumption of wine, beer and spirits (cider and long drinks were included in the 1997 questionnaire): “How often do you usually drink wine/beer/spirits?” and “How much wine/beer/spirits do you usually drink at time?” The estimated alcohol content per standard drink was 12.5 g for beer, 14.0 g for cider, 14.0 g for long drinks, 12.0 g for wine and 12.0 g for spirits, and the estimated volume per standard drink was 33 cl for beer, cider and long-drinks, 12 cl for wine and 4 cl for spirits. Based on their average alcohol consumption, participants were categorised into three categories (upper, middle, lower). These categories were labelled hazard-

ous, heavy, moderate drinkers (Study 2) and heavy, moderate, light drinkers (Study 3). The upper category included participants who consumed > 350 g of alcohol per week (28 drinks/week) for men and > 210 g/week (18 drinks/week) for women. These criteria were chosen to follow the screening limits used in brief interventions to reduce alcohol consumption (183). The middle category comprised subjects below these screening limits, but who consume < 230 g/week (21 drinks/week) for men and > 150 g/week (14 drinks/week) for women. These cut-off points correspond to the screening limits used in some brief interventions. The lower category included the rest (183). Average alcohol consumption was measured for those participants who reported any alcohol consumption within the previous 12 months. Based on their responses, abstainers were classified as lifelong teetotallers and ex-drinkers.

4.2.4 Measurement of binge drinking

A definition for a binge drinking pattern was six or more drinks of the same alcoholic beverage on a single drinking occasion for men and four or more drinks of the same alcoholic beverage for women. The criterion for binge drinking was chosen according to the AUDIT screening questionnaire, which includes a question about consuming six or more drinks at a time (9).

4.3 Definition of endpoints

The study cohorts were linked to the Finnish hospital Discharge register for non-fatal cases and to the Causes of Death Register for fatal cases. The linkage was accomplished through the personal identification number assigned to every resident of Finland. International Classification of Diseases (ICD) coding was used to recognise the diagnoses under consideration. The ICD-9 coding was used until the end of 1995, and the ICD-10 coding was used from the beginning of 1996, as they are standard in Finland.

The causes of deaths were classified according to the following ICD codes: for cardiovascular disease, ICD-9 codes 390-459 and ICD-10 codes I00-I99; for ischemic heart disease, ICD-9 codes 410-414 and ICD-10 codes I20-I25; for malignant neoplasm, ICD-9 codes 140-208 and ICD-10 codes C00-C97; for external causes of death, ICD-9 codes E8000-E999 and ICD-10 codes V01-Y99 and X60-X84 (with the exception of alcohol-induced poisonings, E85 was excluded from this category. ICD-9 codes for alcohol-related diseases were as follows: 291, 303, 3575, 4255, 5353, 5710-5713, 5770D-5770F, 5771C, 5771D, 607A, 7795A and E85. The respective ICD-10 codes were F10.0-F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4 and X45.

Fatal and non-fatal strokes used ICD-9 code 431, and intracerebral haemorrhage used ICD-10 code I61. ICD-9 code 430 and ICD-10 code I60 were used for subarachnoid haemorrhage (SAH), and ICD-9 codes 436, 4340 A, 4331 A, 4339 A, 4330 A, 4341 A, 4349A and ICD-10 code I63 were used for ischemic stroke.

In Study IV, the outcome definition was a coronary event that included nonfatal myocardial infarctions, hospitalised attacks of unstable angina pectoris, revascularisations and coronary deaths. ICD-9 codes 410-4110 and ICD-10 codes I21, I22 and I20.0 were used for non-fatal events. For fatal coronary events, we used ICD-9 codes 410-414 and 798 and ICD-10 codes I20-I25, I46, R96 and R98. Revascularisations were identified with codes of the Nordic Medico-Statistical Committee (NOMESCO) classification.

A history of a myocardial infarction was assessed with a self-reported infarction diagnosed by a physician (Study I). In addition to the self-reported diagnosed myocardial infarction, participants were classified as having a history of myocardial infarction if they had been hospitalised with ICD-9 codes 410, 411, 412 or ICD-10 codes I21, I22, I20.0 or I25.2 prior to the baseline examination (Study III, IV).

A history of previous stroke was identified based on either a self-reported stroke diagnosed by a physician or hospitalisation with a diagnosis of stroke (the ICD codes used were identical to the definitions of stroke outcome) (Study III).

Participants were classified as having diabetes if they reported either physician-diagnosed diabetes or impaired glucose tolerance or if they had been hospitalised with a diagnosis indicating diabetes (ICD-9 code 250 or ICD-10 codes E10, E11).

4.4 Study designs

Study I

In study I, we investigated whether the binge drinking habit predicted mortality independently of average alcohol consumption and other potential confounders in cohort design. Only men were studied in this first study. The study population included participants in the FINRISK-87 and -92 samples. The mean follow-up period was 7.3 years. The outcome measures included all-cause mortality, mortality due to cardiovascular diseases, mortality due to ischemic heart disease, malignant neoplasms, external causes of deaths and mortality due to alcohol-related diseases. The study design included an average follow-up period of 7.3 years. Because of the interaction found between drinking habit and previous myocardial infarctions, analyses for all-cause mortality and IHD mortality were carried out both including and excluding cases with previous MI.

Study II

In study II, we used a cross-sectional study design to investigate whether the binge drinking habit and non-drinking behaviour were associated with depression. The study population included the participants studied in the FINRISK-97 psychosocial sub-sample. In the primary analysis, we studied whether the BDI mean scores differed by drinking habit. Participants were classified into eight groups: ex-drinkers, lifelong teetotallers, moderate drinkers with or without a binge drinking habit, heavy drinkers with or without a binge drinking habit, and hazardous drinkers with or without a binge drinking habit. Because of the interaction between drinking habit, gender and age, further analyses were carried out separately for men and women; dummy variables were used for age and drinking habit. Young participants with no binge drinking pattern served as the reference category. In further analyses, we examined whether the binge drinking habit associated with depression after controlling for long-term average alcohol consumption, marital status, chronic diseases, employment status and education.

Study III

In study III, we investigated the role of the binge drinking habit on stroke risk. The study population consisted of participants in the FINRISK-87, -92 and -97 samples. The study cohort was followed up for ten years. The first stroke event (fatal or non-fatal) served as the endpoint. Analyses were carried out separately for all strokes, including ischemic and haemorrhagic strokes. To evaluate the effect of the binge drinking habit on the entire study cohort, analyses were conducted separately for all participants as well as for those who had consumed alcohol within the previous 12 months, with a focus on those who reported consuming alcohol. To evaluate the independent contribution of the binge drinking habit on stroke risk, the analyses were adjusted for long-term average alcohol consumption, age, study area, hypertension, smoking, diabetes, BMI, education, history of myocardial infarction and study year. To investigate the role of average alcohol consumption on stroke risk, a logarithmically transformed average alcohol consumption variable without binge drinking was added to the Cox proportional hazard models.

Study IV

In study IV we examined the role of fibrinogen as a potential mechanism linking the binge drinking habit to increased CHD morbidity. The study sample included subjects studied within the Finnish Platelet Aggregation and Inflammation Study (PAIS) and The FINRISK-92 Haemostasis Study. The study cohort was followed up for ten years, and the first coronary event served as the endpoint. First, we examined the probability of binge drinkers to have high fibrinogen concentrations after controlling for the potential confounders known to increase fibrinogen concentrations (sex, average alcohol consumption, smoking, infections, education, age and BMI). We used a logistic regression model in these cross-sectional analyses. To evaluate whether fibrinogen affects the association between binge drinking and ischemic heart disease morbidity, we used the Cox proportional hazard model with binge drinking habit, average alcohol consumption, age, sex and study year as variables taken from the basic model. To identify the effect of other traditional CVD risk factors, we added smoking, hypertension, cholesterol, education, diabetes and, finally, fibrinogen to the model.

4.5 Statistical methods

We investigated the differences between the background characteristics of binge drinkers and non-binge drinkers with the t test and chi square test (Studies I-IV). Because of the skewed distribution of long-term alcohol consumption and fibrinogen levels, we used the Wilcoxon U-test to compare the consumption and fibrinogen levels of binge drinkers and non-binge drinkers (Study IV). Differences in the mean BDI scores between eight drinking groups were analysed pairwise with the Tukey mean separation test (Study II). Multiplicative interactions were tested using ANOVA (Study II) and Cox proportional hazards regression models (Studies I and III). Because of the three-way interaction found between gender, age and drinking habit, and the two-way interaction between age and drinking habit in depressive symptoms among men, we analysed the data separately for men and women and used a dummy variable for age and drinking habit (Study II). We used a logistic regression model with adjustments for the main confounders to calculate odds ratios (OR) with 95% confidence intervals for depression (Study II) and for high fibrinogen concentration (Study IV). The Cox proportional hazard regression model served to analyse the independent effect of binge drinking on the risk for selected endpoints (Studies I, III, IV). Participants with missing information for one or more of the selected variables were excluded from the respective analyses. The level of significance was $p < 0.05$ (two tailed) in all analyses. All analyses were performed with the SAS statistical package version 8.2 (SAS, Inc, Cary, NC).

5 Results

5.1 General characteristics of the study population

Characteristics of the study population presented here apply to the study sample, which comprised participants studied in the FINRISK studies of 1987, 1992 and 1997. This sample was used in Study III, whereas the other studies utilised parts of this larger sample. The study cohort included a total of 26 000 subjects, of which 19 689 participated in the baseline survey. Those subjects who participated in the baseline survey more than once were considered eligible only for the first study year (n = 480). Those with previous strokes were excluded from the sample (n = 318), leading to a total of 18 891 subjects. The number of participants reporting any alcohol consumption was 16 143, and information on all covariates used was available for 15 256 participants.

The study sample included 3558 subjects (22%) with a binge drinking habit and 12 407 subjects (77%) with no binge drinking habit. Of the binge drinkers, 70% were men (n = 2505). The mean age was 41.3 (SD 10.5) years among binge drinkers and 44.8 (SD 11.2) years among non-binge drinkers. Average alcohol consumption was greater among binge drinkers than among non-binge drinkers. Furthermore, binge drinkers, more often had hypertension, higher BMI, lower education status and smoked more than did non-binge drinkers. No difference in diabetes prevalence was observed between binge drinkers and non-binge drinkers. (Table 3)

Table 3. Characteristics of participants by drinking pattern

Characteristics	Binge drinking pattern	No binge drinking pattern	p-value
Number of participants (%)	3558 (22)	12407 (77)	< 0.001
Number of ischemic strokes	122	57	
Number of hemorrhages	50	20	
Men (%)	2505 (70)	5510 (44)	< 0.001
Age, y (SD) *	41.3 (10.5)	44.8 (11.2)	< 0.0001
Alcohol intake g/ week (%)			
Light drinkers †)	76.1%	96.4%	
Moderate drinkers ‡)	9.6 %	2.4%	
Heavy drinkers §)	14.3%	1.2%	< 0.0001
Body mass index (kg/m2) * (SD)	26.9 (4.6)	25.9 (4.26)	< 0.0001
History of myocardial infarction (%)	70 (2)	330 (2.7)	0.019
Hypertension (%)	1614 (45)	5125 (41)	< 0.0001
Diabetes (%)	138 (3,9)	471 (3.8)	NS
Smoking (%)	1945 (55)	2690 (22)	< 0.0001
Education			
Lower (%)	1751 (50)	4677 (38)	<0.001
Medium (%)	1048 (30)	3739 (31)	
Higher (%)	717 (20)	3814 (32)	

Values are frequencies (percentages) and Chi-Square test (χ 2) is used as a statistical test.
* values are means (SD) and Student's t-test is used as a statistical method.

†) Total alcohol consumption 0-230 g/week for men and 0-150g/week for women
‡) Total alcohol consumption 231-350 g/week for men and 151-210 g/week for women
§) Total alcohol consumption >350 g/week for men and >210 g/week for women
NS = statistically non significant

5.2 Binge drinking and mortality (Study I)

During the follow-up period, a total of 347 deaths were registered. Of these deaths, 123 were due to ischemic heart disease, 47 to external causes and 32 to alcohol-related diseases. Analyses of beverage choices showed that of 1528 participants with heavy drinking pattern, 1264 reported consuming spirits, and only 264 reported consuming heavily only beer or wine. Approximately 50% reported consuming only spirits on binge occasions (Study I, Table 3). Age-adjusted mortality was higher among binge drinkers than among non-binge drinkers in all mortality categories (Table 4). After excluding subjects with prior myocardial infarctions, the HR for total mortality was significantly higher for binge drinkers than for non-binge drinkers (RR 2.27; 95% CI 1.78-2.88). When average alcohol consumption, smoking and education were added to the model, the RR diminished somewhat, but remained significant (RR 1.57; 95% CI 1.17-2.10). The fully adjusted RR for IHD mortality was 1.77 (95% CI 1.01-3.08) (Table 5).

Table 4. Mortality among men studied in the National FINRISK Study in 1987 and 1992 by drinking pattern

	Drinkers with heavy pattern				No heavy drinking occasions			
Cause of death	n	Person years	Crude mortality rate/ 100 000	Age adjusted mortality rate/ 100 000 *	n	Person years	Crude mortality rate/ 100 000	Age adjusted mortality rate/ 100 000 *
All causes	128	11205	1142	1301	219	26187	836	730
Cardiovascular diseases	48	11508	417	484	109	26603	409	343
Ischaemic heart diseases	38	11550	329	371	85	26718	318	264
Cerebrovascular diseases	3	11673	25	31	18	27042	66	56
Malignant neoplasms	21	11605	180	206	59	26923	219	186
External causes †	27	11565	233	239	20	27029	73	73
Alcohol related diseases ‡	20	11633	171	190	12	27084	44	42

* Standardised to European population
† Alcohol poisonings excluded
‡ Alcohol poisonings included

Table 5. Relative risk for total mortality and ischaemic heart disease mortality among drinkers with heavy pattern compared with other drinkers. Proportional hazard models are adjusted for potential confounders and other covariates. The previous covariates remain in the model when the new one is added. Previous myocardial infarctions are excluded.

	Total mortality		IHD mortality	
Adjustments	**Relative Risk**	95% Confidence Interval	**Relative Risk**	95% Confidence Interval
Age	2.27	(1.78-2.88)	2.26	(1.41-3.63)
+ Average alcohol use *	1.92	(1.45-2.53)	2.14	(1.25-3.67)
+Smoking	1.63	(1.23-2.17)	1.78	(1.03-3.07)
+Education	1.57	(1.17-2.10)	1.77	(1.01-3.08)

* Average alcohol use grouped into three categories. 0- 95.9 g/week, 96-199.9 g/week and 200+ g/week.

5.3 Binge drinking and depression (Study II)

Alcohol drinking patterns in the study sample were distributed as follows: lifelong teetotallers 6.9%, ex-drinkers 3.7%, moderate drinkers 81.1%, heavy drinkers 4.0% and hazardous drinkers 4.3%. The proportion of binge drinkers in the study sample was 24% (33% men and 17% women). The proportion of binge drinkers among those with moderate long-term alcohol consumption was 20%. The respective proportion of binge drinkers among heavy drinkers was 52%, and 74% among hazardous drinkers. The mean BDI scores showed no difference between the drinking groups among women, but did show a statistically significant difference among men. Ex-drinking men and men with a habit of binge drinking reported more depressive symptoms than did the other groups (Study II, Table 1). Furthermore, detailed analyses were conducted among the study subjects that reported alcohol consumption. The analysis of variance and multivariate logistic regression analysis showed that both older age and binge drinking associated positively with higher number of depressive symptoms. This was true for both men and women. (Study II, Table 3). The association among older age group was verified conducting a subgroup analysis separately for men and women including only persons aged 45-64 and compared binge drinkers with non-binge drinkers. The OR for depression among male binge drinkers compared to non-binge drinkers was 1.70 (95% CI 1.19-2.43) in fully adjusted model. Among women there was no difference in occurrence of depression among old binge and non-binge drinkers.

5.4 Binge drinking and stroke (Study III)

During the follow-up, a total of 249 strokes were registered. Of those, 33 were intracerebral haemorrhages, 37 subarachnoid haemorrhages and 179 ischemic strokes. Furthermore, of all the strokes, 26 were fatal and 223 non-fatal. Intracerebral and subarachnoid strokes were analysed together because of the small number of events. The risk for any stroke was significantly higher among the binge drinkers than among the non-binge drinkers (HR 1.85; 95% CI 1.35-2.54). The risk attenuated, but remained significant after adjustments for average alcohol consumption, age, sex, study area, hypertension, smoking, diabetes and BMI. After further adjustments for education and prior myocardial infarctions, the risk diminished and marginally lost significance (HR 1.39; 95% CI 0.99-1.95) (Table 6).

The risk for ischemic stroke was significantly higher in the binge drinking group than among subjects with no pattern of heavy alcohol consumption. The HR was 1.99 (95% CI 1.39-2.87) after controlling for age, sex and average alcohol consumption. In addition, when the analyses were controlled for all potential confounders, the risk somewhat attenuated, but remained significant (HR 1.56; 95% CI 1.06-2.31) (Table 7). No association was found between binge drinking and haemorrhages (HR 1.50; 95% CI 0.79-2.83), nor was any association found between average alcohol consumption and any type of stroke. The age and sex-adjusted HR for any stroke was 1.07 (95% CI 0.99-1.16), 1.09 (95% CI 0.99-1.21) for ischemic stroke, and 1.00 (95% CI 0.86-1.17) for haemorrhages. When the analyses were rerun to include the non-drinking participants in the non-binge drinker category, the risk for any stroke and ischemic stroke among binge drinkers increased. After adjusting for all confounders, the HR for any stroke was 1.47 (95% CI 1.06-2.04), and 1.72 (95% CI 1.18-2.50) for ischemic stroke.

Table 6. Hazard rations (95 % CI) for any stroke event among binge drinkers compared with non-binge drinkers.

	Model 1	**Model 2**
	HR (95 % CI)	HR (95 % CI)
Binge drinking pattern	1.85 (1.35-2.54)	1.39 (0.99-1.95)
Long term average alcohol consumption *)	1.00 (0.92-1.01)	0.98 (0.89-1.07)
Age (years)	1.10 (1.09-1.21)	1.09 (1.07-1.11)
Gender (0,1)	0.52 (0.39-0.71)	0.61 (0.44-0.83)
Study area		
North-Karelia		1,00
Kuopio region		1,07 (0,76-1,53)
South western Finland		0,90 (0,62-1,32)
Helsinki region		1,21 (0,79-1,84)
Oulu region		0,67 (0,32-1,39)
Hypertension (0,1)		1,64 (1,20-2,24)
Smoking (0,1)		2,21 (1,67-2,93)
Diabetes (0,1)		2,01 (1,35-2,98)
Body Mass Index (kg/m2)		1,04 (1,01-1,08)
Level of education (1,2,3)		1,03 (0,87-1,22)
History of myocardial infarction (0,1)		1,74 (0,94-1,01)
Study year		0,98 (0,94-1,01)

Model 1, adjusted for average long term alcohol consumption, age and gender
Model 2, adjusted for covariates in model 1 and additionally for study area, study year, hypertension, smoking, diabetes, BMI, education and coronary heart disease
*) Log transformed

Table 7. Hazard rations (95 % CI) for ischemic stroke event among binge drinkers compared with non-binge drinkers.

	Model 1	**Model 2**
	HR (95 % CI)	HR (95 % CI)
Binge drinking pattern	1,99 (1,39-2,87)	1,56 (1,06-2,31)
Long term average alcohol consumption*)	1,02(0,92-1,13)	1,00 (0,89-1,12)
Age (years)	1,13 (1,11-1,15)	1,12(1,09-1,14)
Gender (0,1)	0,49 (0,34-0,71)	0,57 (0,39-0,84)
Study area		
North Karelia		1,00
Kuopio region		1,02 (0,67-1,550)
South western Finland		0,79 (0,51-1,25)
Helsinki region		1,22 (0,76-1,98)
Oulu region		0,78 (0,35-1,72)
Hypertension (0,1)		1,34 (0,94-1,91)
Smoking (0,1)		1,99(1,43-2,78)
Diabetes (0,1)		2,04(1,30-3,20)
Body Mass Index (kg/m2)		1,06 (1,03-1,10)
Level of education (1,2,3)		1,03 (0,84-1,23)
History of myocardial infarction (0,1)		1,49 (0,91-2,48)
Study year		0,97 (0,93-1,02)

Model 1, adjusted for average long term alcohol consumption, age and gender
Model 2, adjusted for covariates in model 1 and additionally for study area, study year, hypertension, smoking, diabetes, BMI, education and coronary heart disease
*) Log transformed

5.5 Binge drinking and fibrinogen (Study IV)

During the follow-up, a total of 206 coronary events or revascularisations were registered. Of these, 150 were coronary events. The risk for a coronary event or revascularisation was higher in binge drinkers than in non-binge drinkers. The HR for a coronary event or revascularisation was 1.91 (95% CI 1.35-2.69) after adjusting for age, sex, long-term alcohol consumption and study year. Further adjustments for smoking, hypertension, cholesterol, education and diabetes diminished the risk (HR 1.47; 95% CI 1.03-2.10) (Study IV, Table 3). Adding fibrinogen to the model attenuated the risk somewhat (HR 1.36; 95% CI 0.94-1.95). The risk for a coronary event only (revascularisations excluded) was significantly higher in binge drinkers than in non-binge drinkers. The HR for a coronary event was 1.79 (95% CI 1.19-2.71) after adjustments for age, long-term alcohol consumption, study year, smoking, hypertension, cholesterol, education and diabetes. Further adjustment for fibrinogen diminished the risk somewhat, but it remained statistically significant (HR 1.61; 95% CI 1.06-2.44) (Study IV, Table 4).

An analysis at baseline showed that binge drinkers were more likely to belong to the upper quartile of fibrinogen concentrations. When compared to non-binge drinkers, the fully adjusted OR for high fibrinogen values was 2.17 (95% CI 1.17-3.99) in binge drinking women and 1.81 (95% CI 1.33-2.47) in binge drinking men (Study IV, Table 2).

6 Discussion

6.1 Summary of the Main Findings

The results of this study showed that binge drinking was a risk factor for all-cause mortality, coronary events and stroke independent of average alcohol consumption and other potential confounders. Furthermore, binge drinking was shown to associate with depression.

The more specific findings can be summarised as follows:

1. Binge drinking was found to be a risk factor for all-cause mortality, mortality due to external causes, alcohol-related diseases and ischemic heart disease independent of average alcohol consumption and other potential confounders.

2. Ex-drinkers and binge drinkers were found to have more depressive symptoms than lifelong abstainers and subjects with no binge drinking habit. Furthermore, binge drinking was found to associate with depression independent of average alcohol consumption and other potential confounders.

3. Binge drinking was shown to be a risk factor for all strokes and ischemic stroke, but showed no association in relation to haemorrhages. Furthermore, no association was found between average alcohol consumption and any subtype of stroke.

4. Binge drinking was associated with a high fibrinogen concentration. However, the higher risk for coronary events related to binge drinking was only slightly mediated through fibrinogen.

6.2 Methodological aspects

6.2.1 Study population and design

This thesis is based on large representative population samples that can be considered to represent the general population of the study areas. Even though the participation rates declined from 81% in 1987 to 76% in 1997, the study samples can still be considered representative and sufficient for a population survey. The prospective population-based study design with a representative population sample and an average ten-year follow-up period increases the reliability of the findings (Studies I, III, IV). The cross-sectional study design used in Study II imposes restrictions on interpretations of the results gained in that sub-study, and no causality conclusions can be drawn. The baseline examinations followed the WHO MONICA protocol and were identical each year. All surveys were carried out by the research team at the National Public Health Institute to ensure that standard procedures were followed in all data collection from year to year, including highly standardised laboratory analyses. The FINRISK studies have been carried out first to evaluate the North Karelia Project, and later to assess the effectiveness of the national cardiovascular disease prevention strategy. The baseline examination therefore provides adequate information on CVD risk factors, laboratory markers and lifestyle-related factors, and can be considered a strength of this thesis, which focuses mainly on cardiovascular diseases.

6.2.2 Alcohol consumption measurements

6.2.2.1 Self-reported alcohol consumption

The assessment of alcohol consumption with self-reports is always imprecise, and underreporting of actual alcohol consumption is a well-recognised problem in population surveys (8, 164, 165, 166). The quantity-frequency method used in this thesis is widely used in epidemiological studies that focus on habitual or typical alcohol intake. Comparative studies that assess differences in captured alcohol volume by using different recall methods have found that, compared to the daily diary method, the quantity-frequency method yielded on average lower estimates of alcohol consumption, whereas the graduated frequency method resulted in overestimation of alcohol consumption (167).

The quantity-frequency method includes a few questions on habitual alcohol consumption which respondents find are relatively easy to complete and which can

thus be included in epidemiological surveys with self-reported questionnaires. Disadvantages related to the quantity-frequency method include underestimation of the actual level of consumption, which results more from the underreporting not only of drinking occasions with an unusually high alcohol intake, but also of drinking frequency; the quantity consumed per drinking occasion, however, is usually reported more precisely (164).

The degree of underestimation is arguably dependent on the respondent's actual consumption. This was tested in a Finnish observational study, which found that the degree of underreporting was positively associated with the actual amount of alcohol consumed (168), suggesting that heavy drinkers underreport their consumption relatively more than do light drinkers. This may have biased the estimates of average alcohol consumption in our study. As is customary in large population studies, alcohol consumption and other predictors of mortality and morbidity were assessed only in the beginning of the follow-up period. A common, but implicit assumption in data analysis is that one measurement, even over a relatively short period of recall, represents the subject's long-term average alcohol consumption. This may not always be true, however, as changes may take place which attenuate the observed associations between alcohol consumption and health outcomes.

6.2.2.2 Binge drinking measurement

In this study, binge drinking was defined to include those who drink six or more drinks on a typical drinking occasion for men and four or more drinks for women. This criterion is widely used in epidemiological studies and is consistent with the criterion used in the AUDIT questionnaire (9) in men, whereas we used a lower limit for women. The self-administered questionnaire allowed us to define only those participants who reached the criteria for binge drinking by consuming one beverage above the set criteria (six drinks per occasion for men, four for women), whereas those who met the criteria only by combining the number of different alcoholic beverages were classified as non-binge drinkers. This has most likely influenced our results by diluting the observed associations; the real associations would have been stronger.

The chosen definition for binge drinking presents a pattern of alcohol consumption with heavy drinking occasions in contrast to a pattern of steady alcohol consumption. No information was available on the time period in which alcohol was consumed. However, the NIAAA recommended criteria of five or more (four or more for women) drinks in two hours for binge drinking typically result in a blood alcohol content of 0.8 g/l(10) which is somewhat comparable if alcohol is consumed in rapid binges, as has been habitual in Finland.

6.2.3 Outcome measures

The outcome definitions of mortality and morbidity were based on the ICD-9 and ICD-10 diagnosis available in the two administrative registers used in Finland: the National Hospital Discharge Register and the National Causes of Death Register. These registers have high coverage and diagnosis accuracy (169, 170, 171, 172). The validity of stroke diagnoses in the administrative registers was tested by comparing the identified cases with the FINSTROKE-register. The sensitivity for all first stroke events was 85%, for fatal strokes 86%, and for non-fatal strokes 85%. The sensitivity for subarachnoid haemorrhage and intracerebral haemorrhage was higher than for cerebral infarctions; sensitivity was 93% for SAH, 95% for ICH and 81% for cerebral infarctions when fatal and non-fatal cases were combined.(169) The validity of diagnosis for myocardial infarction (MI), according to the National Hospital Discharge Register and the National Causes of Death Register, was tested by comparing the diagnoses with those in the FINMONICA/ FINAMI registers. The sensitivity of the ICD codes combining both registers was 83% for MI. After including the diagnosis of unstable angina pectoris, the sensitivity improved to 85%.(171) The assessment of depression with the Beck Depression Inventory (BDI) has been considered a valid measurement consistent with methods of psychiatric diagnosis in both clinical and community samples (162).

6.2.4 Residual confounding

The possibility of bias due to the presence of confounding factors must be addressed. Binge drinkers have been shown to smoke more, to have lower socio-economic status, higher BMI, hypertension and generally unhealthier lifestyles than do non-binge drinkers. Despite adjustments to correct for the differences between binge drinkers and non-binge drinkers, some residual confounding may exist. We were unable to control for some factors, and some of the variables used may have been unable to capture all the dimensions of the phenomenon in question. All covariates are measured with some inaccuracy, thus leaving the possibility of a residual confounding effect.

6.3 Results: Interpretation of the findings

6.3.1 Binge drinking and all-cause mortality

The results of this study showed higher risk for all-cause mortality among binge drinkers than among non-binge drinkers. The association was attenuated somewhat by adjusting for average alcohol consumption, smoking and education. As discussed previously, binge drinking is associated with unhealthy lifestyles, higher smoking rates, lower socio-economic status and higher average alcohol consumption than are non-binge drinkers. Most probably, we were unable to control for some confounding factors, so some residual confounding may exist.

Our results are in accordance with those of other studies reporting higher all-cause mortality in subjects with a binge drinking pattern than in either non-binge drinkers or abstainers (5, 26, 27, 28). However, the definitions for binge drinking have varied between studies from three drinks in one to two hours (27) to eight drinks per occasion (26), where the lowest amounts of alcohol hardly caused intoxication.

Causes of death that contributed to all-cause mortality among binge drinkers in our study included cardiovascular diseases, malignant neoplasm, external causes (accidents, violence) and alcohol-related diseases (including alcohol poisonings). These results were based on age-adjusted mortality rates without controlling for the average amount of alcohol consumed. Consequently, excess mortality related to malignant neoplasm in binge drinkers must be interpreted with caution and under the assumption that heavy alcohol consumption with or without a habit of binge drinking increases the risk for several cancers (2). With respect to the other categories of mortality, further analyses were controlled for average alcohol consumption and other covariates, and showed a higher risk for mortality related to the binge drinking pattern.

The possible mechanisms by which binge drinking has been shown to associate with excess mortality include the acute effects of heavy alcohol consumption (intoxications and withdrawal), which were further associated with higher risk for arrhythmias, sudden coronary death, strokes, accidents and other external causes of deaths. In addition to these acute effects, a pattern of heavy alcohol consumption has been shown to accelerate atherosclerosis, increase blood pressure and affect coagulation, and thus increase mortality due to CHD and ischemic stroke over the long term.

6.3.2 Binge drinking and stroke

We found a higher risk for all strokes and ischemic stroke among binge drinkers than among non-binge drinkers independent of average alcohol consumption. However, no association was observed between haemorrhages and binge drinking. Furthermore, we found no association between average alcohol consumption and any stroke subtypes.

Our results concerning the higher risk for ischemic stroke among binge drinkers are in line with the evidence from the earlier case-control studies that show that consuming over 40 g of alcohol in the 24 hours prior to stroke onset predisposed to ischemic stroke (70). Furthermore, regular moderate alcohol consumption associated with reduced risk for ischemic stroke, whereas an irregular drinking pattern (alcohol consumption up to three times per week) diluted the benefit (57). In addition to these case-control studies, the effect of alcohol consumption patterns on ischemic stroke risk has been studied in only one previous cohort study. This earlier cohort study found a higher risk for ischemic stroke among those men who had a pattern of infrequent drinking, who were intoxicated now and then, or who reported binge drinking, than among abstainers. However, using abstainers as a reference group may have biased the results of that study somewhat, and furthermore, only age and smoking were controlled for in their analyses (64).

We found no association between binge drinking and haemorrhages. This may be due to the small number of haemorrhages in our data and because of combining SAH and ICH, which are known to have different pathogeneses and natural causes; consequently, the real associations might have been diluted. Our results concerning haemorrhages contrast with those of earlier case-control studies that show a higher risk for SAH (67) and ICH (69) among those who were intoxicated prior to stroke onset or who reported heavy alcohol consumption in the 24 hours prior to hospital admission due to ICH. Furthermore, our results are in contrast with the findings from a recent Korean population-based cohort study with a large population sample and long follow-up period (71). That study found a higher risk for total stroke and haemorrhages among binge drinkers who consume alcohol daily than among non-drinkers. However, that study reported a higher risk for stroke only for those binge drinkers who consumed alcohol daily, whereas the risk for stroke was no higher among those with a habit of binge drinking, but who consumed alcohol less often. The use of non-drinkers as a reference group may have influenced the associations in the Korean study and thus hampered comparison with our results.

Curiously, we found no association between average alcohol consumption and any stroke subtype. Most previous studies have found associations between average alcohol consumption and stroke, and the association has been shown to be linear for

haemorrhages and U- or J-shaped for ischemic strokes (50). The diluted associations between average alcohol consumption and stroke in our study are probably due to the underreporting of actual alcohol consumption, and based on accumulating evidence from previous cohort studies, heavy alcohol consumption should be considered a risk factor for all strokes.

The mechanisms behind the association between binge drinking and higher risk for stroke – and particularly for ischemic stroke – remain unknown. Hypertension is considered a major risk factor for all strokes, and alcohol consumption has been shown to raise blood pressure. We analysed the data with and without hypertension as a covariate, and the association between binge drinking and stroke or ischemic stroke was not diluted, thus suggesting that the underlying pathway between binge drinking and stroke is not significantly dependent on hypertension. This is consistent with the findings of previous case-control studies that reported a higher risk for ischemic stroke and ICH among those with heavy alcohol consumption prior to stroke onset after controlling for hypertension (69, 70).

6.3.3 Binge drinking and coronary heart disease

Our first study showed higher mortality due to ischemic heart disease among binge drinkers than among non-binge drinkers after controlling for age, long-term average alcohol consumption, smoking, hypertension, total cholesterol, HDL cholesterol, systolic blood pressure and education. The finding was re-tested in the fourth study with a longer follow-up period and the inclusion of nonfatal myocardial infarctions, hospitalised attacks of unstable angina pectoris, revascularisations and coronary deaths in the definition of a coronary event that served as the endpoint. The analyses were controlled for the same covariates as in the first study, with the exception of HDL cholesterol and the addition of diabetes and fibrinogen to the models. The risk for a coronary event was significantly higher among binge drinkers than among non-binge drinkers, and the risk due to binge drinking was essentially same as that for CHD mortality. The risk was somewhat reduced when revascularisations were included, which suggests that binge drinking particularly predisposes for acute coronary events in which thrombosis plays a mechanistic role.

Our results are in accordance with those of most other studies showing that drinking patterns with infrequent drinking or heavy drinking occasions increase the risk for coronary endpoints. Other studies that assess drinking frequencies have found that a pattern of infrequent drinking, usually defined as consuming alcohol less than once a week, associated with a higher risk for coronary events than did a pattern of frequent drinking, often described as the consumption of alcohol at least three times

per week (4, 44, 45, 46). However, most of these studies investigating the effects of drinking frequency in relation to coronary endpoints have not controlled for the amount of alcohol consumed. If the amount of alcohol consumed is taken into account, the risk for myocardial infarction seems to depend on both the quantity and frequency of alcohol consumption in such a manner that the risk for MI more often decreased with increasing frequency, but increased as the drinking dosage increased (173). Those studies that have taken into account the impact of heavy drinking occasions (i.e., binge drinking) on coronary events have found that binge drinking associated with a higher risk for CVD (47) and coronary endpoints (5, 27, 28).Our results are in accordance with those of other studies showing that binge drinking predisposes to coronary events. However, the diversity of binge drinking measurements and the varied controlling for confounders must be emphasised.

The mechanisms behind the association between binge drinking and coronary endpoints remain unknown. Recent studies have suggested that their effects on coagulation, lipids and atherosclerosis are potential pathways. In our study, we adjusted the analyses for several cardiovascular risk factors, but this changed the risk only slightly. The possibility of residual confounding must be addressed as well as the possibility of arrhythmias known to be related to heavy alcohol consumption and withdrawal.

6.3.3.1 The role of fibrinogen as a mechanism between binge drinking and coronary events

Our results concerning high fibrinogen in binge drinkers are consistent with those of some previous studies showing high concentrations of acute phase inflammation markers in heavy drinkers (120). Furthermore, our results are consistent with those of a Russian study that found a positive linear association between total alcohol consumption and CRP in a population with a notably high prevalence of binge drinking (125).

Fibrinogen is known to associate with average alcohol consumption in a U-shaped manner and to be a risk factor for coronary heart disease (140). Furthermore, fibrinogen is an acute phase inflammation marker and a haemostatic protein (136) and both mechanisms (inflammation and coagulation) are considered potential pathways in the relationship between binge drinking and coronary events. In our study, however, the association between binge drinking and coronary events was attenuated only slightly when the effect of fibrinogen was taken into account, thus suggesting that the underlying mechanism is mostly dependent on alternative pathways.

The effect of fibrinogen on the relation between frequent hangovers and CVD mortality was tested earlier in a Finnish cohort (40). That study suggested, as did our results, that some part of the association between hangovers and CVD mortality was mediated through fibrinogen.

Further analysis with CRP in the models would have provided a better view of the underlying mechanism and the possibility to determine whether the observed pathway through fibrinogen reflects more inflammation or coagulation.

6.3.4 Alcohol consumption, binge drinking and depression

Our results showed that binge drinkers and ex-drinkers more often experienced symptoms of depression than did lifelong abstainers or subjects with no binge drinking habit. The results concerning higher rates of depression among binge drinkers are in line with those of earlier studies reporting the co-occurrence of depression with alcohol problems and heavy alcohol consumption (146, 147, 148).

Some studies have shown a higher prevalence of depression among non-drinkers than among moderate drinkers (156, 157, 159) which is consistent with our results. However, we found a higher prevalence of depressive symptoms only among ex-drinkers and not among lifelong abstainers. The literature attributes this to a tendency of past problem drinkers to become non-drinkers, but the evidence is inconsistent. Data from ten population studies found that male former drinkers were more often depressed than were lifelong abstainers (156) However, a British cohort study reported a U-shaped association between alcohol consumption and psychological distress, and the association remained unchanged after excluding the past heavy or problem drinkers (158).

The cross-sectional study design did not allow for interpretation of the causality, although the literature has suggested both causal patterns (149) and shared aetiology (150, 151, 152) as potential mechanisms. The causal patterns of association have only partly been investigated, but some evidence suggests that alcohol consumption alleviated depressive symptoms in short term, although the long term effect was opposite. Furthermore, depression associated with higher alcohol consumption in the short term, but reduced consumption in the long term (153).

Strong evidence suggests that gender influenced the sequence of onset of depression and excessive alcohol consumption. Some studies have reported that alcoholism preceded depression in men, whereas in women, depression was often the preceding condition (174, 175). A meta-analysis of eight prospective population studies found a positive correlation between initial depression and subsequent alcohol consumption

in women (176), whereas initial depression had no significant impact on subsequent alcohol consumption in men.

The further analyses in our study were conducted only for those who consumed alcohol; the main focus was on the binge drinking habit. The analyses showed that the binge drinking habit associated with depressive symptoms independently of average alcohol consumption and other controlled confounders, although age and gender did significantly alter the relationship. Our results are in accordance with many earlier findings that report a higher risk for depression among those with alcohol dependence or a habit of binge drinking. A Canadian cohort study found that binge drinking (> 5 drinks per occasion) associated with depression in women, whereas no such difference was observed among men (177, 178). The diluted association in men may stem from the use of the same definition for binge drinking in both genders in the Canadian cohort, whereas alcohol consumption is known to cause higher blood alcohol concentrations in women. A British cohort study reported a higher risk for depression among binge drinking men, whereas the risk for depression was no higher among binge drinking women or those with alcohol dependence (defined according to AUDIT and SAD-Q questionnaires. Furthermore, a US cohort study found a higher risk for depression among those with alcohol dependence at baseline (179), and a Finnish cohort study showed that alcohol consumption with binge drinking contributed – independently of average alcohol consumption – to the occurrence of depressive symptoms five years later (155).

The mechanism by which the binge drinking pattern influenced the risk for depressive symptoms/clinical depression has been identified as the hangovers and withdrawal often observed after heavy drinking occasions. The neural basis of depression both during and after withdrawal has been associated with decreased serotonin concentrations in both states (180). Even if depressive symptoms have been found to abate after a withdrawal period, usually within four weeks after cessation of drinking (181), a history of past severe withdrawals has been shown to predispose to prolonged depression (182).

6.4 Conclusions and future perspectives

Our study investigating the contribution of binge drinking on mortality was one of the first cohort studies to report excessive all-cause mortality and CHD mortality due to the binge drinking pattern. Since then, evidence has been accumulating, and the findings have recurred in other cohorts. Strong evidence now suggests that drinking large amounts of alcohol on one occasion increases the risk for CHD mortality and morbidity even if the total amount of alcohol consumed does not exceed the limits of harmful consumption.

Furthermore, our study found that binge drinking was an independent risk factor for ischemic and all strokes. Previous case-control studies have suggested that alcohol consumption with a pattern of heavy consumption associated with stroke, but evidence from longitudinal studies was lacking. Our findings were re-tested in a recent longitudinal cohort from Korea (71), which reported a higher risk for all strokes and haemorrhages only among binge drinkers who consumed alcohol daily. At the moment, evidence is insufficient to conclude how drinking patterns affect the risk for stroke and whether the drinking pattern has an independent contribution. However, the accumulating evidence of higher risk for CHD endpoints in binge drinkers suggests that binge drinking should also be considered a risk factor for ischemic stroke because their pathogenesis and common risk factors are essentially the same. Whether binge drinking has an independent contribution to haemorrhagic stroke requires additional investigation in future studies.

To date, no studies have investigated the mechanisms by which binge drinking increases the risk for CHD events and stroke, although their effects on coagulation, thrombosis, and atherosclerosis are considered potential pathways. We investigated the impact of fibrinogen as a potential mediating factor between excess CHD morbidity related to binge drinking. We chose fibrinogen because of its inflammatory and haemostatic properties as well as for its associations with CHD and alcohol consumption. Our results showed that excessive CHD morbidity related to binge drinking was somewhat dependent on fibrinogen. This may indicate that binge drinking increases the risk for CHD events through alternative pathways. Adding other acute phase inflammatory markers to the analysis (CRP, IL-6) would have provided a better view of whether inflammation plays a mechanistic role. At the moment, the underlying mechanism remains uncertain and must be evaluated in future.

Depression is known to associate with alcohol dependence in clinical and population samples. However, little has been known about the role of alcohol drinking patterns and depressive symptoms in general population samples. Our study showed that binge drinking associated with depressive symptoms independently of average con-

sumption; this association has been confirmed in a recent longitudinal cohort, which reported that binge drinking induces depressive symptoms in the general population (155). This supports our hypothesis that a pattern of alcohol drinking involving intoxications, hangovers and withdrawals predisposes to depressive symptoms, and that a binge drinking pattern could serve as a proxy measurement for this unfavourable drinking pattern.

6.5 Public health implications

Alcohol consumption is a well-known public health challenge worldwide. Alcohol consumption has been shown to have both beneficial and harmful effects on health, but the harmful effects related to heavy consumption often overtake the benefits. Health benefits are attributed mainly to the lower risk for CHD and ischemic stroke among light to moderate consumers. Over the past few years, however, accumulating evidence suggests that the pattern of alcohol drinking may modify the effects of alcohol beyond the volume of consumption alone. A pattern of infrequent drinking and drinking large amounts of alcohol on one occasion are associated with increased mortality and morbidity due to cardiovascular diseases. The unfavourable effects of binge drinking on cardiovascular health and depression should be considered a great public health challenge in Finland, where drinking patterns that involve heavy drinking occasions (binge drinking) and the intention for rapid intoxication are traditionally customary. Public health recommendations should take into account drinking pattern in addition to volume measurements. The AUDIT questionnaire includes questions on consumption exceeding six drinks per occasion, and thus provides health care workers with a practical tool for evaluating unfavourable drinking patterns.

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