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Askgaard, G; Christensen, Anne I; Nordestgaard, Børge; Grønbæk, Morten; Tolstrup, Janne S

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Alcohol and risk of non-traumatic bleeding events requiring hospital care in the general population: A prospective cohort study

Gro Askgaard [a, b], Anne I. Christensen [a], Børge Nordestgaard [c, d], Morten Grønbæk [a], Janne S. Tolstrup [a]

[a] National Institute of Public Health, University of Southern Denmark, Studiestræde 6, 1455 Copenhagen K, Denmark

[b] Gastro Unit, Bispebjerg Hospital, Copenhagen University Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark

[c] Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark

[d] The Copenhagen City Heart Study, Frederiksberg Hospital, Copenhagen University Hospital, Nordre Fasanvej 57, 2000 Frederiksberg, Denmark

Corresponding author:
Janne S. Tolstrup
National Institute of Public Health
University of Southern Denmark
Studiestræde 6
1455 Copenhagen K
Denmark
Telephone: +45 65507882
Email: jst@si-folkesundhed.dk

Abstract

Alcohol has a direct effect on blood coagulation and fibrinolysis. We studied how alcohol is related to common bleeding events (e.g., nose bleeding), as well as life-threatening bleeding events (e.g., hemorrhagic stroke) that require hospital care in the general population. We used data from The Copenhagen City Heart Study, 1991 to 1994 and 2001 to 2003. Baseline information on alcohol consumption and potential confounders was obtained by questionnaires, and participants were followed for incident bleeding events with nationwide registers until 2013.

Among the 10,259 included participants, we observed 366 nose or other respiratory organ bleeding events, 149 hemorrhagic stroke events, 470 gastrointestinal bleeding events, 266 unspecified bleeding events, and 1088 any-bleeding events (composite endpoint) during follow-up. Compared to drinkers of 1–6 drinks per week, those drinking ≥35 drinks per week had a higher risk of hemorrhagic stroke [hazard ratio, 2.27 (1.14–4.55)] and non-variceal gastrointestinal bleeding [hazard ratio 2.04 (1.37–3.05)], whereas non-drinkers and drinkers of 7–13, 14–20, 21–27, and 28–34 drinks per week had not. Alcohol consumption was not associated with risk of nose or other respiratory organ bleeding or unspecified bleeding. For non-drinkers and drinkers of 7–13, 14–20, 21–27, 28–34, and 35 or more drinks per week, hazard ratios for the composite endpoint of any bleeding were 1.17 (95% CI: 0.99–1.37), 0.97 (95% CI: 0.81–1.15), 1.00 (95% CI: 0.80–1.26), 0.93 (95% CI: 0.69–1.25), 1.39 (95% CI: 1.00–1.94), and 1.83 (95% CI: 1.39–2.41) compared to drinkers of 1–6 drinks per week.

In conclusion, drinking 35 or more drinks per week may be associated with a higher risk of hemorrhagic stroke and non-variceal gastrointestinal bleeding in the general population.

Highlights

- We studied risk of bleeding events according to weekly alcohol consumption.
- Thirty-five drinks increased the risk of gastrointestinal bleeding and hemorrhagic stroke.
- Alcohol was not associated with risk of nose or other respiratory organ bleeding.

Keywords
alcohol

bleeding
general population
hemorrhage
incident
prospective study

Introduction

Alcohol is consumed by the majority of people in Western populations, and its effect on common and potential life-threatening bleeding events such as nose bleeding, hemorrhagic stroke, and gastrointestinal bleeding is therefore important in a public health perspective (Balakrishnan, Allender, Scarborough, Webster, & Rayner, 2009; Kikidis, Tsioufis, Papanikolaou, Zerva, & Hantzakos, 2014; Strate et al., 2016).

Studies on healthy individuals have indicated that alcohol has a direct effect on blood coagulation and fibrinolysis, which during homeostasis are balanced to avoid excess bleeding and thrombosis (Chapin & Hajjar, 2015; Dimmitt et al., 1998; Engström, Schött, & Reinstrup, 2006; Pieters et al., 2010). This relation between alcohol and blood coagulation might be complex, with light-to-moderate alcohol consumption (<2 drinks/day) promoting less coagulation, and heavy alcohol consumption (>3 drinks/day) promoting both impaired blood coagulation and also impaired fibrinolysis (De Lange et al., 2004; Engström et al., 2006; Kiviniemi et al., 2009; Mukamal et al., 2001; Van De Wiel et al., 2001). Therefore, heavy alcohol consumption is expected to increase the risk of both ischemic and bleeding events, which is in accordance with findings from observational studies of individuals with alcohol dependence (Holst, Tolstrup, Sørensen, & Becker, 2017; Roerecke & Rehm, 2014).

Alcohol consumption is considered to be a risk factor for bleeding in users of oral anticoagulants with atrial fibrillation (Pisters et al., 2010). How and whether alcohol is related to risk of bleeding in the general population has only been sparsely investigated, with an exception for hemorrhagic stroke, which was examined in several prospective cohort studies (Larsson, Wallin, Wolk, & Markus, 2016). Heavy alcohol consumption is associated with hemorrhagic stroke (Larsson et al., 2016). Otherwise, the evidence is conflicting regarding an association of alcohol with non-variceal gastrointestinal bleeding and nearly absent for alcohol and anemia or nose and other respiratory organ bleeding (Andersen, Jørgensen, Bonnevie, Grønbæk, & Sørensen, 2000; Gallerani

et al., 2004; Kaplan et al., 2001; Soyka, Schrepfer, & Holzmann, 2012; Stack, Atherton, Hawkey, Logan, & Hawkey, 2002; Strate et al., 2016).

In order to execute evidence-based clinical counseling, and from a public health perspective, it is relevant to study how levels of alcohol consumption (i.e., abstaining from drinking, light, moderate, or heavy drinking) is related to bleeding events requiring hospital care.

Alcohol is associated with trauma and violence, and heavy drinking likely increases the incidence of traumatic bleeding by this mechanism (Balakrishnan et al., 2009). In this paper, we test the hypothesis that heavy alcohol consumption is associated with a higher risk of bleeding events requiring hospital care compared to light alcohol consumption, independently of traumas. We conducted a prospective study in a population-based cohort on alcohol consumption and risk of hospitalization with a non-traumatic bleeding event with 10 years of follow-up.

Materials and methods

This was a historical cohort study based on data on alcohol and other lifestyle factors collected by questionnaire in The Copenhagen City Heart Study. The cohort was followed up in the nationwide healthcare registers for hospitalization with a non-traumatic bleeding event.

Study population

Data came from a Danish prospective cohort study, The Copenhagen City Heart Study, which is described in detail elsewhere (Schnohr, Jensen, Lange, Scharling, & Appleyard, 2001). Briefly, it was initiated in 1976, where a random sample of the Danish general population above age 20 years living in the center of Copenhagen was invited to participate (number of participants, 14,223; response rate, 74%). This initial examination was followed by three subsequent examinations: a second examination in 1981 to 1983, where all previously invited plus 500 new individuals aged 20 to 24 years were invited (n = 12,698, 70%); a third examination in 1991 to 1994, where all previously invited plus 3,000 new individuals aged 20 to 49 years were invited (n = 10,135, 61%); and a fourth examination in 2001 to 2003, where all previously invited plus an additional sample of

1,040 individuals aged 20 to 29 years were invited (n = 6,238, 50%). In this study, we included participants from the third and fourth examination (enrolled 1991–1994 and 2001–2003); only the participant's baseline examination was considered.

At baseline, all participants completed a detailed questionnaire regarding lifestyle and background factors (alcohol, smoking, physical activity, and years of education), and a brief physical examination was performed, which included measurement of blood pressure, height, and weight.

For the present study, we excluded participants who at baseline had any prior hospital diagnosis of a non-traumatic bleeding event requiring hospital care (n = 196) (International classification of disease [ICD] codes are listed below); who had severe liver disease due to its impact on coagulation (ICD-8: 4560 5710 5718 5719 7853; ICD-10: I850, K70, K746, I189) (n = 67); who had a diagnosis of atrial fibrillation or flutter that often leads to persistent use of anticoagulant drugs (ICD-8: 4274; ICD-10: I48) (n = 171) (Pisters et al., 2010); or who had a diagnosis of prior ischemic stroke (ICD-10: I63-68, G45) also leading to persistent use of anticoagulant drugs (n = 248). We used a diagnosis of ischemic stroke that was previously validated among participants in the Copenhagen City Heart Study (Truelsen, Grønbaek, Schnohr, & Boysen, 2002). Participants with missing information on alcohol consumption (n = 249) or confounding variables including smoking, hypertension, and education (n = 249) were also excluded. Hence, the final sample consisted of 10,259 individuals.

Assessment of alcohol consumption

Participants reported their usual consumption of beer (in bottles), wine (in glasses), and spirits (in units) in number per week. The total number of drinks per week was calculated by summing up the individual types of alcohol, where one drink corresponded to about 12 g of alcohol. We used the following categories for alcohol consumption: 0 (non-drinkers), 1–6, 7–13, 14–20, 21–27, 28–35, and >35 drinks per week. This categorization follows several prior investigations of alcohol consumption in the Copenhagen City Heart Study and facilitates the conversion from drinks

per week to drinks on average per day (Christensen, Nordestgaard, & Tolstrup, 2018; Kristiansen, Grønbæk, Becker, & Tolstrup, 2008; Mukamal, Tolstrup, Friberg, Jensen, & Grønbæk, 2005). It was not possible to separate non-drinkers into current and lifetime non-drinkers since no information was available for alcohol consumption earlier in life. We did not assess the influence of type of alcohol with bleeding events in this study. One earlier study reported associations between type of alcoholic drink consumed and coagulation factors, and found no consistent differences between beer, wine, and liquor drinkers in levels of coagulation factors, indicating that the association between alcohol and bleeding is independent of type of alcohol (Mukamal et al., 2001). Regarding the validity of self-reported alcohol consumption, a previous study on the same study cohort of the Copenhagen City Heart Study found that higher levels of self-reported alcohol consumption were associated with higher increments in liver enzymes (gamma-glutamyl transpeptidase, alanine aminotransferase, erythrocyte volume, and alkaline phosphatase) in blood tests that are expected to correlate with alcohol consumption (Tolstrup, Grønbæk, Tybjærg-Hansen, & Nordestgaard, 2009). Moreover, a validation study found a good overall agreement when alcohol consumption was assessed with questionnaire compared to dietary interview (Grønbaek & Heitmann, 1996).

Follow-up for bleeding

We followed participants from baseline until hospital diagnosis of the different bleeding events, migration (n = 151), death (n = 3767), or April 2013 (end of follow-up), whichever came first. Information on diagnoses of bleeding events were obtained from the Danish National Patient Register that holds records of all Danish hospital admissions since 1977 and further outpatient and emergency room visits since 1995 (Schmidt et al., 2015). Diagnoses in the Danish National Patient Register are classified according to the 8th (1978–1993) and 10th (1994–present) ICD codes. All confounders and outcomes in this study were defined by hospital diagnoses sought from 1977. Bleeding events requiring hospital care were defined by an incident diagnosis of nose or other respiratory organ bleeding (ICD-8: 7830-7831; ICD-10: R04), hemorrhagic stroke (ICD-8: 430-431;

ICD-10: I60-I62), non-variceal gastrointestinal bleeding (ICD-8: 5310, 5312, 5320, 5322, 5340, 5342, 7845; ICD-10: K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K920-922), unspecified bleeding that included anemia due to iron deficiency and bleeding (ICD-8: 280; ICD-10: D50 and D62), or as any bleeding event (a composite endpoint of incident diagnoses for nose or other respiratory organ bleeding, hemorrhagic stroke, gastrointestinal bleeding, and unspecified bleeding). Note that the numbers of the different bleeding events sum up to more than the number of any bleeding events since only incident events were considered. The diagnosis of hemorrhagic stroke was validated independently and blindlyby two experienced medical doctors, and was based on medical records, radiologic imaging, and autopsy reports (Truelsen et al., 2002). Hematuria is usually caused by urinary tract infection or urinary tract catheters and we did not find it relevant as an outcome in this study.

Statistics

We tested whether weekly alcohol consumption reported at study baseline was associated with risk of an first-time bleeding event requiring hospital care during follow-up. Hazard ratios (HRs) for bleeding according to weekly alcohol consumption were estimated using a Cox proportional hazard regression model, with delayed entry and age as the underlying time axis to ensure maximal adjustment for confounding by age. The risk estimates were further adjusted for potential confounders of bleeding events identified in the literature such as those included in the HAS-BLED score (Pisters et al., 2010). Confounders included sex, smoking (never, former, <10 g, 10–20 g, or >20 g tobacco/day) (Andersen et al., 2000), hypertension (systolic blood pressure >160 mmHg) (Christensen et al., 2018; Kikidis et al., 2014; Pisters et al., 2010), somatic comorbidity by means of the Charlson comorbidity index score (CCI) (0, >0) (Crooks, West, & Card, 2013; Thygesen, Christiansen, Christensen, Lash, & Sørensen, 2011), and years of education (<8, 8 to 11, and >11, corresponding to lower primary school, higher primary school, and secondary school). Other variables in the HAS-BLED score of diagnosis of kidney failure (ICD-10: N18) and

admissions for drug abuse (ICD-10: F11–19) were not found among the participants. HRs were estimated separately for each bleeding event requiring hospital care of nose or other respiratory organ bleeding, hemorrhagic stroke, gastrointestinal bleeding, unspecified bleeding, and the composite endpoint of any bleeding. The Cox proportional hazards assumption was examined graphically by plots of log (time) by log (−log [survival probability]), and statistically, by introducing interaction terms between age and alcohol intake in the model. No violations were detected ($p > 0.05$). A trend test on weekly alcohol consumption and risk of a bleeding event requiring hospital care was performed on those reporting any weekly alcohol consumption by excluding alcohol abstainers.

Weekly alcohol consumption was also modeled continuously by cubic splines to account for a non-linear association with the event of any bleeding requiring hospital care. To avoid outliers to influence results inexpediently, participants reporting weekly alcohol amount above the 99th percentile of the distribution of weekly alcohol consumption were excluded in this analysis (n = 99).

To test the relevance of some of the included measures, we tested the included measures on other associations reported in the literature, e.g., alcohol consumption and risk of alcoholic liver cirrhosis and hypertension and risk of bleeding requiring hospital care (Christensen et al., 2018; Kikidis et al., 2014; Pisters et al., 2010; Rehm, 2011). Analyses were carried out in Stata, Release 15.

Results

Of the 10,259 participants included, 4455 were men and 5804 were women. Heavy drinkers consuming 28–35 and 35 or more drinks per week were more often men and more often current smokers than light drinkers consuming 1–6 or 7–13 drinks per week, but the numbers with somatic comorbidity were comparable (Table 1).

During a mean follow-up of 14 person-years (147,333 person-years in total), we observed 366 nose or other respiratory organ bleeding events, 149 hemorrhagic stroke events, 470

gastrointestinal bleeding events, 262 unspecified bleeding events, and 1088 any-bleeding events (composite endpoint).

Participants who consumed 35 drinks or more per week had a higher risk of a gastrointestinal bleeding event compared to drinkers of 1–6 drinks per week, and an increasing weekly alcohol amount was significantly associated with higher risk of gastrointestinal bleeding (*p* for trend 0.001) (Table 2). Risk for hemorrhagic stroke was higher for participants who consumed 35 drinks or more per week compared to 1–6 drinks per week (HR; 2.27, 95% confidence interval [CI]: 1.14–4.55), but not for participants consuming fewer than 35 drinks per week (*p* for trend 0.11). There was no association between weekly alcohol consumption and risk of a nose or other respiratory organ bleeding event requiring hospital care or an unspecified bleeding event requiring hospital care, respectively.

The HR for the composite endpoint of any bleeding requiring hospital care was 1.17 (95% CI: 0.99–1.37) for non-drinkers, 0.97 (95% CI: 0.81–1.15) for consuming 7–13 drinks per week, 1.00 (95% CI: 0.80–1.26) for consuming 14–20 drinks per week, 0.93 (95% CI: 0.69–1.25) for consuming 21–27 drinks per week, 1.39 (95% CI: 1.00–1.94) for consuming 28–34 drinks per week, and 1.83 (95% CI: 1.39–2.41) for consuming 35 drinks or more per week compared to drinkers of 1–6 drinks per week (*p* for trend 0.0003).

When alcohol consumption was modeled continuously, risk of any bleeding requiring hospital care was higher for drinkers of 35 or more drinks per week compared to the reference of 3.5 drinks per week (Figure 1). There was evidence of a non-linear relationship between alcohol consumption and risk of any bleeding requiring hospital care ($p = 0.009$).

Testing the included measures on other associations reported in the literature indicated a fair relevance of the included measures (Table 3). Alcohol consumption of 28 drinks per week or more was strongly associated with a higher risk of alcoholic liver cirrhosis, HR 5.96 (95% CI: 2.20–16.1).

Hypertension (systolic blood pressure ≥160 mmHg) was associated with a higher risk of all the different bleeding events assessed except unspecified bleeding.

Discussion

In this prospective cohort study of 10,259 participants in the Copenhagen City Heart Study, self-reported heavy alcohol consumption (>35 units/week) was associated with higher risks of non-variceal gastrointestinal bleeding, hemorrhagic stroke, and the composite endpoint of an any-bleeding event requiring hospital care, compared to light alcohol consumption. Alcohol consumption was not associated with risk of nose or other respiratory organ bleeding or unspecified bleeding (anemia). Further, analyses indicated a fair relevance of the included measures of alcohol consumption and hypertension of the study analyses.

Strengths and limitations

Study strengths include the large number of individuals and bleeding endpoints. Further, the National Danish Patient Register covers all hospitalizations in Denmark including outpatients and emergency wards since 1995, and the information would be lacking only if participants were treated in another country . Hence, loss to endpoint findings is considered to be negligible for our outcome of non-traumatic bleeding requiring hospital care. The validity of hospital-discharge diagnoses is high: the positive predictive value of the primary hospital-discharge diagnosis in the registry was 81% when compared with a medical chart review of a random sample of 1000 admissions (Schmidt et al., 2015).

An important limitation is the inability to detect all hospitalization recorded in the hospital register that did involve bleedings. For example, it is likely that hospitalizations with gastrointestinal ulcer may involve bleeding even if the diagnostic code only indicates “gastrointestinal ulcer”. Therefore, we may underestimate the actual risk of hospitalizations associated with bleeding. Other limitations include possible bias regarding the valid representation of heavy drinkers in our study cohort from the Copenhagen City Heart Study. If heavy alcohol consumption was associated with

non-participation in the cohort study and with risk of bleeding events requiring hospital care, results could be influenced. Hence, heavy drinkers who participate may be of better health than heavy drinkers in the underlying population, whereas light and moderate drinkers who volunteer may be more representative of moderate and light drinkers (Larsen et al., 2012). Ultimately, such a mechanism underestimates bleeding risk among heavy drinkers, whereas results among light to moderate drinkers are more accurate, hence obscuring a true association between heavy alcohol consumption and risk of a bleeding event. It was not possible to adjust for use of anticoagulant drugs or nonsteroidal anti-inflammatory drugs that are known to increase the risk of bleeding events (Stack et al., 2002). However, we did adjust for comorbidity and we excluded participants with a diagnosis of atrial fibrillation or flutter and ischemic stroke, which often leads to persistent use of anticoagulant drugs. Finally, we did not have information on drinking frequency or binge drinking, which may also be relevant for bleeding risk.

Comparison with other studies

We did not find an association between alcohol consumption and risk of nose or other respiratory bleeding requiring hospital care. To our knowledge, only one prior study looked at this association. This cross-sectional study found elevated blood alcohol markers among 5% of hospital patients with epistaxis (Soyka et al., 2012).

For hemorrhagic stroke, our results correspond to the results in a recent meta-analysis of 27 prospective cohort studies, suggesting a potential J-shaped correlation between alcohol intake and the risk of hemorrhagic stroke, and that an alcohol intake of 10–20 g/day has a potential beneficial effect compared to >30 g/day (Zhang et al., 2014). Further, another meta-analysis of prospective cohort studies found that alcohol consumption exceeding 28 drinks per week was associated with risk of hemorrhagic stroke (Larsson et al., 2016).

Our findings regarding alcohol consumption and non-variceal gastrointestinal bleeding risk are in accordance with earlier studies that investigated this association for different levels of alcohol

consumption or as heavy drinking (Andersen et al., 2000; Gallerani et al., 2004; Strate et al., 2016). These studies found an increased risk of non-variceal gastrointestinal bleeding in drinkers of 28 units per week or more, when compared to light drinkers or abstainers. Other studies did not find this observation. However, these studies did not specifically address the level of alcohol consumption; hence, these studies defined alcohol consumption as drinking 7 or more drinks per week (Kaplan et al., 2001), or as current vs. non-current alcohol use (Stack et al., 2002).

Finally, to our knowledge, it has not been addressed previously whether alcohol consumption is associated with severe anemia due to iron deficiency or bleeding.

Plausible explanations

Acute exposure to high concentrations of ethanol causes severe gastric epithelial damage and necrosis of deeper layers of the mucosa, and causes microvascular damage leading to engorgement, increased permeability, and intramucosal hemorrhage (Andersen et al., 2000). In addition to the local irritative effects of ethanol, it has been shown that moderate to high concentrations of ethanol delay gastric emptying (Andersen et al., 2000). Together, this might explain the observed association between alcohol consumption and risk of gastrointestinal bleeding. Heavy alcohol consumption may be associated with an increased risk of hemorrhagic stroke because heavy alcohol intake is associated with decreased platelet aggregation, increased fibrinolysis, decreased plasma fibrinogen levels, and increased high-density lipoprotein cholesterol levels (Zhang et al., 2014). To our knowledge, it has not been addressed previously whether alcohol consumption is associated with severe iron deficiency anemia requiring hospitalization. Moderate to heavy alcohol consumption is associated with iron overload, which may decrease development of an unspecific bleeding event and iron deficiency anemia (Ioannou, Dominitz, Weiss, Heagerty, & Kowdley, 2004).

Implications

Implications for clinical counseling may be that heavy drinkers at increased risk of bleeding (patients with prior bleeding, anticoagulant users, or with poorly controlled hypertension) should be

advised to reduce their alcohol consumption. From a public health perspective, our findings suggest non-traumatic bleeding risk to be increased for alcohol consumption well above the recommended alcohol limits (Department of Health, 2016). Population-level preventive interventions, such as introducing minimum unit pricing that in particular can decrease heavy drinking, may also decrease non-traumatic bleeding events (Burton et al., 2017).

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Conflict of interest: All authors declare that they have no financial or non-financial interests that may be relevant to the submitted work.

Author contributions: Janne Tolstrup conceived the study idea. Gro Askgaard performed the analyses. All authors declare that they have contributed to the design and manuscript of the study. All authors have approved the final article.

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Data availability: Data are available upon application and approval of the steering committee and the data protection agency.

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Table 1. Baseline characteristics according to alcohol consumption in drinks per week in participants of the Copenhagen City Heart Study 1991-2003, n = 10,259. Values are numbers (%) unless otherwise indicated.

Characteristic	Non-drinkers	1-6	7-13	14-20	21-27	28-34	≥35
Cohort	2225	3366	2308	1086	541	322	411
Sex, men	550 (25)	1121 (33)	1121 (49)	665 (61)	378 (70)	261 (81)	359 (87)
Age in year, mean (range)	63 (21-92)	55 (20-93)	55 (21-93)	56 (21-94)	56 (22-87)	56 (23-86)	56 (23-91)
Current smokers	948 (43)	1379 (41)	1076 (47)	590 (54)	322 (60)	196 (61)	300 (73)
Systolic blood pressure ≥	441 (62)	470 (55)	324 (14)	139 (13)	89 (16)	48 (15)	68 (17)
Charlson comorbidity index, score ≥1	650 (29)	768 (23)	497 (22)	247 (23)	120 (22)	76 (24)	101 (25)
School education < 8 years	1091 (49)	994 (30)	599 (26)	267 (25)	120 (22)	96 (30)	127 (31)

Table 2. Hazard ratios and 95% confidence intervals for incident bleeding events requiring hospital care according to weekly alcohol consumption in participants of the Copenhagen City Heart Study (1991-2003), n = 10,259.

Drinks/week	No.	Events	Hazard ratio (95%CI)*	P for trend **
Nose or other respiratory organ bleeding				
Non-drinkers	2225	89	1.13 (0.85 - 1.50)	
1-6	3366	107	1.00	
7-13	2308	75	0.95 (0.70 - 1.28)	
14-20	1086	36	0.94 (0.64 - 1.38)	
21-27	541	18	0.82 (0.50 - 1.37)	
28-34	322	15	1.20 (0.69 - 2.08)	
≥35	411	26	1.50 (0.96 - 2.36)	0.16
Hemorrhagic stroke				
Non-drinkers	2225	36	1.01 (0.65 - 1.57)	
1-6	3366	44	1.00	
7-13	2308	31	1.09 (0.69 - 1.73)	
14-20	1086	16	1.25 (0.70 - 2.20)	
21-27	541	8	1.20 (0.56 - 2.55)	
28-34	322	4	1.10 (0.40 - 3.08)	
≥35	411	10	2.27 (1.14 - 4.55)	0.11
Gastrointestinal bleeding				
Non-drinkers	2225	128	1.20 (0.93 - 1.53)	
1-6	3366	133	1.00	
7-13	2308	88	0.93 (0.70 - 1.21)	
14-20	1086	38	0.86 (0.60 - 1.25)	
21-27	541	30	1.22 (0.81 - 1.83)	
28-34	322	19	1.52 (0.92 - 2.49)	
≥35	411	34	2.04 (1.37 - 3.05)	0.001
Unspecified bleeding				
Non-drinkers	2225	73	1.11 (0.80 - 1.53)	
1-6	3366	79	1.00	
7-13	2308	51	0.96 (0.67 - 1.37)	
14-20	1086	31	1.29 (0.84 - 1.97)	
21-27	541	11	0.84 (0.44 - 1.60)	
28-34	322	10	1.59 (0.81 - 3.13)	
≥35	411	11	1.37 (0.71 - 2.65)	0.29
Any bleeding (composite endpoint)				
Non-drinkers	2225	290	1.17 (0.99 - 1.37)	
1-6	3366	317	1.00	
7-13	2308	213	0.97 (0.81 - 1.15)	
14-20	1086	103	1.00 (0.80 - 1.26)	
21-27	541	53	0.93 (0.69 - 1.25)	
28-34	322	42	1.39 (1.00 - 1.94)	
≥35	411	70	1.83 (1.39 - 2.41)	0.0003

**Adjusted for age, sex, smoking, hypertension, charlson comorbidity index score, and length of education*

***Non-drinkers were not included in tests for trend*

Table 3. Hazard ratios and 95% confidence intervals for incident bleeding events requiring hospital care and alcoholic liver cirrhosis by heavy alcohol consumption and hypertension in participants of the Copenhagen City Heart Study (1991-2003), n = 10,259.

	Events	Events per 1000 person-years	Hazard ratio (95% CI)	
			Heavy alcohol consumption* (≥28 drinks/week)	Hypertension** (systolic blood pressure ≥ 160)
Nose or other respiratory organ	366	2.5	1.22 (0.81 - 1.82)	1.62 (1.27 - 2.06)
Hemorrhagic stroke	149	1.0	1.67 (0.86 - 3.25)	1.72 (1.13 - 2.62)
Gastrointestinal bleeding	470	3.2	1.52 (1.06 - 2.16)	1.48 (1.21 - 1.83)
Unspecified bleeding	266	1.8	1.32 (0.78 - 2.25)	1.22 (0.92 - 1.62)
Any bleeding (composite endpoint)	1088	7.4	1.40 (1.10 - 1.78)	1.48 (1.29 - 1.70)
Alcoholic liver cirrhosis	55	0.4	5.96 (2.20 - 16.1)	2.06 (1.10 - 3.85)

**Compared to drinking <28 drinks/week. Adjusted for age, sex, smoking, hypertension, charlson comorbidity index score, and length of education*

***Compared to systolic blood pressure <160. Adjusted for age, sex, smoking, alcohol consumption, charlson comorbidity index score, and length of education*

Figure 1. Hazard ratio (solid curve) and 95% confidence intervals (dashed lines) for any bleeding (composite endpoint) according to weekly alcohol consumption in men and women participating in The Copenhagen City Heart study (1991–2003), n = 10,259.