Alcohol use disorder increases the risk of non-fatal and fatal cardiovascular disease events: an 11-year observation of a Polish population-based cohort.

The HAPIEE Study

Authors: Magdalena Kozela, Agnieszka Doryńska, Martin Bobak, Andrzej Pająk

Article type: Original article

Received: July 29, 2020.

Accepted: September 20, 2020.

Published online: September 24, 2020.

ISSN: 1897-9483
Alcohol use disorder increases the risk of non-fatal and fatal cardiovascular disease events: an 11-year observation of a Polish population-based cohort. The HAPIEE Study

Magdalena Kozela¹, Agnieszka Doryńska¹, Martin Bobak², Andrzej Pająk¹.

¹. Department of Epidemiology and Population Studies, Institute of Public Health, Jagiellonian University Medical College, Krakow, Poland
². Department of Epidemiology and Public Health, University College London, London, UK

Address for Correspondence:

Magdalena Kozela, MPH, PhD
Department of Epidemiology and Population Studies, Institute of Public Health, Faculty of Health Sciences, Jagiellonian University Medical College,
20 Grzegorzecka ST. 31–531 Krakow, Poland,
tel: +48 12 433 28 38,
e-mail: m.kozela@uj.edu.pl

Conflict of interest: The Authors declare that there is no conflict of interest.

Short title: Alcohol use disorder increases the risk of cardiovascular disease.
What’s new?

Although public perception seems to be dominated by the cardio-protective effect of moderate alcohol consumption, a recent Mendelian randomization study suggested no beneficial effects of moderate alcohol consumption. Moreover, the accuracy of measuring self-reported alcohol intake, especially in heavy drinkers, is limited. Our findings from a large population-based cohort study suggest a dose-related association between alcohol use disorder assessed by simple 4-item CAGE questionnaire and cardiovascular disease (CVD) incidence. The CAGE questionnaire might potentially be an additional tool to identify persons at high CVD risk.
Abstract

Introduction: Self-reported alcohol intake is not an accurate measure, especially in heavy drinkers. The simple 4-item CAGE questionnaire assessing alcohol use disorder was found to be positively related with alcohol consumption and mortality.

Objectives: To assess the relationship between alcohol use disorder assessed with CAGE questionnaire and the cardiovascular disease (CVD) incidence in a population-based Polish sample.

Patients and methods: A cohort study with an 11-year-follow-up was conducted. A random sample of 10,728 residents of Krakow aged 45–69 completed baseline examination, including the CAGE questionnaire. Information on new CVD cases was obtained from further questionnaires, confirmed by clinical diagnosis. Information on deaths with causes was obtained from the local registry, Central Statistical Office and participants’ families. The effect of CAGE score on CVD risk was assessed using Cox proportional hazard models.

Results: The analysis included 7,112 persons who had completed the CAGE questionnaire and were free of CVD at baseline. No alcohol use disorder was found in 94% of participants. There was a positive association between CAGE score and the CVD risk. In the fully adjusted model, compared to participants scoring 0, the HRs among those scoring 3 and 4 points were 2.19 (95%CI:1.43–3.37) and 2.79 (95%CI:1.65–4.73), respectively. The association was somewhat stronger for fatal CVD.

Conclusions: We found a strong graded association between CAGE score and risk of CVD incidence which was independent from other CVD risk factors. The CAGE questionnaire might be considered as an additional tool to identify persons at high CVD risk.

Key words: alcohol use disorder, cardiovascular disease, incidence, CAGE questionnaire
Introduction

Alcohol use disorder is associated with multiple, well-known health risks such as violence, accidents, suicide, cirrhosis, and cancers of the digestive system and with higher mortality[1,2]. Although public perception seems to be dominated by the cardio-protective effect of moderate alcohol consumption, a recent Mendelian randomization study suggested that there is no beneficial effect of moderate alcohol consumption. [3, 4]. Epidemiological studies which assess relationships between alcohol consumption and health face several substantial limitations in terms of the validity and accuracy of alcohol consumption measurement. The accuracy of methods based on self-reporting, especially in heavy drinkers, has been found to be limited [5]. Questionnaire-based methods for alcohol consumption assessment are sensitive to recall bias, interviewer attitude, and social norms and the accuracy differs between social groups and even within families [6]. By contrast, the CAGE score is simpler and it was found to be positively related with alcohol consumption, even if used as an ordinal measure, rather than a cut-off of two or more [7]. A British study found increased risk of mortality in persons reporting symptoms of alcohol use disorder assessed by CAGE questionnaire [8]. This relationship was also confirmed in the meta-analysis of studies using a different tool for harmful drinking assessment i.e.: Alcohol Use Disorders Identification Test (AUDIT) [9].

Alcohol is a highly addictive substance that can lead to physical and psychological dependence and, in fact, the cardiovascular disease (CVD) outcomes of alcohol dependence are not fully described in population-based research. There is evidence that, in patients with alcohol dependence, the risk of death from ischemic heart disease is substantially higher in comparison to that in the general population [10] and that alcohol dependence is associated with unfavorable cardiovascular risk profiles [11].
The issue of heavy drinking and alcohol use disorder seems especially interesting in Central and Eastern Europe. Alcohol has been postulated to influence mortality in the region as associations have been found between alcohol intake and alcohol-related deaths in Central and Eastern Europe [12]. There is evidence that changes in alcohol intake coincide with mortality trends [13,14]. Studies from Russia have reported increased CVD mortality in heavy drinkers [15,16]. In Poland, the State Agency for the Prevention of Alcohol-Related Problems (PARPA) estimates that alcohol consumption has been increasing since 1990s, reaching an average 9.4 liters of pure alcohol per capita in 2016. Similarly, the number of consultations for persons addicted to alcohol has increased by about 20% over the last decade [17].

The aim of the present study was to assess the relationship between alcohol use disorder assessed with the CAGE questionnaire and the incidence of CVD in a population-based Polish sample.
Patients and Methods

Study design

We conducted a cohort study with an 11-year follow-up based on the Polish part of the HAPIEE project (Health, Alcohol and Psychosocial factors In Eastern Europe). The rationale of the study and the methodology of the whole project were subjected to a detailed description in an earlier publication [18]. Brief information relevant for this report is presented below.

Study sample

The studied group was a random sample of 19,865 men and women selected from a population registry of permanent residents of Krakow aged 45–69 years, after stratification by gender, district and 5 years age groups. The response rate was 61%. After excluding those participants who did not agree for the follow-up, the study sample included 10,012 persons. All participants gave written consent for participation in the study. The study was approved by the Bioethical Committee at the Jagiellonian University Medical College.

At baseline (2002-2005), trained nurses interviewed participants who completed an extensive structured questionnaire and then underwent a physical examination in a clinic, and provided a fasting blood sample. Given the two-stage examination procedure, the participation rate for the clinical examination was by approximately 10% lower than for the interview.

Assessment of alcohol use disorder

Alcohol use disorder was assessed using the CAGE questionnaire, a widely used and validated instrument in alcohol research [19]. The questionnaire consists of the following 4 items: 1) Have you ever felt you should Cut down on your drinking?; 2) Have people Annoyed you by criticizing your drinking?; 3) Have you ever felt bad or Guilty about your drinking?; 4) Have you ever had a drink first thing in the morning to steady your nerves or to get rid of hangover (Eye opener)? The answers ‘no’ or ‘yes’ for each of the questions were coded 0 or 1, respectively. The number of positive answers were summed. The score range
was 0 to 4. The higher the score the higher the probability of alcohol use disorder. A total score of 2 or greater is considered clinically significant for alcohol use disorder. In the current analysis we adopted two approaches: 1) estimation of the risk of CVD event for persons with CAGE scores ≥2 compared to persons with CAGE scores 0–1; and 2) estimation of the risk of an incident of CVD for each number of points on the CAGE scale, with reference category of 0 points.

**Covariates**

Covariates, measured at baseline, included age, education (vocational or lower, secondary, university), marital status (married/cohabiting vs. single/separated/divorced/widowed), smoking pack-years, self-reported history or presence of major cardiovascular chronic conditions (myocardial infarction, stroke; coded yes vs. no). Alcohol consumption was self-reported using the graduated frequency questionnaire (GFQ) containing nine mutually exclusive categories of frequency and amounts, in local units of beer, wine and spirits [19]. Annual alcohol intake was assessed in grams of pure ethanol per year. Participants reporting no alcohol consumption (0 g of pure alcohol) in the past year were categorized as non-drinkers. BMI from clinical examination was calculated in kg/m$^2$; Hypertension was defined as blood pressure ≥ 140/90 mm Hg or receiving treatment for hypertension. Hypercholesterolemia was defined as total cholesterol ≥ 5 mmol/l or low density lipoprotein cholesterol ≥ 3 mmol/l or receiving lipid-lowering treatment [3, 20]. Diabetes was defined as having fasting plasma glucose ≥ 7 mmol/l or having diabetes diagnosed by a doctor.

**Follow up**

Data on deaths by cause were obtained through linkage with the mortality register of residents of the city of Krakow, Central Statistical Office and by contacting the respondents’ families. The causes of deaths were coded according to the 10$^{th}$ Revision of the International Statistical Classification of Diseases and Health Problems (ICD-10). Deaths due to CVD were accepted
for ICD-10 codes from I.00 to I.99. New cases of non-fatal CVD, including myocardial infarction, stroke, coronary artery bypass graft (CABG), percutaneous coronary interventions (PCI) and unstable coronary disease (confirmed by coronary angiography), were identified in the respondents through three postal questionnaires (2005–06, 2008–10 and 2012–13) and re-examination interview (2006–08) and verified by the review of medical documentation. The postal questionnaires and re-examination used identically worded questions on whether the participant had had a myocardial infarction, stroke or coronary angiography, CABG or PCI. For each respondent, the status at the end of the observation was determined and the exact survival time was calculated. The follow up was completed on December 31, 2014. For participants who were lost to follow-up, the censorship date was the date of last contact.

Statistical analysis

Distribution of categorical variables was presented as number and percentage and for continuous variables as mean (SD) or median (Inter quartile range), as appropriate. The Cox regression was used to estimate hazard ratios (HR) with 95 % confidence intervals (CIs) for associations between the CAGE score and CVD risk using time-on-study as the time scale. Three models were fitted: 1) adjusted only for age and sex; 2) adjusted for age, sex and smoking; 3) adjusted for age, sex, smoking, education, marital status, hypertension, hypercholesterolemia, diabetes, BMI, and physical activity. In the supplementary tables CAGE was considered also as continuous variable (p-value for trend). The analysis was restricted to participants with all complete records in all covariates.

The moderation analysis was done to check whether the association between CAGE and CVD risk is homogeneous across age groups and districts. There was no interaction between CAGE and age category as well as between CAGE and districts ($\chi^2=1.37$, p=0.85 and $\chi^2=1.32$, p=0.72, respectively). All analyses in the full study sample were repeated among alcohol
consumers (after excluding abstainers). STATA v. 14 (StataCorp LP, TX, USA) was used for all analyses.
**Results**

From the 10,012 participants recruited in the study, 8,537 persons provided information on CAGE; 1,425 participants with a positive history of CVD at baseline were excluded, and the final analytical sample consisted of 7,112 persons. The mean baseline age was 56.8 years (SD=6.88), and 50.9% (n=3,622) of the sample were males. Among 76,869 person-years, 616 new CVD cases occurred. The median follow up time was 11 years (IQR=0.85 year).

Persons with CAGE scores ≥2 accounted for nearly 6% of the sample. They were younger than the rest of the participants (p<0.001). Among persons with CAGE scores of ≥2, there were significantly more males and persons who were economically active, hypertensive, more exposed to tobacco smoke and alcohol drinking than in the group of CAGE=0–1. Detailed characteristics of study participants by CAGE category are presented in Table 1.

Compared to persons reporting CAGE scores 0 or 1, the age and sex adjusted risk of incident CVD event among those with CAGE ≥2 was 1.90 (95% CI:1.45–2.48) (Table 2). Adjustment for smoking slightly attenuated the relationship, but further inclusion of covariates did not materially change the estimate (HR=1.83 95%CI:1.36–2.47) in the fully adjusted model. Stratification by sex groups showed that the strength of the association in men was lower than in women. However, due to the low number of new CVD cases in women, the fully adjusted model did not show meaningful estimates.

The association between the continuous CAGE score and the risk of incident CVD is presented in Table 3. There was a positive association between CAGE score and the risk of a CVD event. In the fully adjusted model, the HRs among those scoring 3 and 4 points were 2.19 (95%CI:1.43–3.37) and 2.79 (95%CI: 1.65–4.73), respectively. Associations in analyzes restricted to drinkers (i.e. excluding abstainers) provided similar effect estimates. The
observed associations between CAGE score and CVD incidence was stronger for fatal events rather than non-fatal cases; the associations between CAGE and CVD deaths were moderate but robust, and relationships with non-fatal cases were modest and not statistically significant (Table S1). A more pronounced association between CAGE and CVD was observed in the case of myocardial infarction than in other CVD events (Table S2).
**Discussion**

Our findings in this large population-based cohort suggest a dose-related association between alcohol use disorder assessed by the CAGE questionnaire and incident fatal and non-fatal CVD.

The increased risk of CVD incidence among those with a high CAGE score observed both in the total sample as well as in drinkers only seems to be independent of the reported current alcohol intake. This seems plausible, as previous heavy drinking, even after long abstinence, is associated with endothelial dysfunction and hemodynamic, vascular and metabolic abnormalities leading to an unfavorable cardiovascular and metabolic risk profile in apparently disease-free former alcoholics [11].

Our results are consistent with previous studies indicating higher CVD risk in persons with alcohol use disorders [21-24]. For example, in the study by Whitman IR, alcohol abuse diagnosis increased the risk of atrial fibrillation, myocardial infarction, and heart failure to a similar degree as other well-established risk factors. Participants not exposed to classic CVD risk factors were substantially more likely to develop cardiac diseases if they abused alcohol [22].

Bearing in mind several limitations of the CAGE questionnaire, such as its variability of performance by sex, age, and race/ethnicity or poor identification of non-disordered risk drinking, we speculate, based on our results, that the CAGE questionnaire might be considered not only as a screening method to identify alcohol use disorder, but also a tool to assess increased CVD risk. However, our data do not provide evidence strong enough to allow a definitive statement on this issue. A high CAGE score may be a proxy of current (or former) heavy alcohol consumption which is known to increase the risk of CVD [4,15]. Self-
reported alcohol intake is notoriously unreliable and under-reported. The CAGE questionnaire might be seen as less sensitive to recall bias and disclosure of information on undesirable behavior, such as heavy drinking, particularly in women. This may explain why the previous analysis done on the HAPIEE cohort which investigated the associations between the volume, frequency and pattern of drinking and mortality from all causes, CVD, and alcohol-related deaths found that, in both sexes, binge-drinking was weakly associated with mortality from alcohol-related deaths, but not with all-cause or CVD mortality [25]. However, in the Polish part of the HAPIEE study, CAGE score was positively related with declared alcohol drinking and mean average alcohol intake. Additional analysis of Gamma-glutamyl-transferase (GGT) concentration in a random subsample of 666 participants found higher GGT levels in persons with CAGE ≥2 compared to participants with CAGE <2 (p<0.001) [unpublished data].

Besides the large amount of alcohol consumed by participants with alcohol use disorder, a higher CVD incidence may be the result of lower adherence to CVD treatments, and the lower effectiveness of these treatments in alcohol-dependent persons [26].

In our analysis, we addressed the potential confounding by CVD risk factors by including the main risk factors in the model, but we were not able to address other potential reasons for higher CVD risk. In a separate analysis in our sample, we found no significant effect of mediation by the main CVD risk factors in the relationship between CAGE and CVD incidence [data not shown]. As in other observational studies, reversed causation cannot be excluded. However, the notion that persons with asymptomatic CVD are more likely to have alcohol use disorder at baseline does not seem to be plausible. The sensitivity analysis which was performed after exclusion of cases occurring in the first 2 years of observation did not show substantial changes in the estimates (Table S3). The strength and direction of the association in both men and women was similar in current alcohol consumers and in the
whole study sample. The number of participants with high CAGE scores in self-declared non-drinkers was too small for meaningful analysis.

It is worth considering that the CAGE assessed at baseline might not precisely reflect the real status at baseline because it addresses prolonged experience.

The moderate participation rate (55%) could have affected the representativeness of the study sample. There is evidence that study participants are typically the healthier part of the general population [27]. However, we expect that participation rate could substantially bias the main result if the association between CAGE and CVD would be opposite in non-participants, which seems unlikely. Also, there is evidence that declines in participation rates observed in epidemiological studies in the last decades do not necessarily affect the associations studied [28,29]; this seems credible, especially given that the results obtained are consistent with findings from other studies [22-24].

This study has several important strengths. The prospective design, the population-based, culturally homogenous study sample, and the carefully standardized research procedures ensure high quality of the data.

In conclusion, we found an association between CAGE score and subsequent risk of incident CVD which was independent of current alcohol consumption and the main CVD risk factors. The CAGE questionnaire might be considered as an additional tool to identify persons at high CVD risk.
Contribution statement: MK drafted manuscript, did the analysis, AD contributed to the analysis, interpretation and critically revised the manuscript, AP, MB contributed to the design of the study, interpretation of the results and critically revised the manuscript. All authors edited and approved the final version of the manuscript.

Funding: This study was supported by the Wellcome Trust (grant number WT081081) and the US National Institute of Aging (grant number R01AG23522), National Science Centre of Poland (grant number 2018/29/B/NZ7/02118)

Acknowledgements: The authors are grateful to all investigators of the HAPIEE project and to the participants of the surveys.
References

1. Roerecke M, Rehm J. Alcohol use disorders and mortality: a systematic review and meta-analysis. Addiction. 2013; 108: 1562–1578.

2. Rehm J, Baliunas D, Borges GL, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. Addiction. 2010; 105: 817–843.

3. Piepoli MF, Hoes AW, Agewall S, et al. European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2016; 1;37: 2315–2381.

4. Holmes MV, Dale CE, Zuccolo L, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ 2014; 349: g4164

5. Northcote J, Livingston M. Accuracy of self-reported drinking: observational verification of ‘last occasion’ drink estimates of young adults. Alcohol Alcohol. 2011; 46: 709–713.

6. Sobell L, Sobell M. Alcohol consumption measures. In: Allen JP, Wilson WB, eds. Assessing Alcohol Problems: A Guide for Clinicians and Researchers. National Institute on Alcohol Abuse and Alcoholism, 2003 pp 71–77.

7. Skogen JC, Overland S, Knudsen AK, et al. Concurrent validity of the CAGE questionnaire. The Nord-Trøndelag Health Study. Addict Behav. 2011; 36: 302–307.

8. Batty GD, Hunt K, Emslie C, et al. Alcohol problems and all-cause mortality in men and women: predictive capacity of a clinical screening tool in a 21-year follow-up of a
large, UK-wide, general population-based survey. J Psychosom Res. 2009;66: 317-321.

9. Kuitunen-Paul S, Roerecke M. Alcohol Use Disorders Identification Test (AUDIT) and mortality risk: a systematic review and meta-analysis. J Epidemiol Community Health. 2018; 72: 856-863

10. Roerecke M, Rehm J. Chronic heavy drinking and ischaemic heart disease: a systematic review and meta-analysis. Open Heart. 2014; 6:1(1).

11. Di Gennaro C, Biggi A, Barilli AL, et al. Endothelial dysfunction and cardiovascular risk profile in long-term withdrawing alcoholics. J Hypertens. 2007; 25: 367–373.

12. Rehm J, Sulkowska U, Mańczuk M, et al. Alcohol accounts for a high proportion of premature mortality in central and eastern Europe. Int J Epidemiol. 2007; 36: 458–467.

13. Razvodovsky YE. Beverage-specific alcohol sale and cardiovascular mortality in Russia. J Environ Public Health. 2010; 253853.

14. Wojtyniak B, Moskalewicz J, Stokwiszewski J, et al. Gender-specific mortality associated with alcohol consumption in Poland in transition. Addiction. 2005; 100: 1779–1789.

15. Malyutina S, Bobak M, Kurilovitch S, et al. Relation between heavy and binge drinking and all-cause and cardiovascular mortality in Novosibirsk, Russia: a prospective cohort study. Lancet. 2002; 360: 1448–1454.

16. Zaridze D, Lewington S, Boroda A et al. Alcohol and mortality in Russia: prospective observational study of 151 000 adults. Lancet. 2014; 26; 383: 1465–1473.
17. The State Agency for the Prevention of Alcohol-Related Problems. Statistics, http://www.parpa.pl/index.php/badania-i-informacje-statystyczne/statystyki (2018, accessed 11 October 2019).

18. Peasey A, Bobak M, Kubinova R, et al. Determinants of cardiovascular disease and other non-communicable diseases in Central and Eastern Europe: rationale and design of the HAPIEE study. BMC Public Health. 2006; 18; 6: 255.

19. Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA. 1984; 12;252: 1905–1907.

20. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice. The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) Eur Heart J. 2012; 33: 1635–1701

21. Rehm J. Measuring quantity, frequency, and volume of drinking. Alcohol Clin Exp Res. 1998; 22: 4S–14S.

22. Whitman IR, Agarwal V, Nah G, et al. Alcohol Abuse and Cardiac Disease. J Am Coll Cardiol. 2017; 3; 69: 13–24.

23. Roerecke M, Rehm J. Cause-specific mortality risk in alcohol use disorder treatment patients: a systematic review and meta-analysis. Int J Epidemiol. 2014; 43: 906–919.

24. Schwarzinger M, Thiébaut SP, Baillot S, et al. Alcohol use disorders and associated chronic disease—a national retrospective cohort study from France. BMC Public Health. 2017; 21;18: 43.
25. Bobak M, Malyutina S, Horvat P, et al. Alcohol, drinking pattern and all-cause, cardiovascular and alcohol-related mortality in Eastern Europe. Eur J Epidemiol. 2016; 31: 21–30.

26. Beck CA, Southern DA, Saitz R, et al. Alcohol and drug use disorders among patients with myocardial infarction: associations with disparities in care and mortality. PLoS One. 2013; 11;8(9):e66551.

27. Topór-Mądry R. 5-year mortality in respondents and nonrespondent for the cohort study of 20 000 randomly selected middle aged men and women. The HAPIEE Project. Eur J Prev Cardiol. 2012; 19(1 suppl): S71.

28. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol. 2007; 17: 643–653.

29. Nohr EA, Frydenberg M, Henriksen TB, et al. Does low participation in cohort studies induce bias? Epidemiology. 2006; 17: 413–418.
Table 1. Distribution of new cardiovascular disease cases and covariates by CAGE score

| CAGE score | 0 | 1 | 2 | 3 | 4 | CAGE category | 0–1 | ≥2 |
|------------|---|---|---|---|---|---------------|-----|----|
| N          | 6,432 | 263 | 165 | 172 | 80 | P | 6,695 | 417 | P |
| All CVD cases, n(%) | 527 (8.19) | 25 (9.51) | 18 (10.91) | 29 (16.86) | 17 (21.25) | P | 652 (8.24) | 64 (15.35) | P |
| Fatal CVD, n(%) | 219 (3.04) | 14 (5.32) | 11 (6.67) | 13 (6.98) | 9 (10.0) | P | 233 (3.48) | 33 (7.91) | P |
| Non-fatal CVD, n(%) | 308 (4.79) | 11 (4.18) | 7 (4.24) | 16 (9.30) | 8 (10.0) | 0.016 | 319 (4.76) | 31 (7.43) | 0.014 |
| Men, n(%) | 3038 (47.23) | 213 (80.99) | 147 (89.09) | 150 (87.21) | 74 (92.50) | P | 3251 (48.56) | 371 (88.97) | P |
| Age, years, x(SD) | 57.1 (6.91) | 54.8 (6.28) | 55.5 (6.58) | 53.8 (5.84) | 54.1 (5.32) | P | 56.99 (6.90) | 54.5 (6.09) | P |
| Education, n(%) | | | | | | | | |
| vocational | 1,937 | (30.13) | 78 (29.66) | 56 (33.94) | 58 (33.72) | 31 (38.75) | 2,015 | (30.11) | 145 (34.77) | 0.13 |
| high | 2,493 | (38.78) | 76 (28.90) | 50 (30.30) | 68 (39.53) | 33 (41.25) | <0.001 | 2,569 | (38.39) | 151 (36.21) |
| university | 1,999 | (31.09) | 109 (41.44) | 59 (35.76) | 46 (26.74) | 16 (20.00) | 2,108 | (31.50) | 121 (29.02) |
| Marital status, n(%) |  |  |  |  |  |  |  |
|----------------------|------------------|---|---|---|---|---|---|
| married/cohabiting   | 4,999 (77.85)    | 222 (85.06) | 128 (77.58) | 139 (80.81) | 65 (81.25) | 5,221 (78.14) | 332 (79.62) | 0.07 |
| single/widowed       | 1,422 (22.15)   | 39 (14.94)  | 37 (22.42)  | 33 (19.19)  | 15 (18.75) | 1,461 (21.86) | 85 (20.38)  | 0.48 |
| Hypertension*, n(%)  | 3,601 (60.44)   | 138 (58.23) | 101 (70.63) | 99 (64.71)  | 47 (67.14) | 3,739 (60.36) | 247 (67.49) | 0.06 |
| Hypercholesterolemia*, n(%) | 4,990 (85.93) | 194 (83.98) | 126 (87.50) | 134 (90.54) | 60 (86.96) | 5,184 (85.86) | 320 (88.64) | 0.14 |
| Diabetes*, n(%)      | 764 (13.19)     | 36 (15.65)  | 18 (12.50)  | 24 (15.69)  | 12 (17.14) | 800 (13.28)  | 54 (14.71)  | 0.58 |
| BMI*, kg/m², x(SD)   | 28.0 (4.49)     | 27.8 (4.24) | 27.5 (4.62) | 27.1 (4.20) | 26.4 (3.68) | 28.01 (4.49) | 27.1 (4.29) | <0.001 |
| Smoking pack-years, Me(Q1-Q3) | 7.5(0-28) | 23 (5-36.5) | 24.2 (4.4-40.1) | 27.4 (8.5-41.0) | 33.8 (21.3-46.5) | <0.001 | 8.1 (0-28.5) | 28.5 (8.5-42.3) | <0.001 |
| Alcohol drinker      | 5,078 (79.2)    | 259 (99.62) | 164 (99.9) | 170 (99.4)  | 78 (97.5)  | 5,337 (80.0) | 412 (99.8)  | <0.001 |
| Alcohol consumption, g/year, Me (Q1-Q3) | 300 (40–1,340) | 3,140 (1,055–) | 3,720 (1,650–) | 5,460 (2,420–) | 12,460 (3,300–) | 350 (40–1680) | 5,460 (2,100–) | <0.001 |
|          | 7,580) | 10,950) | 14,770) | 30,520) |          | 14,770) |
|----------|---------|---------|---------|---------|----------|---------|

Abbreviations: BMI, body mass index; CVD, cardiovascular disease

*missing data due to lower participation rate in the clinical examination
Table 2. Association between alcohol use disorder and cardiovascular disease risk by sex in the total sample and in drinkers.

|               | HR$^a$ (95%CI) | HR$^b$ (95%CI) | HR$^c$ (95%CI) |
|---------------|----------------|----------------|----------------|
| **All participants N=7,112** |                |                |                |
| CAGE score    |                |                |                |
| 0–1           | ref.           | ref.           | ref.           |
| ≥2            | 1.90 (1.45–2.48) | 1.77 (1.35–2.31) | 1.83 (1.36–2.47) |
| **Drinkers N=5,749** |                |                |                |
| CAGE score    |                |                |                |
| 0–1           | ref.           | ref.           | ref.           |
| ≥2            | 1.90 (1.45–2.48) | 1.76 (1.34–2.32) | 1.83 (1.35–2.47) |
| **All men N=3,622** |                |                |                |
| CAGE score    |                |                |                |
| 0–1           | ref.           | ref.           | ref.           |
| ≥2            | 1.77 (1.34–2.34) | 1.65 (1.25–2.19) | 1.85 (1.36–2.51) |
| **Men drinkers N=3,209** |                |                |                |
| CAGE score    |                |                |                |
| 0–1           | ref.           | ref.           | ref.           |
| ≥2            | 1.79 (1.35–2.37) | 1.67 (1.26–2.22) | 1.87 (1.37–2.56) |
| **All women N=3,490** |                |                |                |
| CAGE score    |                |                |                |
| 0–1           | ref.           | ref.           | ref.           |
| ≥2            | 2.52 (1.03–6.14) | 2.32 (0.95–5.65) | 0.65 (0.09–4.68) |
| **Women drinkers N=2,540** |                |                |                |
| CAGE score    |                |                |                |
| 0–1           | ref.           | ref.           | ref.           |
| ≥2            | 3.01 (1.23–7.40) | 2.73 (1.11–6.73) | 0.74 (0.10–5.37) |

a-adjusted for age, sex (in all participants)
b-adjusted for age, sex (in all participants), and smoking
c-adjusted for age, sex (in all participants), education, marital status, hypertension, hypercholesterolemia, smoking, diabetes, body mass index, physical activity.
Table 3. Association between CAGE score and cardiovascular disease risk in the total sample and in drinkers

|                  | HR\(^a\) (95%CI) | HR\(^b\) (95%CI) | HR\(^c\) (95%CI) |
|------------------|------------------|------------------|------------------|
|                  | CAGE score       |                  |                  |
| All participants | N=7,112          |                  |                  |
| 0                | ref.             | ref.             | ref.             |
| 1                | 1.16 (0.77–1.74) | 1.11 (0.73-1.66) | 1.11 (0.69-1.78) |
| 2                | 1.23 (0.76–1.97) | 1.17 (0.73-1.88) | 1.15 (0.67-1.96) |
| 3                | 2.25 (1.54–3.30) | 2.08 (1.42-3.05) | 2.19 (1.43-3.37) |
| 4                | 2.95 (1.81–4.81) | 2.61 (1.60-4.28) | 2.79 (1.65-4.73) |

Drinkers N=5,749

|                  | HR\(^a\) (95%CI) | HR\(^b\) (95%CI) | HR\(^c\) (95%CI) |
|------------------|------------------|------------------|------------------|
|                  | CAGE score       |                  |                  |
| 0                | ref.             | ref.             | ref.             |
| 1                | 1.12 (0.74–1.70) | 1.08 (0.71-1.63) | 1.05 (0.64-1.71) |
| 2                | 1.22 (0.76–1.97) | 1.17 (0.73-1.88) | 1.15 (0.67-1.97) |
| 3                | 2.27 (1.54–3.32) | 2.09 (1.42-3.06) | 2.19 (1.42-3.37) |
| 4                | 2.90 (1.78–4.75) | 2.57 (1.57-4.22) | 2.75 (1.61-4.67) |

\(^a\)-adjusted for age, sex

\(^b\)-adjusted for age, sex and smoking (pack-years)

\(^c\)-adjusted for age, sex, education, marital status, hypertension, hypercholesterolemia, smoking (pack-years), diabetes, body mass index physical activity