ORIGINAL ARTICLE

Alcohol use disorder increases the risk of nonfatal and fatal cardiovascular disease: an 11-year follow-up of a Polish population-based cohort. The HAPIEE study

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ABSTRACT

INTRODUCTION Self-reported alcohol intake is an inaccurate measure, especially in heavy drinkers. The simple 4-item CAGE questionnaire assessing alcohol use disorder was found to be positively associated with alcohol consumption and mortality.

OBJECTIVES This study aimed to investigate the relationship between alcohol use disorder assessed with the CAGE questionnaire and the incidence of cardiovascular disease (CVD) 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 Kraków aged 45 to 69 years completed baseline examination, including the CAGE questionnaire. Information on new cases of CVD was obtained from further questionnaires and confirmed by clinical diagnosis. Data on mortality and causes of death were obtained from the local registry, the Central Statistical Office, and the participants' families. The effect of the CAGE score on the risk of CVD was assessed using Cox proportional hazard models.

RESULTS The analysis included 7112 individuals who completed the CAGE questionnaire and were free of CVD at baseline. No alcohol use disorder was reported in 94% of the participants. There was a positive association between the CAGE score and the risk of CVD. In the fully adjusted model, compared with participants scoring 0, the hazard ratios 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 the CAGE score and the risk of CVD incidence, which was independent of other risk factors for CVD. The CAGE questionnaire might be considered as an additional tool to identify individuals at high risk of CVD.

INTRODUCTION Alcohol use disorder is associated with multiple, well-known health risks such as violence, accidents, suicide, cirrhosis, and cancers of the digestive system as well as with higher mortality.[1,2] Although public perception seems to be dominated by the cardioprotective 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 that 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 the assessment of alcohol consumption are sensitive to recall bias, interviewer's 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 to

WHAT'S NEW?

Although public perception seems to be dominated by the cardioprotective effect of moderate alcohol consumption, a recent mendelian randomization study showed no benefits 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 that there is a dose-related association between alcohol use disorder assessed by the simple 4-item CAGE questionnaire and the incidence of cardiovascular disease. The CAGE questionnaire might serve as an additional tool to identify persons at high risk of developing cardiovascular disease.

alcohol consumption, even if used as an ordinal measure rather than a cutoff of 2 or more measures.[7] A British study demonstrated an increased mortality risk in persons reporting symptoms of alcohol use disorder assessed by the CAGE questionnaire.[8] This relationship was also confirmed in a meta-analysis of studies using a different tool for harmful drinking assessment, ie, the Alcohol Use Disorders Identification Test (AUDIT).[9]

Alcohol is a highly addictive substance that can lead to physical and psychological dependence and, in fact, cardiovascular disease (CVD) outcomes of alcohol dependence are not fully described in population-based research. There is evidence showing that, in patients with alcohol dependence, the risk of death due to ischemic heart disease is substantially higher in comparison to that noted 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 to be especially interesting in Central and Eastern Europe. Alcohol has been postulated to influence mortality in this region, as associations have been found between alcohol intake and alcohol-related deaths in Central and Eastern Europe.[12] It has been shown that changes in alcohol intake coincide with mortality trends.[13,14] Studies from Russia have reported increased mortality due to CVD in heavy drinkers.[15,16] In Poland, the State Agency for the Prevention of Alcohol-Related Problems (Państwowa Agencja Rozwiązywania Problemów Alkoholowych [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 (Health, Alcohol and Psychosocial Factors in Eastern Europe) project. The rationale for the study and the methodology of the whole project were described in detail elsewhere.[18] Brief information relevant for this report is presented below.

Study sample The study group was a random sample of 19 865 men and women selected from a population registry of permanent residents of Kraków aged 45 to 69 years, after stratification by sex, district, and 5-year age groups. The response rate was 61%. After excluding those participants who did not agree for follow-up, the study sample included 10 012 persons. All participants provided written consent to participate in the study. The study was approved by the bioethical committee at Jagiellonian University Medical College.

At baseline (2002–2005), trained nurses interviewed participants who completed an extensive, structured questionnaire, then underwent a physical examination in a clinic, and had a fasting blood sample taken. The examination procedure included 2 stages, and the participation rate for the clinical examination was approximately 10% lower than for the interview.

Assessment of alcohol use disorder Alcohol use disorder was assessed by 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 as 0 or 1, respectively. The number of positive answers were summed. The score ranged between 0 and 4. The higher the score, the higher the probability of alcohol use disorder. A total score of 2 or greater was considered clinically significant for alcohol use disorder. In the current analysis, we adopted 2 approaches: 1) the estimation of the risk of CVD event for persons with CAGE score ≥2 compared with persons with a CAGE score of 0 to 1; and 2) the estimation of the risk of an incident of CVD for each number of points on the CAGE scale, with the reference category of 0 points.

Covariates Covariates, measured at baseline, included age, education (vocational or lower, secondary, university), marital status (married or cohabiting versus single, separated, divorced, or widowed), smoking status (pack-years), self-reported history or presence of major cardiovascular chronic conditions (myocardial infarction, stroke; coded as yes versus no). Alcohol consumption was self-reported by the participants using the graduated frequency questionnaire that included 9 mutually exclusive categories of frequency and amounts, in local units, of beer, wine, and spirit.[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. Body mass index on clinical examination was calculated in kg/m². Hypertension was defined as blood pressure ≥140/90 mm Hg or receiving treatment for hypertension. Hypercholesterolemia was regarded as total cholesterol level ≥5 mmol/l or low-density lipoprotein cholesterol level ≥3 mmol/l, or receiving lipid-lowering treatment.[3,20] Diabetes was defined as fasting plasma glucose level ≥7 mmol/l or having diabetes diagnosed by a doctor.

Follow-up Data on deaths by cause were obtained using the mortality registry of residents of the city of Kraków, the Central Statistical Office, and by contacting the respondents' families. The causes of deaths were coded according to the *International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)*. Deaths due to *ICD-10* codes from I00 to I99 were regarded as caused by CVD. New cases of nonfatal CVD including myocardial infarction, stroke, coronary artery bypass grafting, percutaneous coronary interventions, and unstable coronary artery disease (confirmed by coronary angiography) were identified in the respondents through 3 postal questionnaires (2005–2006, 2008–2010, and 2012–2013) and an re-examination interview (2006–2008) and verified by the review of medical documentation. The identically worded questions as to whether the participant had had myocardial infarction, stroke, coronary angiography, coronary artery bypass grafting, or percutaneous coronary intervention were used in the postal questionnaires and during re-examination. At the end of the follow-up, the status of each respondent 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 the last contact.

Statistical analysis The distribution of categorical variables was presented as number and percentage and as mean (SD) or median (interquartile range) for continuous variables, as appropriate. The Cox regression was used to estimate hazard ratios (HRs) with 95% CIs for associations between the CAGE score and the risk of CVD, based on 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 status; 3) adjusted for age, sex, smoking status, education, marital status, hypertension, hypercholesterolemia, diabetes, body mass index, and physical activity. In the supplementary tables, CAGE was also regarded as a continuous variable (*P* value for trend). The analysis was restricted to participants with complete records for all covariates.

Moderation analysis was performed to check whether the association between the CAGE score and the risk of CVD was homogeneous across age groups and districts. There was no interaction between the CAGE score and age as well as between

the CAGE score and districts (χ^2 = 1.37, *P* = 0.85 and χ^2 = 1.32, *P* = 0.72, respectively). All analyses in the full study sample were repeated among alcohol consumers (after excluding abstainers). The STATA software, version 14 (StataCorp LP, College Station, Texas, United States) was used for all analyses.

RESULTS Out of the 10 012 participants recruited in the study, 8537 persons provided information on the CAGE score; 1425 participants with a positive history of CVD at baseline were excluded, and the final study sample consisted of 7112 persons. The mean (SD) baseline age was 56.8 (6.88) years, and men comprised 50.9% of the sample (n = 3622). Among 76 869 person-years, 616 new cases of CVD were noted. The median (IQR) follow-up time was 11 (10.84–11.74) years.

Individuals with CAGE score ≥2 accounted for nearly 6% of the sample. They were younger than the rest of the participants (*P* <0.001). Among those with CAGE score ≥2, there were significantly more men and persons who were economically active, hypertensive, and more exposed to tobacco smoke and alcohol drinking than in the group of participants with a CAGE score of 0 to 1. The detailed characteristics of the study participants by CAGE category are presented in **TABLE 1**.

Compared with persons reporting a CAGE score of 0 or 1, the age- and sex-adjusted risk of CVD event among those with CAGE score ≥2 was 1.9 (95% CI, 1.45–2.48) (**TABLE 2**). Adjustment for smoking status slightly attenuated the relationship, but further inclusion of covariates did not 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 significant estimates.

The association between the continuous CAGE score and the risk of CVD is presented in **TABLE 3**. There was a positive association between the 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 analyses restricted to drinkers (ie, excluding abstainers) provided similar effect estimates. The observed associations between the CAGE score and the incidence of CVD was stronger for fatal events rather than nonfatal cases; the associations between the CAGE score and CVD-related deaths were moderate yet robust, and relationships with nonfatal cases were modest and nonsignificant (Supplementary material, *Table S1*). A more pronounced association between the CAGE score and CVD was observed in the case of myocardial infarction compared with other CVD events (Supplementary material, *Table S2*).

DISCUSSION Our findings obtained in this study of a large, population-based cohort suggested a dose-related association between alcohol use

TABLE 1   Distribution of new cases of cardiovascular disease and covariates by the CAGE score

Variable		CAGE score						CAGE category		
		0	1	2	3	4	P value	0–1	≥2	P value
Participants, n		6432	263	165	172	80	–	6695	417	–
All CVD cases		527 (8.19)	25 (9.51)	18 (10.91)	29 (16.86)	17 (21.25)	<0.001	552 (8.24)	64 (15.35)	<0.001
Fatal CVD		219 (3.04)	14 (5.32)	11 (6.67)	13 (6.98)	9 (10)	<0.001	233 (3.48)	33 (7.91)	<0.001
Nonfatal CVD		308 (4.79)	11 (4.18)	7 (4.24)	16 (9.30)	8 (10)	0.016	319 (4.76)	31 (7.43)	0.014
Male sex		3038 (47.23)	213 (80.99)	147 (89.09)	150 (87.21)	74 (92.5)	<0.001	3251 (48.56)	371 (88.97)	<0.001
Age, y, mean (SD)		57.1 (6.91)	54.8 (6.28)	55.5 (6.58)	53.8 (5.84)	54.1 (5.32)	<0.001	56.99 (6.9)	54.5 (6.09)	<0.001
Education	Vocational	1937 (30.13)	78 (29.66)	56 (33.94)	58 (33.72)	31 (38.75)	<0.001	2015 (30.11)	145 (34.77)	0.13
	Secondary	2493 (38.78)	76 (28.9)	50 (30.3)	68 (39.53)	33 (41.25)		2569 (38.39)	151 (36.21)	
	University	1999 (31.09)	109 (41.44)	59 (35.76)	46 (26.74)	16 (20)		2108 (31.5)	121 (29.02)	
Marital status	Married or cohabiting	4999 (77.85)	222 (85.06)	128 (77.58)	139 (80.81)	65 (81.25)	0.07	5221 (78.14)	332 (79.62)	0.48
	Single or widowed	1422 (22.15)	39 (14.94)	37 (22.42)	33 (19.19)	15 (18.75)		1461 (21.86)	85 (20.38)	
Hypertension[a]		3601 (60.44)	138 (58.23)	101 (70.63)	99 (64.71)	47 (67.14)	0.06	3739 (60.36)	247 (67.49)	0.007
Hypercholesterolemia[a]		4990 (85.93)	194 (83.98)	126 (87.5)	134 (90.54)	60 (86.96)	0.45	5184 (85.86)	320 (88.64)	0.14
Diabetes[a]		764 (13.19)	36 (15.65)	18 (12.5)	24 (15.69)	12 (17.14)	0.58	800 (13.28)	54 (14.71)	0.43
BMI[a], kg/m², mean (SD)		28 (4.49)	27.8 (4.24)	27.5 (4.62)	27.1 (4.2)	26.4 (3.68)	0.11	28.01 (4.49)	27.1 (4.29)	<0.001
Smoking pack-years, median (IQR)		7.5 (0–28)	23 (5–36.5)	24.2 (4.4–40.1)	27.4 (8.5–41)	33.8 (21.3–46.5)	<0.001	8.1 (0–28.5)	28.5 (8.5–42.3)	<0.001
Alcohol drinker		5078 (79.2)	259 (99.62)	164 (99.9)	170 (99.4)	78 (97.5)	<0.001	5337 (80)	412 (99.8)	<0.001
Alcohol consumption, g/year, median (IQR)		300 (40–1340)	3140 (1055–7580)	3720 (1650–10 950)	5460 (2420–14 770)	12 460 (3300–30 520)	<0.001	350 (40–1680)	5460 (2100–14 770)	<0.001

Data are presented as number (percentage) of participants unless otherwise indicated.

a   Missing data due to the lower rate of participation in the clinical examination

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

TABLE 2 The association between alcohol use disorder and the risk of cardiovascular disease by sex in the total study sample and in drinkers

		HR[a] (95%CI)	HR[b] (95%CI)	HR[c] (95%CI)
All participants (n = 7112)				
CAGE score	0–1	Reference	Reference	Reference
	≥2	1.9 (1.45–2.48)	1.77 (1.35–2.31)	1.83 (1.36–2.47)
Drinkers (n = 5749)				
CAGE score	0–1	Reference	Reference	Reference
	≥2	1.9 (1.45–2.48)	1.76 (1.34–2.32)	1.83 (1.35–2.47)
All men (n = 3622)				
CAGE score	0–1	Reference	Reference	Reference
	≥2	1.77 (1.34–2.34)	1.65 (1.25–2.19)	1.85 (1.36–2.51)
Male drinkers (n = 3209)				
CAGE score	0–1	Reference	Reference	Reference
	≥2	1.79 (1.35–2.37)	1.67 (1.26–2.22)	1.87 (1.37–2.56)
All women (n = 3490)				
CAGE score	0–1	Reference	Reference	Reference
	≥2	2.52 (1.03–6.14)	2.32 (0.95–5.65)	0.65 (0.09–4.68)
Female drinkers (n = 2540)				
CAGE score	0–1	Reference	Reference	Reference
	≥2	3.01 (1.23–7.4)	2.73 (1.11–6.73)	0.74 (0.1–5.37)

a   Adjusted for age and sex (in all participants)

b   Adjusted for age, sex (in all participants), and smoking status

c   Adjusted for age, sex (in all participants), education, marital status, hypertension, hypercholesterolemia, smoking status, diabetes, body mass index, and physical activity

Abbreviations: HR, hazard ratio

TABLE 3 The association between the CAGE score and the risk of cardiovascular disease in the total study sample and in drinkers

		HR[a] (95% CI)	HR[b] (95% CI)	HR[c] (95% CI)
All participants (n = 7112)				
CAGE score	0	Reference	Reference	Reference
	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 (1.54–3.3)	2.08 (1.42–3.05)	2.19 (1.43–3.37)
	4	2.95 (1.81–4.81)	2.61 (1.6–4.28)	2.79 (1.65–4.73)
Drinkers (n = 5749)				
CAGE score	0	Reference	Reference	Reference
	1	1.12 (0.74–1.7)	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	2.9 (1.78–4.75)	2.57 (1.57–4.22)	2.75 (1.61–4.67)

a   Adjusted for age and sex

b   Adjusted for age, sex, and smoking status (pack-years)

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

Abbreviations: see **TABLE 2**

disorder assessed by the CAGE questionnaire and incident fatal and nonfatal CVD.

The increased risk of CVD incidence among individuals 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 a higher risk of CVD in persons with alcohol use disorders.[21-24] For example, in a study by Whitman et al,[22] the diagnosis of alcohol abuse increased the risk of atrial fibrillation, myocardial infarction, and heart failure to a similar degree as other well-established risk factors. Study participants not exposed to classic risk factors for CVD were substantially more likely to develop cardiac diseases if they abused alcohol.

Considering several limitations of the CAGE questionnaire, such as its variability of performance regarding sex, age, and race/ethnicity or poor identification of nondisordered risky drinking behaviors, we speculate, based on our results, that the CAGE questionnaire might be regarded not only as a screening tool to identify alcohol use disorder but also as an instrument to assess an increased risk of CVD. However, our data do not provide evidence strong enough to formulate 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 conducted in 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 alcohol-related deaths, but not with all-cause or CVD mortality.[25] However, in the Polish part of the HAPIEE study, the CAGE score was positively related to declared alcohol drinking and mean alcohol intake. The additional analysis of the γ-glutamyl transferase (GGT) concentration in a random subsample of 666 participants showed higher GGT levels in persons with CAGE score ≥2 compared with those with CAGE score <2 (P <0.001) (data not shown).

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

In our analysis, we addressed the potential confounding by risk factors for CVD through including the main risk factors in the model, but we could not address other potential reasons for a higher risk of CVD. In a separate analysis in our

sample, we found no significant effect of mediation by the main CVD risk factors in the relationship between the CAGE score and CVD incidence (data not shown). Like in other observational studies, reverse causation cannot be excluded. However, it does not seem to be plausible that persons with asymptomatic CVD are more likely to have alcohol use disorder at baseline. The sensitivity analysis, which was performed after the exclusion of cases of death occurring in the first 2 years of follow-up, did not show substantial changes in the estimates (Supplementary material, *Table S3*). The strength and direction of the association in both men and women were similar in current alcohol consumers and in the whole study sample. The number of participants with high CAGE scores among self-declared nondrinkers was too small for reliable analysis.

It is worth considering that the CAGE score 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 showing that study participants typically represent the healthier part of the general population.[27] However, we expect that the participation rate could substantially bias the main result if the association between the CAGE score and CVD would be opposite in nonparticipants, which seems unlikely. Also, it has been shown that declines in participation rates observed in epidemiological studies in the last decades do not necessarily affect the analyzed associations[28,29]; this seems credible, especially given that the results obtained are consistent with findings from other studies.[22-24]

This study had several relevant strengths. The prospective design, the population-based, culturally homogeneous study sample, and the carefully standardized research procedures ensured that the obtained data were of high quality.

In conclusion, we found an association between the CAGE score and the subsequent risk of incident CVD, which was independent of current alcohol consumption and the main risk factors for CVD. The CAGE questionnaire might be considered an additional tool to identify persons at high risk of developing CVD.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

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