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Alcohol Consumption as a Risk Factor for Atrial Fibrillation: a Systematic Review and Meta-Analysis

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Abstract

Background—Alcohol exposure is one of the major risk factors for global burden of disease, but atrial fibrillation (AF) had not yet been included in these estimates. The purpose of this contribution was to examine the dose-response relationship between alcohol consumption and AF and to explore potential causal pathways.

Design and methods—Systematic literature review and meta-analyses

Results—Overall, a consistent dose-response relationship between the amount of alcohol consumed daily and the probability of the onset of AF was found. Women consuming 24, 60, and 120 grams of alcohol daily had RRs of 1.07 (95% CI: 1.04,1.10), 1.42 (95% CI: 1.23,1.64) and 2.02 (95% CI: 1.60,2.97) respectively, relative to non-drinkers. Among men, the corresponding RRs were 1.08 (95% CI: 1.04,1.11), 1.44 (95% CI: 1.23,1.69) and 2.09 (95% CI: 1.52,2.86). Based on the categorical analyses, we could not exclude the existence of a threshold (3 drinks a day for men and 2 drinks a day for women). Several pathogenic mechanisms for the development of atrial fibrillation in alcohol users were identified.

Conclusions—Epidemiological criteria for causality were met to conclude a causal impact of alcohol consumption on the onset of AF with a monotonic dose-response relationship. However, the impact of light drinking is not clear.

Keywords

alcohol; heavy drinking; atrial fibrillation; cardiac rhythm disorders; causality

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Introduction

Alcohol consumption is one of the most important risk factors for the global burden of disease and disability [1;2]. Besides the health states directly related to alcohol consumption such as alcohol dependence or alcoholic liver cirrhosis, alcohol use is also causally linked to a wide range of acute and chronic conditions traditionally considered to be outside the addiction field [3;4]

Several cardiovascular disease categories have been linked to alcohol, especially to heavy consumption [5-7], but the relationship to cardiac arrhythmias has not been included in most studies on alcohol-attributable mortality or burden of disease. Within the category of arrhythmias, atrial fibrillation (AF) has been discussed to be potentially caused by alcohol for several decades [8]. AF is the most common arrhythmia in clinical practice with approximately 2.2 million people in America having paroxysmal or persistent AF. During the past 20 years there has been a 66% increase in hospital admission due to AF [9;10].

In 1978, Ettinger linked heavy alcohol consumption on week-ends or holidays with the higher risk of the subsequent onset of cardiac disturbances, mainly AF [11], currently known as the “Holiday Heart Syndrome”. Different studies have subsequently assessed the association between alcohol consumption and AF [12-17]. All but one of these studies were conducted after the publication of the two meta-analyses on this topic, both of which dealt with the larger category of cardiac rhythm disorders based on the same two studies with the same pooled results, showing no significant differences for any drinking category [18;19].

Several publications since the last meta-analysis highlighted the association between heavy alcohol consumption and increased risk of cardiac arrhythmias [8]. For instance, significant risk was associated with 6+ drinks per day on average ($= >48$ g/day of pure ethanol) in a UK-study [16]; 5+ drinks ($= >60$ g) per day for men in the Copenhagen City Heart study [12] or 3+ drinks ($= >36$ g) per day in the Framingham study [13]. On the other hand, the effects of light to moderate alcohol consumption on the onset of AF in the same studies could not be clearly established. The cited and other recently published studies enable not only a better quantification of the risks of the onset of AF related to alcohol consumption, but also the testing of the hypothesis of whether there is a threshold for the effect of alcohol exposure.

Objectives

The main objective was to quantify the dose-response relationship between average volume of alcohol consumption and onset of AF. The second objective was to test for a potential threshold for the effect of alcohol exposure, the third objective to examine criteria to establish causality of this relationship.

Methods

Definition of outcome

The outcome of the studies was atrial fibrillation diagnosed by physician on the basis of clinical findings verified by ECG data, according to the diagnostic criteria of the International Statistical Classification of Diseases and Related Health Problems (ICD), 9th and 10th revisions, correspondingly (ICD-10 code: I48 – atrial fibrillation and flutter; ICD-9 code: 427.31).

Systematic literature search and extraction of data

A systematic literature search was performed for studies on the association between alcohol consumption and atrial fibrillation using multiple electronic bibliographic databases, including: Ovid MEDLINE, EMBASE, Web of Science, CINAHL, PsychINFO, ETOH and Google Scholar. The period of search was from January 1960 to April 2009, with no language restrictions. The search was performed in April 2009 using the following combinations of the key words: alcohol* (truncated), alcohol, alcohol consumption, alcohol intake, drinking, alcoholism, alcohol abuse, alcohol misuse, rhythm* (truncated), arrhythmia, dysrhythmia, tachyarrhythmia, bradyarrhythmia, tachycardia, bradycardia, conduction, fibrillation, flutter, atrial, ventricular, paroxysmal, extrasystol* (truncated). Additionally, major epidemiological journals and reference lists of relevant articles were reviewed manually. The first iteration of the search was performed by AVS; the full-text review of selected articles, the decision of inclusion into analysis and the data extraction were performed by AVS and HI.

The inclusion criteria for reviewed articles were:

1. A case-control or cohort design.
2. The inclusion of hazard ratios (HR), relative risks (RR) or odds ratios (OR), with 95% confidence intervals (CI) (or information allowing for their calculation) associated with different levels of alcohol consumption compared to abstinence.
3. The endpoint being AF morbidity.
4. Three or more categories of alcohol consumption reported for dose-response analysis.

If multiple published reports based on the same study data were found, the one with the most comprehensive data on alcohol consumption was included in the meta-analysis. The bibliographic database search resulted in 1,431 articles, 16 of which were potentially relevant. Based on inclusion criteria 6 studies, comprising of 8 independent datasets were selected for analysis of the risk for the onset of atrial fibrillation related to alcohol consumption (Figure 1). Also, in order to minimize the chances of missing relevant studies in which no association between alcohol consumption and development of AF was found and thus alcohol consumption was included neither into keywords nor abstract, we have performed additional broad search using keywords “atrial fibrillation”, “rhythm*” (truncated) and “risk factor” – 2,230 articles were screened for retrieval, no new studies that would meet inclusion criteria were found. Characteristics of selected studies are presented in Table 1.

Alcohol consumption was converted to average grams pure alcohol per day. A midpoint was calculated when alcohol consumption was given in ranges. In cases of open-ended categories, 75% of the width of the previous range category was added to the lower bound of such categories.

Causal criteria

Causal relationship between alcohol consumption and atrial fibrillation was established on the basis of the standard criteria for causality in epidemiology [20;21]: association and strength of association, temporality, consistency, dose-response relationship, plausibility of biological pathways, exclusion of confounding and alternative explanations, and reversibility following interventions.

Statistical Analysis

To examine the dose-response relationship between alcohol consumption and risk of atrial fibrillation (objective 1), the method proposed by Greenland and colleagues [22;23] was used to back-calculate and pool the risk estimates. The midpoints described above were used for the regression analyses. To derive the dose-response curve, we fitted a family of first and second degree fractional polynomial models [24]. All models were fitted using DerSimonian and Laird's [25] random-effects model to incorporate the between-study variability. The best fitting model was selected based on a closed-test comparison between fractional polynomial models [24] and overall model fit was assessed using the Q statistic [26]. These analyses were completed using the GLST command in Stata 10.1 [27].

Regression analysis might provide distorted results for levels of drinking, where no or few data points exist, as it tries to minimize the overall deviation of data points from the regression line. Categorical analyses can give a better indication on the risk for specific categories, and thus is better suited to detect thresholds (objective 2). To assess whether a threshold exists, that is, a level of alcohol consumption under which the risk of atrial fibrillation was not increased, we also modeled alcohol intake using the following categories: 0 (reference group), >0-2, >2-3, >3-4, and >4 drinks daily. A drink was equivalent to 12 grams.

Statistical heterogeneity between studies was assessed using both the Cochrane Q statistic and the I^2 statistic. For the Q-statistic, a p-value of <0.10 was considered to be representative of statistically significant heterogeneity. I^2 ranges between 0% and 100% and describes the percentage of total variation across studies that is due to heterogeneity. A value of zero indicates no observed heterogeneity, and larger values show increasing heterogeneity [26;28]. Publication bias was assessed by visual inspection of Begg's funnel plot [29] and by applying two statistical tests: Begg-Mazumdar adjusted rank correlation test [30], and the Egger regression asymmetry test [29]. A p-value of <0.10 was considered as indication of statistically significant publication bias. All statistical analyses were completed using Stata Version 10.1 [27].

Results

The meta-analysis on alcohol consumption and AF yielded an overall pooled relative risk of 1.08 per drink (or the equivalent of 12 g pure alcohol) per day (95% CI: 1.04,1.12). Similar effects were observed among women and men (Figure 2). Figure 2 also displays the relative contribution of the individual studies based on the assumption that the RR per drink remained constant over the full range of exposure.

Using the methods described above, we found that the best fitting models were the linear models on logarithmized risk. The model fit statistics revealed that these models fitted the data well and there was no statistically significant heterogeneity among the results of individual studies for both sexes combined (Q-test = 31.64 d.f. = 30 p-value = 0.385; I^2 = 5%, 95% CI: 0%,35%), for women (Q-test = 22.51 d.f. = 20 p-value = 0.314; I^2 = 11%, 95% CI: 0%,46%), and for men (Q-test = 22.6 d.f. = 19 p-value = 0.255; I^2 = 16%, 95% CI: 0%, 51%). The fitted dose-response curves that summarize the association between alcohol consumption and risk of AF are shown in Figure 3. Women who consumed 24, 60, and 120 grams of alcohol daily had RRs of 1.07 (95% CI: 1.04,1.10), 1.42 (95% CI: 1.23,1.64) and 2.02 (95% CI: 1.60,2.97) respectively, relative to non-drinkers. Among men, the corresponding RRs were 1.08 (95% CI: 1.04,1.11), 1.44 (95% CI: 1.23,1.69) and 2.09 (95% CI: 1.52,2.86).

Table 2 shows the results from the categorical meta-analyses on potential thresholds. Compared with non-drinkers, alcohol consumption of two or fewer drinks per day was not significantly associated with the risk of AF among women. In fact, the risk of average low volume consumption was almost identical to the risk of non-drinkers (RR = 0.99, 95% CI: 0.91,1.07; p-value = 0.775). On the other hand, women who consumed >2-3 drinks daily had a 17% increased risk of AF, while those consuming more than 4 drinks daily had a twofold increase in the risk of AF. Among men, alcohol consumption of up to 3 drinks daily was not significantly associated with the increased risk of AF. However, in comparison with non-drinkers, alcohol consumption of >3-4 drinks per day was significantly associated with the increased risk of AF (RR = 1.25, 95% CI: 1.01,1.55; p-value 0.045), as was consumption of 4+ drinks daily (RR =1.53, 95% CI: 1.23,1.91).

Publication Bias

There was no evidence of publication bias. Both Begg's adjusted rank correlation test and Egger's regression asymmetry test indicated no evidence of substantial publication bias among women (p=0.707 for Begg's test; p=0.841 for Egger's test) or among men (p=0.462 for Begg's test; p=0.477 for Egger's test).

Discussion

Association and strength of association

The meta-analysis of the existing case-control and cohort studies revealed a clear association between alcohol consumption and the risk of onset of AF.

Consistency

An association between alcohol consumption and the risk of incidence of atrial fibrillation was observed in 5 out of 6 studies carried out in different settings (or in 7 out of 8 datasets). Though the strength of association varied among the studies, it was consistent.

Dose-response relationship and threshold testing

In our study, a dose-response relationship between level of daily consumption and the risk of AF was found. Results from the categorical analysis suggest that there may be a threshold, under which there is no significant increase of AF.

Temporality

Several of the cited studies measured alcohol consumption at baseline and then followed up for extensive times. Also, the onset of AF after days with excessive drinking can serve as indirect proof.

Reversibility following interventions

AF rarely becomes a chronic condition that makes reversibility criterion non-applicable.

Biological pathways

The primary pathogenic mechanism of development of AF is atrial re-entries [31]. Prerequisites of development of re-entries are the unidirectional impulse blockage and relative increase of recirculation time so that it exceeds the refractory period of initial segment of the circuit [8;32].

Alcohol consumption, acute or chronic, has various effects on electrical activity of the heart. This includes direct alcohol cardiotoxicity, hyperadrenergic activity during drinking and withdrawal, impairment of vagal tone and increase of intra-atrial conduction time [8].

Pathophysiologically, each of the factors described above leads to either decrease of conduction velocity or to shortening of refractory period, thus in combination they promote the development of re-entries that corresponds to major mechanism of development of AF.

Another potential explanation of the onset of alcohol-related AF is the remodelling of left atrium due to hypertension, which in turn is associated with alcohol consumption and has been shown to be an independent risk factor for AF in multiple studies [33]; for the relationship between alcohol and hypertension see [34–38].

In summary, there is enough clinical and pathophysiological evidence to conclude that alcohol consumption may cause the onset of AF.

Conclusions

Epidemiological criteria for causality were met to conclude a causal impact of alcohol consumption on the onset of AF with a monotonic dose-response relationship. However, the impact of light drinking is not clear.

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Reference List

1. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet*. 2009; 373:2223–2233. [PubMed: 19560604]
2. Ezzati M, Lopez AD, Rodgers AD, Vander Horn S, Murray CJL, Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet*. 2002; 360:1347–1360. [PubMed: 12423980]
3. Rehm J, Room R, Graham K, Monteiro M, Gmel G, Semplos C. The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease - an overview. *Addiction*. 2003; 98:1209–1228. [PubMed: 12930209]
4. Rehm J, Baliunas D, Borges GLG, Graham K, Irving HM, Kehoe T, et al. The relation between different dimensions of alcohol consumption and burden of disease - an overview. *Addiction*. In press.
5. Gray L, Hart CL, Smith GD, Batty GD. What is the predictive value of established risk factors for total and cardiovascular disease mortality when measured before middle age? Pooled analyses of two prospective cohort studies from Scotland. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2010; 17:106–112. [PubMed: 19952759]
6. Puddey IB, Rakic V, Dimmitt SB, Beilin LJ. Influence of pattern of drinking on cardiovascular disease and cardiovascular risk factors - a review. *Addiction*. 1999; 94:649–663. [PubMed: 10563030]
7. Marques-Vidal P, Montaye M, Arveiler D, Evans A, Bingham A, Ruidavets JB, et al. Alcohol consumption and cardiovascular disease: differential effects in France and Northern Ireland. The PRIME study. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2004; 11:336–343. [PubMed: 15292768]

8. Balbão CEB, de Paola AAV, Fenelon G. Effects of alcohol on atrial fibrillation. *Ther Adv Cardiovasc Dis.* 2009; 3:53–63. [PubMed: 19124390]
9. Conen D, Osswald S, Albert CM. Epidemiology of atrial fibrillation. *Swiss Med Wkly.* 2009; 139:346–352. [PubMed: 19562528]
10. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation.* 2006; 114:e257–e354. [PubMed: 16908781]
11. Ettinger PO, Wu CF, de la Cruz C, Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the “holiday heart”: alcohol associated cardiac rhythm disorders. *Am Heart J.* 1978; 95:555–562. [PubMed: 636996]
12. Mukamal KJ, Tolstrup JS, Friberg J, Jensen G, Gronbaek M. Alcohol consumption and risk of atrial fibrillation in men and women - the Copenhagen City Heart Study. *Circulation.* 2005; 112:1736–1742. [PubMed: 16157768]
13. Djoussé L, Levy D, Benjamin EJ, Blease SJ, Russ A, Larson MG, et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham study. *Am J Cardiol.* 2004; 93:710–713. [PubMed: 15019874]
14. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter. *Arch Intern Med.* 2004; 164:1993–1998. [PubMed: 15477433]
15. Conen D, Tedrow UB, Cook NR, Moorthy MV, Buring JE, Albert CM. Alcohol consumption and risk of incident atrial fibrillation in Women. *JAMA.* 2008; 300:2489–2496. [PubMed: 19050192]
16. Ruigómez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. *J Clin Epidemiol.* 2002; 55:358–363. [PubMed: 11927203]
17. Koskinen P, Kupari M, Leinonen H, Luomanmäki K. Alcohol and new onset atrial fibrillation: a case-control study for a current series. *Br Heart J.* 1987; 57:468–473. [PubMed: 3593617]
18. English, D.; Holman, C.; Milne, E.; Winter, M.; Hulse, G.; Codde, G., et al. The quantification of drug caused morbidity and mortality in Australia 1995. Commonwealth Department of Human Services and Health; Canberra, Australia: 1995.
19. Gutjahr E, Gmel G, Rehm J. The relation between average alcohol consumption and disease: an overview. *Eur Addict Res.* 2001; 7:117–127. [PubMed: 11509842]
20. Hill A. The environment and disease: association or causation? *Proc R Soc Med.* 1965; 58:295–300. [PubMed: 14283879]
21. Rothman, KJ.; Greenland, S.; Lash, TL. *Modern epidemiology.* 3rd ed. Lippincott Williams & Wilkins; PA, USA: 2008.
22. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol.* 1992; 135:1301–1309. [PubMed: 1626547]
23. Orsini NBR, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata Journal.* 2006; 6:40–57.
24. Royston, P.; Sauerbrei, W. *Multivariable model-building: a pragmatic approach to regression analysis based on fractional polynomials for modelling continuous variables.* John Wiley & Sons; Hoboken, NJ: 2008.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986; 7:177–188. [PubMed: 3802833]
26. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002; 21:1539–1558. [PubMed: 12111919]
27. Stata Corporation. Release 10.1. Stata Corporation; College Station, TX: 2007.
28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003; 327:557–560. [PubMed: 12958120]
29. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997; 315:629–634. [PubMed: 9310563]

30. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994; 50:1088–1101. [PubMed: 7786990]
31. Barnett AG, Dobson AJ. Excess in cardiovascular events on Mondays: a meta-analysis and prospective study. *J Epidemiol Community Health*. 2005; 59:109–114. [PubMed: 15650141]
32. Rensma PL, Allessie MA, Lammers WJEP, Bonke FIM, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. *Circulation Research*. 1988; 62:395–410. [PubMed: 3338122]
33. Schoonderwoerd BA, Smit MD, Pen L, Van Gelder IC. New risk factors for atrial fibrillation: causes of ‘not-so-lone atrial fibrillation’. *Europace*. 2008; 10:668–673. [PubMed: 18480076]
34. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart*. 2001; 86:516–521. [PubMed: 11602543]
35. Krahn AD, Manfreda J, Tate RB, Mathewson FAL, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba follow-up study. *Am J Med*. 1995; 98:476–484. [PubMed: 7733127]
36. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. *J Intern Med*. 2001; 250:382–389. [PubMed: 11887972]
37. Kupari, M.; Koskinen, P. Alcohol, cardiac arrhythmias and sudden death. In: Chadwick, D.; Goode, J., editors. *Alcohol and Cardiovascular Disease* (Novartis Foundation Symposium No. 216, London, 7-9 October 1997). John Wiley and Sons, Ltd.; Chichester, UK: 1998. p. 68-79.
38. Taylor B, Irving HM, Baliunas D, Roerecke M, Patra J, Mohapatra S, et al. Alcohol and hypertension: gender differences in dose-response relationships determined through systematic review and meta-analysis. *Addiction*. 2009; 104:1981–1990. [PubMed: 19804464]

Figure 1.
Study selection process

Figure 3.
Dose-response relationship between alcohol consumption and risk of atrial fibrillation
(continuous analysis using fractional polynomials)

Table 1

Characteristics of the included studies

Author	Place and time of study	Gender	Study Design	Cases	Controls	Exposure categories
Ruigómez et al, 2002 [15]	United Kingdom. Time period not specified.	Both	Cohort	781	3791	Alcohol consumption (none; 1-5 units/week; 6-15 units/week; 16-42 units/week; >42 units/week). 1 unit was considered to be 8 g of pure ethanol.
Djoussé et al, 2004 [13]; Dataset A.	Massachusetts, US. Time period not specified.	Women	Cohort	511	2295	Alcohol consumption (no consumption; 0.1-12 g/day; 12.1-24 g/day; 24.1-36 g/day; 36+ g/day)
Djoussé et al, 2004 [10]; Dataset B.	Massachusetts, US. Time period not specified.	Men	Cohort	544	2377	Alcohol consumption (no consumption; 0.1-12 g/day; 12.1-24 g/day; 24.1-36 g/day; 36+ g/day)
Conen et al, 2008 [10]	United States, 2004-2006	Women	Cohort	653	34715	Alcohol consumption (no consumption; <1 drink/day; 1-2 drinks/day; 2+ drinks/day)
Koskinen et al, 1987 [12]	Helsinki, Finland. January 1 st – September 20 th 1985.	Both	Case-control	100	100	Alcohol consumption (no consumption; 1-30 g/day; 30+ g/day)
Mukamal et al, 2005 [14]; Dataset A.	Copenhagen, Denmark. 1976-1994.	Women	Cohort	523	8304	Alcohol consumption (<1 drink/week; 1-6 drinks/week; 7-13 drinks/week; 14-20 drinks/week; 21+ drinks/week)
Mukamal et al, 2005 [9]; Dataset B.	Copenhagen, Denmark. 1976-1994.	Men	Cohort	548	7040	Alcohol consumption (<1 drink/week; 1-6 drinks/week; 7-13 drinks/week; 14-20 drinks/week; 21-27 drinks/week; 28-34 drinks/week; 35+ drinks/week)
Mukamal et al., 2007 [36]	USA, 1989-1999	Both	Cohort	1107	4502	Alcohol consumption (none; <1 drink/week; 1-6 drinks/week; 7-13 drinks/week; 14+

Author	Place and time of study	Gender	Study Design	Cases	Controls	Exposure categories
drinks/week;)						

* Several studies had two sets of data, named correspondingly Dataset A and Dataset B. For statistical purposes the datasets taken from the same study were used separately.

Table 2

Relative risk of arrhythmias by alcohol consumption (categorical analysis)

Exposure category	RR	p-value	(95% CI)
Both sexes			
>0-2 drinks/day [†]	1.00	0.989	(0.92, 1.09)
>2-3 drinks/day [†]	1.11	0.097	(0.98, 1.25)
>3-4 drinks/day [†]	1.22	0.028	(1.02, 1.46)
More than 4 drinks/day [†]	1.50	0.000	(1.22, 1.85)
Women			
>0-2 drinks/day [†]	0.99	0.775	(0.91, 1.07)
>2-3 drinks/day [†]	1.17	0.032	(1.01, 1.36)
>3-4 drinks/day [†]	1.17	0.353	(0.84, 1.65)
More than 4 drinks/day [†]	2.18	0.001	(1.38, 3.43)
Men			
>0-2 drinks/day [†]	1.02	0.718	(0.90, 1.16)
>2-3 drinks/day [†]	1.09	0.275	(0.94, 1.26)
>3-4 drinks/day [†]	1.25	0.045	(1.01, 1.55)
More than 4 drinks/day [†]	1.53	0.000	(1.23, 1.91)

RR = Relative risk; CI = Confidence interval

1 drink = 12 grams

[†]Reference group is non-drinkers