Annals of Epidemiology 24 (2014) 291–296

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Original article

Alcohol consumption and mortality: a dose-response analysis in terms of time

Andrea Bellavia MSc [a,b,*], Matteo Bottai PhD [b], Alicja Wolk DMSc [a], Nicola Orsini PhD [a,b]

[a] Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[b] Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 23 May 2013
Accepted 23 December 2013
Available online 4 January 2014

Keywords:
Alcohol
Mortality
Survival
Percentile
Laplace
Dose-response

ABSTRACT

Purpose: Low-to-moderate alcohol consumption is associated with decreased mortality. However, many aspects of this association are still debated. Our aim was to complement available information by conducting a dose-response analysis of the association between alcohol consumption and survival time.
Methods: In a Swedish population-based cohort of 67,706 middle-aged and elderly men and women, frequency and amount of drinking were assessed through a self-administrated questionnaire. During 15 years of follow-up, 13,323 participants died. Differences in survival (10th percentile differences, PDs) according to levels of alcohol consumption were estimated using Laplace regression.
Results: We found evidence of nonlinearity between alcohol consumption and survival. Among women, we observed a rapid increase in survival up to 6 g/d of alcohol consumption (0.5 drinks/d) where survival was 17 months longer (PD = 17 months, 95% confidence interval, 10 to 24). After this peak, higher alcohol consumption was progressively associated with shorter survival. Among men, survival improved up to 15 g/d (1.5 drinks/d) where we observed a PD of 15 months (95% confidence interval, 8 to 22).
Conclusions: Low alcohol consumption was associated with improved survival up to 1.5 years for women with an average consumption of 0.5 drinks per day and to 1.3 years for men with an average consumption of 1.5 drinks per day.

Introduction

The association between alcohol consumption and overall mortality is usually described by a *J*-shape curve. Many observational studies have documented that low-to-moderate alcohol intake is associated with a decreased risk of overall mortality and there is a growing consensus that the effect may be causal [1–5]. The *J*-shape curve has been observed both in men and women even if results suggest that the dose-response profile could be different between genders [1,3].

However, although the shape of the association is well assessed, there is no general agreement on other important aspects such as the optimal dose where the major benefits accrue, the safe range of alcohol consumption, and the difference in the dose-response between men and women. Many studies presented results only according to crude categories of alcohol consumption (i.e., infrequent, light, moderate, heavy drinkers) so that results are influenced by the arbitrary choices of the categories, dependent on cultural differences in the studies population, and the selected reference population [4,6,7]. In addition, results from previous observational studies are usually presented only in terms of relative measures (i.e., hazard ratio, risk ratio, odds ratio) without indication of the background risk, which sometimes can make conveying the results to general public difficult [2,3]. Moreover, different sources of potential bias have been identified in studies evaluating effects of alcohol on mortality, including lack of detail about drinking frequency (i.e., occasional vs. regular drinkers) and the misclassification of former drinkers in the analyses [7,8].

The direct estimation of the relation between survival percentiles (i.e., months, years) and levels of alcohol consumption in a dose-response analysis can facilitate the interpretation of the *J*-shape curve and give important advantages in both clinical and public health contexts [9]. The aim of this study was to perform a dose-response analysis evaluating survival percentiles according to levels of alcohol consumption in a large population-based cohort of middle-aged and elderly men and women.

Materials and methods

Study population

This study included 88077 participants from the population-based Cohort of Swedish Men and the Swedish Mammography Cohort. In brief, the Cohort of Swedish Men was established

* Corresponding author. Institute of Environmental Medicine, Karolinska Institutet, Box 210, 171 77 Stockholm, Sweden. Tel: +46 8 52487578.
E-mail address: andrea.bellavia@ki.se (A. Bellavia).

1047-2797/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.annepidem.2013.12.012

between 1997 and 1998, when all eligible men aged 45–79 years residing in Västmanland and Örebro counties (central Sweden) received an invitation to participate in the study along with a self-administrated questionnaire. Information was collected on alcohol consumption, physical activity, body weight and height, smoking habits, educational level, and other lifestyle factors. A total of 48850 men returned the questionnaire.

Swedish Mammography Cohort is a population-based cohort of women born between 1914 and 1948 who were recruited between 1987 and 1990 in Västmanland and Uppsala counties (central Sweden). Women completed a questionnaire with questions regarding alcohol consumption, body weight and height, education level, and other factors. In late fall 1997, a second questionnaire to include information regarding smoking status, physical activity, and other lifestyle factors was sent to participants who were still alive and residing in the study area. A total of 39227 women aged between 48 and 83 years returned this second questionnaire and were included in the current analysis. This study was approved by the Regional Research Ethics Board at Karolinska Institutet, and all participants gave their informed consent.

In this analysis, we excluded participants who reported incorrect or missing personal numbers ($n = 540$), those who died before the start of follow-up ($n = 97$), those who had diabetes ($n = 3534$) or any history of cardiovascular diseases (CVD) ($n = 6994$) and cancer ($n = 4390$), and those with missing information on all alcohol-related items ($n = 2301$). Former drinkers ($n = 2515$) were also excluded from the analysis. After exclusions, a total of 67706 (36561 men and 31145 women) participants were included in the current analysis.

Alcohol consumption assessment

Information about alcohol consumption was collected using a food-frequency questionnaire. The questionnaire included predefined questions on the consumption frequency of beer, wine, and liquor. Participants were asked to report whether they had never had alcohol (lifetime abstainers), whether they had stopped drinking (former drinkers), or whether they were current drinkers. In the latter case, a final open question was used to collect information about the amount of beer, wine, and liquor consumed on each occasion. The main continuous variable we used for our analyses was obtained combining information about frequency and amount of drinking and indicates the average amount of alcohol intake per day (12 g of alcohol = 1 standard glass of alcoholic beverage [10], i.e., 330 mL of beer, 120 mL of wine, 40 mL of liquors). Based on the findings from a Swedish study, evaluating the "zero approach" partial nonresponse for alcohol consumption was assumed to mean none or seldom consumption [11]. This study showed that 74.1% of missing answers for alcohol beverages corresponded to true nonconsumption. The estimates of alcohol consumption based on the 1997 questionnaires showed good validity. Validation has been assessed by calculating Spearman rank correlation coefficient between our estimates based on the food-frequency questionnaires and four 1-week weighted diet records, evaluated 3–4 months apart (correlation were 0.9 for women and 0.8 for men) [12].

Case ascertainment and follow-up

From January 1, 1998, through December 31, 2012, during 15 years of follow-up, we documented 13,323 deaths (5432 women; 7891 men). Major causes of death were CVD (3590 cases) and cancer (3292 cases). Information on death and cause of death was ascertained through linkage to the Swedish Register of Death Causes at the National Board of Health and Welfare.

Statistical analysis

We used Laplace regression to estimate percentiles of survival time according to different levels of alcohol consumption [9,13,14]. This approach focuses on time from entry into the study to the event and directly estimates differences in survival according to the levels of exposure. Although percentiles of survival range between 1% and 99%, the possibility of estimation depends on the fraction of participants who experienced the event of interest. In our entire cohort, 20% of the participants died during the 15 years of follow-up. Given our settings, modeling percentiles beyond this range, such as the median survival (50th percentile), would require data extrapolation. We focused our primary analysis on the 10th survival percentile, the point of time by which the first 10% of the cohort has died. The measure of exposure-disease association was defined as 10th percentile difference (PD). To allow comparison with previous studies, we also estimated hazard ratios (HRs) with Cox proportional-hazard regression. Proportional hazards assumption was checked by calculating Schoenfeld residuals, regressed against survival time, and tested for a nonzero slope. We found no evidence of departure from the assumption.

In multivariate analyses, we adjusted for baseline age (<50, 50–54, 55–59, 60–64, 65–69, 70–74, and ≥75 years), body mass index (BMI; <25, 25–29, ≥30 kg/m^2), total physical activity (quartiles of total physical activity, metabolic equivalent hours per day), smoking status and pack-years of smoking (current ≥ 40, current 20–39, current < 20, former ≥ 40, former 20–39, former < 20, never), and education level (1–9, 10–12, >12 years). Analyses were performed separately for men and women due to gender differences in alcohol consumption and metabolism [15] that were confirmed in our data. Missing data were handled with a complete-case approach.

We first considered alcohol consumption as a categorical variable. In our cohorts, 90% of men reported a drinking status corresponding to a daily alcohol intake lower than 30 g/d, whereas more than 90% of women reported a consumption corresponding to less than 15 g/d of alcohol intake. We, therefore, focused on the low and moderate levels of daily alcohol consumption categorizing alcohol intake in narrow intervals (lifetime abstainers, <5 g/d, 5–10, 15–20, 20–25, 25–30, >30 for men; lifetime abstainers, <5 g/d, 5–10, >15 for women). Because of the large number of female participants and cases in the lowest category of consumption, the second group of women (<5 g/d) was divided in two subgroups (<1.5; 1.5–5 g/d in consistency with previous studies [4,16]). We also performed a sensitivity analysis by replicating the categorical analysis with the inclusion of former drinkers, previously excluded ($n = 2515$).

We next investigated alcohol consumption as a continuous variable evaluating the shape of the dose-response association between the average daily alcohol intake and time to death. We flexibly modeled daily alcohol intake by using right-restricted cubic splines with three knots of the distribution (10, 20, 30 g/d for men and 2, 5, and 8 g/d for women) [17]. Knots positions were chosen to maximize the number of cases in each interval. The shape of the dose-response relation was fairly insensitive to the location of the knots [18]. Linearity was evaluated testing the null hypothesis that the coefficients of the unrestricted spline transformations are jointly equal to zero [17].

To take into account the potential effects of undiagnosed diseases (patients with a diagnosis of cancer, diabetes or CVD-related disease were already excluded at baseline) on alcohol consumption, we performed a sensitivity analysis evaluating the dose-response relation without considering those participants who died in the first 3 years of follow-up ($n = 1075$).

We next modeled a range of possible survival percentiles (i.e., 1st–20th) comparing lifetime abstainers and those persons in the