Alcohol consumption, cigarette smoking and incidence of aortic valve stenosis

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Abstract. Larsson SC, Wolk A, Bäck M (Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden). Alcohol consumption, cigarette smoking and incidence of aortic valve stenosis. J Intern Med 2017; 282: 332–339.

Background. Alcohol consumption and cigarette smoking are modifiable lifestyle factors with important impact on public health. It is unclear whether these factors influence the risk of aortic valve stenosis (AVS).

Objective. To investigate the associations of alcohol consumption and smoking, including smoking intensity and time since cessation, with AVS incidence in two prospective cohorts.

Methods. This analysis was based on data from the Swedish Mammography Cohort and the Cohort of Swedish Men, comprising 69,365 adults without cardiovascular disease at baseline. Participants were followed for AVS incidence and death by linkage to the Swedish National Patient and Causes of Death Registers. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated by Cox proportional hazards regression.

Results. Over a mean follow-up of 15.3 years, 1249 cases of AVS (494 in women and 755 in men) were recorded. Compared with never drinkers of alcohol (lifelong abstainers), the risk of AVS was significantly lower in current light drinkers (1–6 drinks per week [1 drink = 12 g alcohol]; multivariable HR 0.82; 95% CI: 0.68–0.99). The risk of AVS increased with increasing smoking intensity. Compared with never smokers, the HR was 1.46 (95% CI: 1.16–1.85) in current smokers of ≥30 pack-years. Former smokers who had quit smoking 10 or more years previously had similar risk for AVS as never smokers.

Conclusions. This study suggests that current light alcohol consumption is associated with a lower risk of AVS, and indicates that the association between smoking and AVS risk is reversible.

Keywords: alcohol consumption, aortic valve stenosis, cigarette smoking, prospective studies, risk factors.
consumption and prevalence of aortic valve sclerosis [22], the influence of alcohol consumption on the risk of developing AVS is unknown.

Cigarette smoking is the second leading cause of disability and death [23]. Data on current smoking in relation to AVS are limited to a few cross-sectional [10] and prospective studies [7, 8] with small study sizes. No study has investigated the influence of smoking intensity and time since quitting smoking on AVS risk.

The aim of the present study was to establish the associations of alcohol consumption and smoking, including smoking intensity and time since cessation, with the incidence of AVS, using two large prospective studies of almost 70 000 individuals.

Methods

Study population

The Swedish Mammography Cohort was established between 1987 and 1990 when all women who were born between 1914 and 1948 and living in Västmanland or Uppsala County were invited to participate in a breast cancer-screening programme. In the autumn of 1997, 39 227 of these women completed an extensive questionnaire about alcohol use, smoking history and other lifestyle factors and medical history. Simultaneously in 1997, the Cohort of Swedish Men was established when 48 850 men, born between 1918 and 1952 and living in Västmanland or Örebro County completed an identical (except for some sex-specific items) questionnaire. The study was approved by the Ethical Review Board at Karolinska Institutet in Stockholm, Sweden. Completion of the questionnaire was accepted as informed consent.

Assessment of exposures

The questionnaire completed by participants in the autumn of 1997 solicited information on alcohol consumption, smoking status and history, education, weight, height, and history of diabetes, hypertension and hypercholesterolemia. Participants were asked to report if they had never consumed alcohol, if they had stopped drinking alcohol (former drinkers) or if they were current drinkers. Current drinkers were inquired about their frequency of consumption of light beer (alcohol by volume, <2.25%), beer (2.8–3.5%), strong beer (4.4–5.6%), wine (12–13.5%), fortified wine (15–22%) and liquor (40%) as well as the amount consumed on each occasion. Frequency of consumption was assessed with nine predefined categories, ranging from never to ≥3 times per day. Weekly alcohol consumption was computed by multiplying the frequency of consumption of each alcoholic beverage by the amount consumed, assuming 12 g of alcohol per drink. This amount equals about 660 mL light beer, 500 mL beer, 330 mL strong beer, 150 mL wine, 80 mL fortified wine or 40 mL liquor. The questionnaire has been validated against 24-h recall interviews in a random sample of 248 middle-aged and older Swedish men from the study area; the correlation coefficient between the questionnaire-based estimates and the mean of 14 24-h recall interviews was 0.81 for alcohol (ethanol) [24].

In this study, smoking intensity was defined by pack-years of smoking, which was calculated by multiplying the number of years of smoking by the average number of packs of cigarettes smoked. Body mass index was computed from weight and height (kg per height in m²). Diabetes was defined as a diagnosis of type 2 diabetes in the Swedish National Patient or Diabetes Registers, and complemented with self-reported information.

Case ascertainment and follow-up

Using the personal identification number assigned to each Swedish resident, participants were followed for diseases and death by computerized linkage to the Swedish National Patient and Causes of Death Registers. The International Classification of Diseases 10th revision codes I35.0 and I35.2 were used to identify incident cases of AVS. Less than one percentage of the cases was ascertained through the Swedish Causes of Death Register alone. For this analysis, follow-up for each participant started on 1 January 1998 and ended at the date of diagnosis of AVS, date of death, or 31 December 2014, whichever came first.

Study population for analysis

Of the 88 087 participants who completed the 1997 questionnaire, we excluded 540 who had a missing or an incorrect personal identification number and a further 81 who died before start of follow-up (1 January 1998). Excluded were also 4403 individuals with a previous diagnosis of cancer and 7806 individuals with prior cardiovascular disease (AVS, ischemic heart disease, heart
failure or ischemic stroke) because alcohol consumption and smoking habits among these may not reflect long-term exposure due to changes in behaviours after the diagnosis. Furthermore, we excluded 5892 individuals who did not provide information on smoking or alcohol consumption, or were former drinkers as some of these individuals may have stopped drinking alcohol in response to underlying health conditions. The remaining 69,365 individuals (32,253 women and 37,112 men), 45–83 years of age, were included in the analysis.

Statistical analysis
Alcohol consumption was divided into the following six categories: never drinkers (lifelong abstainers [reference group]) and current drinkers of <1 drink per week, 1–6 drinks per week, 7–14 drinks per week, 15–21 drinks per week, or ≥21 drinks per week. To examine whether the association between alcohol consumption and AVS risk differs by type of alcoholic drinks consumed, seven groups were created (wine exclusively, beer exclusively, liquor exclusively, wine and beer, wine and liquor, beer and liquor or all alcoholic drinks), and with never drinkers in the reference group. Participants were categorized into nine groups according to their smoking status and pack-years of smoking: never smokers, former smokers of <10 pack-years, 10–19 pack-years, 20–29 pack-years, or ≥30 pack-years and current smokers of <10-pack-years, 10–19 pack-years, 20–29 pack-years, or ≥30 pack-years.

Hazard ratios (HR) with 95% confidence intervals (CI) of AVS by categories of alcohol consumption and smoking were estimated by Cox proportional hazards regression model, using attained age as the underlying time scale, and stratifying by sex to allow for different baseline hazard for women and men. All multivariable models were additionally adjusted for education (as a marker for socioeconomic status and classified as less than high school, high school or university), body mass index (in kg m⁻²; <22.5, 22.5–24.9, 25.0–29.9 or ≥30) and dichotomous for a history of diabetes, hypertension and hypercholesterolemia. Adjustment was also made for a history of atrial fibrillation (diagnosis prior to baseline) because atrial fibrillation is associated with both alcohol consumption [15] and AVS in this study. Analyses of alcohol consumption were further adjusted for smoking, and those for smoking were adjusted for alcohol consumption. The proportional hazards assumption was evaluated using Schoenfeld residuals and found satisfactory.

We performed a sensitivity analysis without the first 3 years of follow-up to evaluate the possibility that associations with alcohol consumption and smoking might reflect changes in these habits caused by subclinical disease (reverse causation). For alcohol consumption, we also conducted a sensitivity analysis restricted to never smokers to remove potential residual confounding by smoking. Tests for interaction by sex and between alcohol consumption and current smoking in relation to AVS risk were conducted using the likelihood ratio test that compared models with and without interaction terms. All statistical tests were two-sided, and deemed statistically significant at P < 0.05. The analyses were performed in SAS (version 9.4, SAS Institute, Cary, NC).

Results
During a mean follow-up of 15.3 years (1,062,514 person-years), we ascertained 1,249 AVS cases (494 in women and 755 in men). Compared with never drinkers (lifelong abstainers), participants who reported consumption of ≥1 drinks per week of alcohol were younger, more likely to have a post-secondary education and to be current smokers but less likely to have diabetes (Table 1). Median alcohol consumption in current drinkers was 4.2 (interquartile range, 1.6–8.7) drinks per week. Compared with never smokers, current smokers were younger and less likely to have a postsecondary education (Table 1).

Compared with never drinkers (lifelong abstainers), the multivariable HR of AVS for current light drinkers (1–6 drinks per week) was 0.82 (95% CI, 0.68–0.99); moderate-to-high alcohol consumption was not associated with AVS risk (Table 2). The HR estimate for light alcohol consumption and AVS risk was similar for women and men but the CIs were wide and results were not statistically significant (women: HR 0.80 [95% CI: 0.62–1.03]; men: HR 0.83 [95% CI: 0.61–1.11]), and no interaction by sex was observed (P for interaction = 0.62). Excluding the first 3 years of follow-up did not change the results for light drinking (HR 0.82; 95% CI: 0.68–0.99). Likewise, the association remained when restricting the analysis to never smokers (HR 0.76; 95% CI: 0.61–0.95). There were no appreciably differences in risk estimates for those who drank wine, beer, or liquor exclusively,
or a mixture of two or all three alcoholic beverages, but the statistical power in this analysis was low and none of the associations were statistically significant (Figure S1). There was no interaction between alcohol consumption and current smoking in relation to AVS risk ($P$ for interaction = 0.23).

Compared with never smoking, current smoking (multivariable HR 1.30; 95% CI: 1.12–1.51) but not former smoking was associated with an increased risk of AVS (Table 3). The risk in current smokers increased with increasing smoking intensity; the multivariable HR was 1.46 (95% CI: 1.16–1.85) in current smokers of ≥30 pack-years (Table 3). Excluding the first 3 years of follow-up did not change the results appreciably (corresponding HR 1.47; 95% CI: 1.16–1.87). The association between smoking and AVS was not modified by sex ($P$ for interaction = 0.93). The multivariable HR for current smokers of ≥30 pack-years was 1.43 (95% CI: 0.84–2.41) in women and 1.47 (95% CI: 1.13–1.91) in men.

We observed a time-dependent decrease in AVS risk in former smokers depending on the time passed since smoking cessation (Fig. 1). Former smokers who had quit smoking 10 or more years previously had similar risk for AVS as never smokers (Fig. 1).

### Discussion

In this large prospective study of middle-aged and older adults, light alcohol consumption (1–6 drinks per week) was associated with a lower risk of AVS. Our data also showed an increased risk of AVS in current smokers and indicated that the increased risk of AVS due to smoking is potentially reversible, with the risk of AVS approaching

### Table 1  Baseline characteristics by alcohol consumption and smoking in 69 365 Swedish adults

| Characteristics | Alcohol drinking status and drinks$^a$ per week | Smoking status |
|-----------------|-----------------------------------------------|----------------|
|                 | Never$^c$ | Current | Current | Current | Current | Never | Former | Current |
| No. of participants | 5730 | 11 239 | 31 938 | 13 333 | 4104 | 3043 | 31 424 | 21 310 | 16 631 |
| Men, % | 37.1 | 32.0 | 50.2 | 73.1 | 84.7 | 89.1 | 46.2 | 65.3 | 55.1 |
| Mean age at baseline, years | 66.4 | 62.7 | 59.6 | 57.5 | 56.7 | 56.5 | 61.5 | 59.0 | 58.4 |
| Mean body mass index, kg m$^{-2}$ | 25.8 | 25.5 | 25.2 | 25.3 | 25.7 | 26.1 | 25.3 | 25.8 | 25.0 |
| Postsecondary education, % | 14.1 | 15.5 | 19.4 | 22.2 | 22.1 | 20.2 | 21.5 | 18.9 | 15.5 |
| Smoking | | | | | | | | | |
| Never smokers, % | 83.6 | 56.7 | 44.5 | 31.7 | 25.5 | 20.8 | 100 | 0 | 0 |
| Current smokers, % | 8.7 | 21.4 | 24.1 | 27.0 | 30.8 | 38.3 | 0 | 0 | 100 |
| Pack-years of smoking | 19.1 | 19.3 | 20.3 | 22.8 | 25.4 | 29.5 | – | – | 21.6 |
| Former smokers, % | 7.7 | 21.9 | 31.4 | 41.3 | 43.7 | 40.9 | 0 | 100 | 0 |
| Pack-years of smoking | 10.7 | 13.1 | 13.9 | 16.0 | 18.1 | 20.1 | – | 14.9 | – |
| Years since cessation | 21.0 | 18.6 | 18.7 | 18.5 | 18.2 | 17.3 | – | 18.5 | – |
| Diabetes, % | 6.2 | 5.1 | 4.0 | 4.0 | 4.0 | 4.0 | 5.6 | 4.1 | 5.0 |
| Hypertension, % | 20.7 | 21.4 | 20.1 | 20.8 | 21.7 | 25.6 | 20.5 | 22.3 | 19.2 |
| Hypercholesterolemia, % | 8.2 | 9.5 | 10.2 | 11.6 | 14.0 | 15.1 | 9.6 | 12.0 | 11.0 |
| Atrial fibrillation, % | 1.1 | 1.2 | 1.3 | 1.7 | 1.9 | 1.9 | 1.3 | 1.6 | 1.2 |

$^a$One drink is equivalent to 12 g of alcohol.

$^b$Age-standardized to the age distribution of the study population at baseline.

$^c$Lifelong abstainers.
that of never smokers 10 years following smoking cessation.

This is the first study revealing an inverse association between light alcohol consumption and risk of AVS, a finding that is consistent with light-to-moderate alcohol consumption being inversely associated with risk of ischemic heart disease \[17, 19, 20\], heart failure \[17, 21\], abdominal aortic aneurysm \[17, 25\] and ischemic stroke \[16, 17\].

### Table 2  Association between alcohol consumption and aortic valve stenosis in 69,365 Swedish women and men, 1998-2014

| Alcohol drinking status and amount | No. of cases | Person-years | Incidence rate\(^a\) | Age- and sex-adjusted HR (95% CI)\(^b\) | Multivariable HR (95% CI)\(^b,c\) |
|-----------------------------------|--------------|--------------|----------------------|----------------------------------------|---------------------------------|
| Never drinkers\(^d\)              | 163          | 81,106       | 20.1                 | Ref                                    | Ref                             |
| Current, drinks/week\(^e\)        |              |              |                      |                                        |                                 |
| <1 (0.4)\(^f\)                    | 228          | 168,201      | 13.6                 | 0.89 (0.73–1.09)                       | 0.87 (0.71–1.07)               |
| 1–6 (3.4)                         | 514          | 494,159      | 10.4                 | 0.81 (0.67–0.97)                       | 0.82 (0.68–0.99)               |
| 7–14 (9.6)                        | 224          | 209,175      | 10.7                 | 0.90 (0.72–1.11)                       | 0.91 (0.73–1.14)               |
| 15–21 (16.6)                      | 63           | 64,317       | 9.8                  | 0.85 (0.63–1.15)                       | 0.83 (0.61–1.13)               |
| >21 (28.4)                        | 57           | 45,796       | 12.5                 | 1.08 (0.79–1.48)                       | 1.01 (0.73–1.39)               |

\(^a\)Per 10,000 person-years.  
\(^b\)Hazard ratios from Cox proportional hazards models with age as the underlying time-scale and stratifying by sex.  
\(^c\)Adjusted for education, smoking status and history, body mass index, and history of diabetes, hypertension and hypercholesterolemia.  
\(^d\)Lifelong abstainers.  
\(^e\)One drink is equivalent to 12 g of alcohol.  
\(^f\)Median values in parenthesis. All such values.

### Table 3  Association between smoking and aortic valve stenosis in 69,365 Swedish women and men, 1998-2014

| Smoking status | No. of cases | Person-years | Incidence rate\(^a\) | Age- and sex-adjusted HR (95% CI)\(^b\) | Multivariable HR (95% CI)\(^b,c\) |
|----------------|--------------|--------------|----------------------|----------------------------------------|---------------------------------|
| Never smoker   | 593          | 483,900      | 12.3                 | Ref                                    | Ref                             |
| Former smoker  | 372          | 329,760      | 11.3                 | 1.06 (0.93–1.22)                       | 1.06 (0.92–1.22)               |
| Current smoker | 284          | 248,854      | 11.4                 | 1.26 (1.09–1.46)                       | 1.30 (1.12–1.51)               |
| Pack-years, former\(^d\) |           |              |                      |                                        |                                 |
| Former <10     | 126          | 134,345      | 9.4                  | 1.02 (0.84–1.23)                       | 1.06 (0.87–1.29)               |
| Former 10–19   | 89           | 93,071       | 9.6                  | 0.97 (0.77–1.22)                       | 0.98 (0.77–1.23)               |
| Former 20–29   | 56           | 49,626       | 11.3                 | 1.04 (0.79–1.37)                       | 1.00 (0.75–1.33)               |
| Former ≥30     | 59           | 32,052       | 18.4                 | 1.33 (1.01–1.75)                       | 1.25 (0.95–1.66)               |
| Pack-years, current\(^d\) |           |              |                      |                                        |                                 |
| Current <10    | 59           | 58,196       | 10.1                 | 1.06 (0.81–1.39)                       | 1.11 (0.85–1.46)               |
| Current 10–19  | 55           | 58,474       | 9.4                  | 1.21 (0.92–1.60)                       | 1.28 (0.97–1.69)               |
| Current 20–29  | 63           | 61,254       | 10.3                 | 1.41 (1.08–1.83)                       | 1.47 (1.12–1.91)               |
| Current ≥30    | 88           | 60,227       | 14.6                 | 1.46 (1.16–1.83)                       | 1.46 (1.16–1.85)               |

\(^a\)Per 10,000 person-years.  
\(^b\)Hazard ratios from Cox proportional hazards models with age as the underlying time-scale and stratified by sex.  
\(^c\)Adjusted for education, alcohol consumption, body mass index, and history of diabetes, hypertension, hypercholesterolemia and atrial fibrillation.  
\(^d\)The reference group is never smokers. The number of cases and person-years does not sum up to the total numbers owing to missing data on pack-years of smoking.
The mechanisms whereby alcohol consumption may reduce the risk of various cardiovascular diseases are incompletely understood. Intervention studies have shown that alcohol increases the levels of high-density lipoprotein cholesterol, apolipoprotein A1 and adiponectin and decreases fibrinogen levels [14, 26], but the role of these cardiovascular biomarkers in the development of AVS is uncertain. Moderate alcohol drinkers have also been observed to have lower levels of inflammatory markers compared with nondrinkers [27]. Another possibility could be beneficial effects of antioxidants in red wine and dark beer, which may theoretically reduce low-density lipoprotein cholesterol oxidation in the aortic valve akin to their effects in the arterial wall [14]. Although the present study did not support that the association between alcohol consumption and AVS risk differed by type of alcoholic beverage, this analysis was underpowered to take alcohol quantities into account.

Our finding indicating that current smoking is a dose-dependent risk factor for AVS extends the results from previous cross-sectional [10] and prospective studies [7, 8]. In a cross-sectional study of 5201 older US men and women, current smoking was associated with a 35% increased risk of prevalent aortic valve sclerosis and AVS [10]. In two smaller prospective studies, including 3243 Norwegian adults (n = 132 AVS cases) [8] and 5079 Swedish adults (n = 69 AVS cases) [7], current smoking was associated with an almost doubled risk of AVS. The somewhat lower risk associated with current smoking and AVS in this study suggested a dose-dependency as smoking intensity was low in our population. Indeed, we established that AVS risk increased with the number of pack-years of smoking. Importantly, our analysis underlines smoking as a modifiable risk factor for AVS as we observed a time-dependent decrease in AVS risk in former smokers depending on the time passed since smoking cessation, approaching the risk observed for never smokers after 10 nonsmoking years. This finding may have both public health and economic implications as promoting smoking cessation could potentially reduce the occurrence of AVS and the number of aortic valve replacements.

Major strengths of this study are the prospective design and the large sample size with a large number of AVS cases identified by linkage with nationwide Swedish registers. To our knowledge, this is the first prospective cohort study investigating the associations of alcohol consumption and smoking intensity and cessation with risk of AVS. A limitation of this study is that alcohol consumption and smoking history was self-reported and only assessed once (at baseline). This may have introduced some degree of exposure misclassification, which would most likely be random and have attenuated the results towards the null. Furthermore, we could not examine drinking pattern. Another limitation is the observational design. Thus, despite adjustment for major risk factors, residual confounding cannot be entirely ruled out as an explanation for the observed findings. Finally, because this study comprised only Swedish middle-aged and older adults, our findings might not be generalizable to other populations with a potentially different drinking pattern.

Conclusions

This study found that light alcohol drinking was inversely associated with the development of AVS. This finding needs to be corroborated by other studies. Previous findings of smoking as a risk
factor for AVS was confirmed and extended by showing that the association between smoking and AVS risk is dependent on smoking intensity and is potentially reversible. Taken together, the results of this large prospective study provide novel insights on how lifestyle factors contribute to the risk of developing AVS.

Conflict of interest statement
No conflicts of interest to declare.

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Multivariable adjusted hazard ratios of aortic valve stenosis by type of alcoholic drink consumed.