Materials and Methods

Study sample

The Study of Health in Pomerania (SHIP)

The Study of Health in Pomerania (SHIP)\(^1\) is a population-based study conducted in West Pomerania, the north-east area of Germany. A more detailed description of the study design and recruitment has been previously described elsewhere.\(^2\) The net sample (without migrated or deceased persons) comprised 6,265 eligible individuals with 4,308 (response 68.8%) of them taking part in the study performed between October 1997 and May 2001. At the baseline examination, echocardiography was restricted to 2,578 individuals (1,274 women, 49.4%) who were 45 years or older. For the present analysis, we excluded participants with missing values for aortic valve sclerosis in the echocardiogram (n=226), for alcohol intake (n=170) or any of the covariables (n=240), as well individuals with reported history of aortic stenosis (n=23) or aortic valve replacement (n=6). The final analytical sample compromised 2,022 (987 women; 48.8%) subjects. All study participants gave written informed consent. The study was approved by the ethics committee of the University of Greifswald\(^3\) and complies with the Declaration of Helsinki.

Interview, medical and laboratory examination

Data on socio-demographics, alcohol consumption, smoking habits, physical activity, and medication use were gathered by trained and certificated medical staff during a standardized computer-assisted interview.\(^2\) The following demographic variables were assessed: age, gender and school educational attainment (in years of education completed). Alcohol consumption was assessed using a beverage-specific quantity-frequency measure: number of days with alcohol consumption (beer, wine,
and spirits) and average daily alcohol consumption for such a day over the last 30 days.\(^4\) Average alcohol consumption (in grams per day) was calculated by multiplying frequency and amount of alcohol from beer, wine, and spirits, respectively, using a standard ethanol content of 4.8 percent (by volume) in beer, 11 percent (by volume) in wine, and 33 percent (by volume) in spirits for conversion.\(^4\) Abstainers were defined as individuals who did not consume alcohol during the last 30 days. As current abstainers are a heterogeneous group of lifetime teetotalers and individuals refraining from alcohol due to ill health or other reasons,\(^5\) we also used alternative definitions of abstaining for the sensitivity analyses: (a) lifetime abstaining; (b) 30 days abstainers, but former drinkers. Smoking status was categorized as never, past only, current. Individuals who did not take part in leisure-time physical activity during summer or winter for at least one hour per week were classified as being physically inactive.\(^6\) Information on medication was categorized according to the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System code.\(^2,7\)

Anthropometric measurements included height, weight and waist circumference. Waist-to-height ratio was calculated as the waist circumference divided by height measured in centimeters. After a 5 minutes rest period, systolic and diastolic blood pressures were measured three times at the right arm of seated participants using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan) with a 3 minutes interval between consecutive measurements.\(^8\) The present analysis used the average of the second and third blood pressure measurement. Arterial hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or current self-reported use of antihypertensive medication.
A non-fasting venous blood sample was obtained from all study participants between 07:00 a.m. and 04:00 p.m. while sitting. Glycated hemoglobin was determined by high-performance liquid chromatography (Bio-Rad Diamat Analyzer, Munich, Germany). Diabetes mellitus was defined as self-reported and/or use of antidiabetic medication defined by the ATC code (A10) and/or glycated hemoglobin ≥ 6.5% and/or non-fasting glucose ≥ 11.1 mmol/l. High-density lipoprotein cholesterol (HDL-C) was measured after precipitation of the apoB-containing lipoproteins with phosphotungstic acid/MgCl2 (EPOS 5060; Boehringer Ingelheim, Mannheim, Germany). Serum concentrations of apolipoprotein A1 were measured with commercially available reagents on a BN II analyzer (Dade Behring, Eschborn, Germany). Lipid-lowering medication was defined by the ATC code (C10). Carotid plaques were defined as stenosis >0% in left or right internal carotid artery. Antiplatelet medication was defined by the ATC code (B01AC). Plasma fibrinogen concentrations were assayed according to Clauss (Electra 1600 analyzer; Instrumentation Laboratory, Barcelona, Spain).

**Echocardiography**

Two-dimensional, M-Mode and Doppler echocardiography were performed using the Vingmed CFM 800A system (GE Medical Systems, Waukesha, USA). The aortic valve was scanned from the parasternal short and long axis as well as from the apical three and five chamber views. An abnormal irregular thickening and a focal or diffuse increase of the echogenicity of the leaflets with or without reduced systolic opening was defined as AVS. Aortic stenosis was present if calcification of the leaflets with a reduced systolic opening and a Doppler gradient of at least 15 mm Hg were found. The examiners were blinded to any clinical data from the patient.
including the presence of murmurs. Certification examinations revealed an agreement measurements between observers of >90%.  

**Statistical analysis**

Data on quantitative characteristics are expressed as median (25th, 75th percentile). Data on qualitative characteristics are expressed as percent values. For descriptive purposes, average alcohol consumption was grouped as: 30 days abstainer, consumption of >0 to <20 g/day, 20 to <40 g/day, 40 to <60 g/day, ≥60 g/day (Table 1). Next, the association between alcohol consumption and AVS was estimated using a logistic regression model with average daily alcohol consumption being modeled as a continuous trait. To fully explore and test potential nonlinear associations, we modeled average alcohol consumption using multivariable fractional polynomials, taking the ‘spike at zero’ into account. Results of the adjusted logistic regression models were displayed by plotting adjusted OR for AVS against average alcohol intake. We plotted these odds ratios on a continuous scale in Figure 1, using an average daily alcohol consumption of 10 g as reference. Furthermore, in Table 2 we display the OR for AVS for selected percentiles of alcohol consumption, (modeled as a continuous trait) compared to an average alcohol intake of 10 g/day.

Three models were estimated accounting for different covariates. The first model was adjusted for age and sex. The second model added educational level, smoking, physical inactivity and waist-to-height ratio. We preferred this variable instead of body mass index or waist-to-hip ratio since a previous analysis of our group revealed that waist-to-height ratio was a better predictor for cardiovascular risk and mortality than body mass index or waist-to-hip ratio in our sample. The third model also included systolic blood pressure and glycated hemoglobin. In separate
models, we tested multiplicative interaction terms of alcohol consumption with sex, age, and smoking status, while adjusting for the other covariates of model 2. We performed a sensitive analysis with an extra model adjusted for age, sex, educational level, smoking, physical inactivity, BMI, triglycerides, HDL, LDL and diabetes. We also tested whether the magnitude of the association differed between subgroups of lifetime teetotalers or 30 days abstainers, and former drinkers.

In model 2, 21.7% of the sample cases had to be excluded due to missing values. Therefore we performed regression analyses using multiple imputation via chained equations using 20 imputed datasets.\(^6\) However, point estimates and confidence intervals were similar to complete-case analysis and we reported estimates from complete-case analysis.

Analyses were performed using Stata/MP4 13.1 (Stata Corp., College Station, TX, USA).

References


health care costs and hospitalization: Results from a prospective observational study. *Growth Horm IGF Res.* 2011;21:89-95


