Alcohol intake and bradyarrhythmia risk: a cohort study of 407 948 individuals

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Aims
There is a paucity of epidemiological evidence on alcohol and the risk of bradyarrhythmias. We thus characterized associations of total and beverage-specific alcohol consumption with incident bradyarrhythmias using data from the UK Biobank.

Methods and results
Alcohol consumption reported at baseline was calculated as UK standard drinks (8g alcohol)/week. Bradyarrhythmia events were defined as sinus node dysfunction (SND), high-level atrioventricular block (AVB), and permanent pacemaker implantations. Outcomes were assessed through hospitalization and death records, and dose–response associations were characterized using Cox regression models with correction for regression dilution bias. We studied 407 948 middle-aged individuals (52.4% female). Over a median follow-up time of 11.5 years, a total of 8 344 incident bradyarrhythmia events occurred. Increasing total alcohol consumption was not associated with an increased risk of bradyarrhythmias. Beer and cider intake were associated with increased bradyarrhythmia risk up to 12 drinks/week; however, no significant associations were observed with red wine, white wine, or spirit intake. When bradyarrhythmia outcomes were analysed separately, a negative curvilinear was observed for total alcohol consumption and risk of SND, but no clear association with AVB was observed.

Conclusion
In this predominantly White British cohort, increasing total alcohol consumption was not associated with an increased risk of bradyarrhythmias. Associations appeared to vary according to the type of alcoholic beverage and between different types of bradyarrhythmias. Further epidemiological and experimental studies are required to clarify these findings.

Keywords
Alcohol • Atrioventricular block • Bradyarrhythmias • Risk factor • Sinus node disease • Pacemaker

Introduction
The demand for permanent pacemaker (PPM) insertions is rising, and this growing trend has significant implications for healthcare resource planning worldwide.1,2 Clinically significant sinus node dysfunction (SND) and high-level atrioventricular block (AVB) represent the most common indications for PPM implantation. These diseases are typically attributed to idiopathic fibrosis of the conduction system, largely thought to be age-related,3,4 and with an increasingly elderly population, the burden of bradyarrhythmias is projected to increase.5 In recent years, there has been an increasing focus on the role of modifiable risk factors in the primary prevention of arrhythmias, particularly for atrial fibrillation.6 However, with the exception of sleep apnoea treatment in the setting of nocturnal bradyarrhythmias, societal guidelines on the management of bradycardia have made few recommendations as to the management of modifiable risk factors for preventing disease.7 This is despite a number of key modifiable risk factors already identified, including sleep apnoea, body mass index (BMI), blood pressure, and elevated fasting blood glucose.5,8,9 Furthermore, few population-based studies have investigated the
role of lifestyle factors on bradyarrhythmia risk. We have previously demonstrated no association of physical activity and bradyarrhythmia risk, contrasting with the protective effects of regular physical activity seen in observational studies for other arrhythmias.\(^{10}\) With regards to alcohol consumption, no significant association has previously been demonstrated with incident SND,\(^{6}\) nor AVB.\(^{8}\) Whether these studies have had sufficient statistical power to detect a more modest or non-linear relationship with alcohol remains uncertain. To our knowledge, the role of individual beverages in bradyarrhythmia risk has also yet to be studied, despite increasing research attention in this area and conflicting data in other arrhythmias.\(^{6}\)

To provide further insights on the potential role of alcohol intake and bradyarrhythmias, we characterized associations of total and beverage-specific alcohol consumption with incident bradyarrhythmias using prospective cohort data from the UK Biobank.

### Methods

#### Study population

We retrospectively analysed data from the UK Biobank, a prospective cohort study of ~500,000 community-dwelling individuals. The UK Biobank has ethical approval from the North West Multicentre Research Ethics Committee. UK Biobank aged 40–69 years were identified from National Health Service (NHS) records and were invited by mail to attend 1 of 22 assessment centres between 2006 and 2010 to participate in the study. At enrolment, participants completed a touchscreen questionnaire collecting information on sociodemographic, diet, lifestyle, reproductive, and environmental factors. Anthropometric measurements were measured using standard protocols, verbal interview was undertaken to ascertain medical comorbidities, and blood and urine samples were also taken. Since recruitment, participants have been followed for hospitalizations and mortality through linkage with NHS records and invited to complete follow-up questionnaires.

#### Assessment of alcohol consumption

Alcohol consumption was included in the model as restricted cubic splines with 4 knots placed at 5th, 35th, 65th, and 95th percentiles, defined apriori. The model was stratified by sex and adjusted for age, race (White, other, unknown), education (college or university degree, vocational qualifications, optional national exams at ages 17–18 years), BMI, total MET-minutes/week, smoking status (never, past, current, and unknown), and the following comorbidities at time-updated covariates: hypertension, coronary artery disease, heart failure, valvular disease, atrial fibrillation, diabetes mellitus, hyperlipidaemia, sleep apnoea.
thyroid disease, and chronic kidney disease. Hospital inpatient diagnoses/operations were used to update the information. Missing values for BMI and total MET-minutes/week were handled using the indicator variable method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by general contrasts of regression coefficients, using the median values of covariates and 0 drink/week as the referent value.

A number of sensitivity analyses were conducted: (i) excluding participants with events that occurred in the first 1 and 2 years of follow-up so as to mitigate any potential effect of reverse causality; (ii) excluding participants with coronary artery disease, heart failure, valvular disease, and/or atrial fibrillation at baseline so as to mitigate any potential bias due to survival; (iii) performing complete case analyses instead of the indicator variable method; (iv) mutually adjusting for the consumption of other beverages in models for individual beverage consumption; and (v) including ex-drinkers in the analyses.

As exploratory analyses, we assessed for a differential effect of alcohol consumption by sex. An interaction term between alcohol consumption and these categories was included in the model, and likelihood ratio tests were performed with the nested model to identify significant interactions. We also performed analyses for each individual bradyarrhythmia outcome (SND, AVB, and PPM implantation). In these analyses, time to first respective outcome was considered without right censoring at the occurrence of other events.

The proportional hazards assumption was tested using Schoenfeld residuals and interaction with time, and no major violations were present after stratifying models by sex. A two-tailed P value was set at 0.05 for statistical significance. Analyses were performed using R, version 4.0.2.

Results

The study population for the primary analyses consisted of 407,948 participants after stepwise exclusion of 1,903 UK Biobank participants with a history of bradyarrhythmias, 17,995 that were ex-drinkers, and 73,000 that were current consumers but did not have specific alcohol consumption information. A total of 8344 incident bradyarrhythmia events occurred over 4,590,804 person-years of follow-up with a median follow-up duration of 11.5 (IQR 10.7–12.3) years. The baseline characteristics of the study population are detailed in Table 1. Median total alcohol consumption in the study population was 8.0 (IQR 3.5–15.5) drinks/week, and 22,275 (5.5%) reported having never consumed alcohol. Participants consuming greater amounts of alcohol were younger, more likely male, white, and largely more comorbid. Ex-drinkers, who were not included in the primary analyses, were more likely older, female, non-White, and comorbid, and were also more likely to have a history of bradyarrhythmias. The distributions of total alcohol and individual beverage consumption in the study population are shown in Supplemental material online, Figure S1. Participants whose alcohol consumption was predominantly beer/cider or spirit consumption were generally more comorbid than participants whose alcohol consumption was predominantly red or white wine consumption (Supplemental material online, Table S3).

For aggregate total alcohol consumption, increasing consumption was not associated with an increased risk of bradyarrhythmias (Figure 1). Negative point estimates were observed across the spectrum of consumption and confidence intervals generally crossed unity, though consumption of 0–7 drinks/week was associated with statistically significant estimates. For beer and cider intake, a positive curvilinear association was observed with bradyarrhythmia risk, though statistically significant estimates were only observed with consumption between 0 and 12 drinks/week. No other clear beverage-specific associations were observed. Sensitivity analyses did not materially change the results (Supplementary material online, Table S4). Ex-drinkers had a similar risk of bradyarrhythmias compared to current and never drinkers (HR 1.03, 95% CI 0.93–1.15), and associations were similar when ex-drinkers were included in the analysis (Supplementary material online, Figure S2), or when never drinkers were excluded from the analysis (Supplementary material online, Figure S3). No statistically significant effect modification by sex was observed for total alcohol or individual beverages and bradyarrhythmia risk.

When individual bradyarrhythmia outcomes were studied, there were 694 incident SND, 2091 incident AVB, and 7725 incident PPM implantations. Disaggregation of bradyarrhythmia outcomes demonstrated contrasting associations with total alcohol consumption (Figure 2). A negative curvilinear or L-shaped association was observed for total alcohol consumption and risk of SND, and statistically significant estimates below unity were observed with consumption between 10 and 65 drinks/week. No significant association was present for total alcohol consumption and risk of AVB. The association of total alcohol consumption and PPM implantation was similar to that of the composite bradyarrhythmias outcome. Individual beverage associations demonstrated a potentially protective association against SND with increasing white wine intake, and a potentially harmful association for AVB with increasing beer and cider intake (Supplementary material online, Figure S4).

Discussion

This is the largest study to our knowledge to characterize associations of total and beverage-specific alcohol consumption with incident bradyarrhythmias. Leveraging the prospective UK Biobank cohort, we studied 407,948 community-dwelling and mostly White British individuals and 8344 bradyarrhythmia events over a median follow-up of 11.5 years. The principal findings of our study are as follows:

1. Increasing total alcohol consumption was not associated with an increased risk of bradyarrhythmias.
2. While light-to-moderate beer and cider consumption appeared to be associated with an increased risk of bradyarrhythmias, other alcoholic beverages, including red wine, white wine, and spirits, did not clearly demonstrate any significant associations.
3. When bradyarrhythmia outcomes were analysed separately, we additionally observed a negative curvilinear or L-shaped association for total alcohol consumption and risk of SND.

Previous population-based studies investigating the characteristics and risk factors associated with incident bradyarrhythmias have been substantially smaller in size, and the focus of these studies has not specifically been on the potential role of alcohol consumption. These studies did not identify any significant linear association of alcohol consumption with incident disease. In this study, allowing for any potential non-linear associations, we found no evidence for any increase in bradyarrhythmia risk with increasing total alcohol consumption. This contrasts with that seen for atrial fibrillation and sudden cardiac death, where heavy alcohol consumption is an established risk factor. Although potentially divergent associations were seen
with specific alcoholic beverages and bradyarrhythmia types, these are exploratory findings that warrant further study.

Interestingly, previous case reports have described AV blocks of varying degrees occurring after binge drinking episodes. Small historic experimental reports in the setting of acute alcohol ingestion have also demonstrated prolongation of sinus node recovery, His-ventricular intervals, and QRS duration, though in contrast, one recent case report described AV blocks of varying degrees occurring after binge drinking episodes. Small historic exploratory findings that warrant further study.

Investigations into potential mechanisms that may underlie both beneficial and adverse associations of alcohol in arrhythmogenesis continue to attract ongoing investigation, and the findings of this study suggest a need for further experimental studies in the field of bradyarrhythmias.

This is the largest study to our knowledge to characterize the relationship between alcohol and incident bradyarrhythmias, and the first to study associations by beverage and sex. Furthermore, adjustment for measurement error and long-term variability via regression calibration has not been previously undertaken. Observational studies relying on single point estimates of exposure variables measured with error suffer from regression dilution bias, where effect estimates are biased towards the null. Correction for such bias as in the present study allows for more accurate estimates of the associations of long-term alcohol exposure. Our analyses also excluded ex-drinkers to limit reverse causality, although analyses including these participants resulted in comparable trends.

**Limitations**

Several limitations warrant discussion. These data are observational in nature, and despite extensive multivariate adjustment and robust sensitivity analyses, we cannot exclude the possibility of residual confounding and reverse causality. The diagnostic codes used in our

| Characteristics | Overall | <7 | 7–14 | 15–28 | >28 |
|-----------------|---------|----|------|-------|-----|
| Number of participants | 407,948 (100%) | 179,602 (44.0%) | 111,557 (27.3%) | 84,255 (20.7%) | 32,534 (8.0%) |
| Female | 212,633 (52.1%) | 122,944 (68.5%) | 58,189 (52.2%) | 27,076 (32.1%) | 4,424 (13.6%) |
| Age (years) | 58.3 (50.6, 63.7) | 58.6 (50.6, 63.9) | 58.2 (50.5, 63.6) | 58.1 (50.8, 63.4) | 57.8 (50.6, 63.2) |
| White race | 385,193 (94.4%) | 162,577 (90.5%) | 108,409 (97.2%) | 82,367 (97.8%) | 31,840 (97.9%) |
| Body mass index (kg/m²) | 26.6 (24.1, 29.6) | 26.4 (23.8, 29.8) | 26.3 (23.9, 29.1) | 26.9 (24.6, 29.7) | 27.7 (25.3, 30.5) |
| Current smokers | 41,297 (10.1%) | 12,975 (7.2%) | 9,672 (8.7%) | 11,179 (13.3%) | 7,471 (23.0%) |
| Physical activity (MET-minutes/week) | 1,790 (819, 3550) | 1,710 (775, 3470) | 1,800 (857, 3490) | 1,870 (873, 3600) | 1,920 (834, 4160) |

One standard drink is defined as 8 g alcohol, the size of a standard drink in the UK. Categorical variables are reported as n (%) and continuous variables are reported as median (Q1, Q3). All comparisons between quartiles were statistically significant.

**Comorbidities**

- Hypertension: 113,347 (27.8%)<br> 111,575 (27.3%)<br> 84,255 (20.7%)<br> 32,534 (8.0%)
- Coronary artery disease: 20,894 (5.1%)<br> 21,297 (5.1%)<br> 12,280 (15.6%)<br> 2,128 (6.5%)
- Heart failure: 1,931 (0.5%)<br> 1,931 (0.5%)<br> 1,931 (0.5%)<br> 1,931 (0.5%)
- Valvular disease: 4,361 (1.1%)<br> 4,361 (1.1%)<br> 4,361 (1.1%)<br> 4,361 (1.1%)
- Atrial fibrillation: 5,612 (1.4%)<br> 5,612 (1.4%)<br> 5,612 (1.4%)<br> 5,612 (1.4%)
- Diabetes mellitus: 19,951 (4.9%)<br> 19,951 (4.9%)<br> 19,951 (4.9%)<br> 19,951 (4.9%)
- Hyperlipidaemia: 55,606 (13.6%)<br> 55,606 (13.6%)<br> 55,606 (13.6%)<br> 55,606 (13.6%)
- Thyroid disease: 21,911 (5.4%)<br> 21,911 (5.4%)<br> 21,911 (5.4%)<br> 21,911 (5.4%)
- Sleep apnoea: 7,965 (2.0%)<br> 7,965 (2.0%)<br> 7,965 (2.0%)<br> 7,965 (2.0%)
- Chronic kidney disease: 1,261 (0.3%)<br> 1,261 (0.3%)<br> 1,261 (0.3%)<br> 1,261 (0.3%)

**Alcohol consumption (UK standard drinks/week)**

- Total alcohol: 8.0 (3.5, 15.5)<br> 8.0 (3.5, 15.5)<br> 8.0 (3.5, 15.5)<br> 8.0 (3.5, 15.5)
- Beer/cider: 0 (0, 4.7)<br> 0 (0, 4.7)<br> 0 (0, 4.7)<br> 0 (0, 4.7)
- Red wine: 1.2 (0.5, 5.8)<br> 1.2 (0.5, 5.8)<br> 1.2 (0.5, 5.8)<br> 1.2 (0.5, 5.8)
- White wine: 0.2 (0, 0.7)<br> 0.2 (0, 0.7)<br> 0.2 (0, 0.7)<br> 0.2 (0, 0.7)
- Spirits: 0 (0, 0.7)<br> 0 (0, 0.7)<br> 0 (0, 0.7)<br> 0 (0, 0.7)
study to identify SND and AVB have not been validated specifically in the UK Biobank cohort; however, a validation study of similar diagnostic codes in the Danish National Patient Registry has demonstrated strong positive predictive values of 87%. A number of SND and AVB events are likely coded under other diagnostic codes, including under the diagnosis of syncope, which would limit power rather than bias results. We did not include bundle branch blocks or other conduction diseases in our definition of bradyarrhythmias as they would not necessarily cause a pathologically slow ventricular response, though these conditions should be examined in future studies. We did not adjust for multiple testing; as we studied several exposures and outcomes, our original findings must therefore be considered exploratory. Additionally, no data were available on participant’s historic consumption patterns, including length and pattern of alcohol consumption. Drinking patterns and lifestyle characteristics vary by race and population; these findings thus require confirmation in different populations beyond our predominantly White British cohort. The representativeness of UK Biobank to general populations is also limited by the ‘healthy volunteer’ phenomenon; however, valid assessment of exposure–disease relationships is nonetheless widely generalizable and do not require participants to be representative of the population at large.
Conclusions

In this predominantly White British cohort, increasing total alcohol consumption was not associated with an increased risk of bradyarrhythmias. Associations appeared to differ according to the type of alcoholic beverage and between different types of bradyarrhythmias. Further experimental and epidemiological studies in other cohorts are required to clarify these findings.

Supplementary material

Supplementary material is available at Europace online.

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Conflict of interest: J.M.L.H. reports that the University of Adelaide has received on his behalf lecture and/or consulting fees from Medtronic and Pfizer/BMS. D.H.L. reports that the University of Adelaide has received on his behalf lecture and/or consulting fees from Abbott Medical, Bayer, Biotronik, Boehringer Ingelheim, Medtronic, Micropor, and Pfizer/BMS. P.S. reports having served on the advisory board of Medtronic, Abbott Medical, Boston Scientific, CathRx, and PaceMate. P.S. reports that the University of Adelaide has received on his behalf lecture, travel, and/or research funding from Abbott Medical, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Servier, St Jude Medical, and Vifor Pharma. The other authors have nothing to disclose.

Data availability

Access to the UK Biobank Resource is available to all bona fide researchers for all types of health-related research that is in the public interest.

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