 doi:10.20944/preprints202205.0385.v1

Article

Urinary Sodium Excretion Enhances the Effect of Alcohol on Blood Pressure

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Abstract: Background: Alcohol consumption is linked to urinary sodium excretion and both of these traits are linked to hypertension and cardiovascular diseases (CVDs). The interplay between alcohol consumption and sodium on hypertension, and cardiovascular diseases (CVDs) is not well-described. Here, we used genetically predicted alcohol consumption and explored relationships between alcohol consumption, urinary sodium, hypertension, and CVDs. **Methods:** We performed a comparative analysis among 295,189 participants from the prospective cohort of the UK Biobank (baseline data collected between 2006 and 2010). We created a genetic risk score (GRS) using 105 published genetic variants in Europeans that were associated with alcohol consumption. We explored relationships between GRS, alcohol consumption, urinary sodium, blood pressure traits, and incident CVD. We used linear, logistic regression and Cox proportional hazards (PH) models in our analysis. **Results:** Our analyses supported an interaction effect between alcohol GRS and urinary sodium on hypertension ($P_{interaction}$ =0.03) and CVD ($P_{interaction}$ =0.03). In presence of high urinary sodium excretion, alcohol GRS increases blood pressure in a more enhanced fashion. **Conclusions:** Our results show that decrease in urinary sodium excretion offsets the risk posed by genetic risk of alcohol consumption.

Keywords: genetics of alcohol; urinary sodium; cardiovascular traits

1. Introduction

Cardiovascular disease (CVD) is a global public health problem killing 17 million people annually [1]. Alcohol consumption plays a role in the development of hypertension and CVD, although the effect might not be linear [2,3].

Sodium balance plays an important role in blood pressure regulation [4,5]. We have previously showed that an increase in genetic risk of urinary sodium is associated with future increase in systolic- (SBP) and diastolic blood pressure (DBP) [6]. Alcohol consumption has been reported to be associated with urinary *sodium* excretion [7,8]. A recent cross-sectional study [9] used data from older adults in Northern China and found that combination of alcohol consumption and sodium intake imposed greater risk of hypertension.

Recent advances in genetic data acquisition and analysis have improved our understanding of complex relationships and the biological mechanisms underpinning complex diseases. Recent Genome-wide association studies (GWAS) among Europeans identified genetic variants in the form of single nucleotide polymorphisms (SNPs) associated with alcohol consumption [10,11] and urinary sodium [12].

To better understand relationships between alcohol consumption, urinary sodium, hypertension and CVDs, we constructed a genetic risk score (GRS) for alcohol consumption based on 105 SNPs associated with alcohol consumption in Europeans [10,11]. We explored the relationship between GRS and alcohol consumption in various subgroups. We also explored the effect of GRS on blood pressure, risk of hypertension, CVD, and the

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interactive effect with urinary sodium using individual-level data from 295,189 UK Biobank (UKB) participants.

2. Materials and Methods

2.1. Ethics Approval

Ethical approval was obtained centrally by the UKB from the UKB Research Ethics Committee and Human Tissue Authority. All participants whose data was used in this study have been given informed consent. We additionally obtained ethics approval from Brunel University London to work on secondary data from the UKB (25527-A-Jun/2021-32860-1).

2.2. Study Population and Exclusion Criteria

UKB is a large prospective cohort set up in 22 centres across the United Kingdom. It consists of over 500,000 participants aged 40 to 69 recruited between 2006 and 2010. [13] Genetic data on 487,409 participants were available for analysis. We applied several exclusion criteria (**Figure 1**). We excluded participants who withdrew consent (N=109), participants of non-European ancestry (N=28,547), 1st or 2nd degree relatives (N=34,876), pregnant women or women unsure of pregnancy status at baseline (N=232), prevalent CVD cases (N=25,561), sex mismatch (N=140), participants with health-related change in drinking habit (N=65,579), non-alcoholic drinkers or participants with missing alcohol consumption data (N=36,023) and missing data in the main study variables (N=1,153). A total of 295,189 participants remained for analysis.

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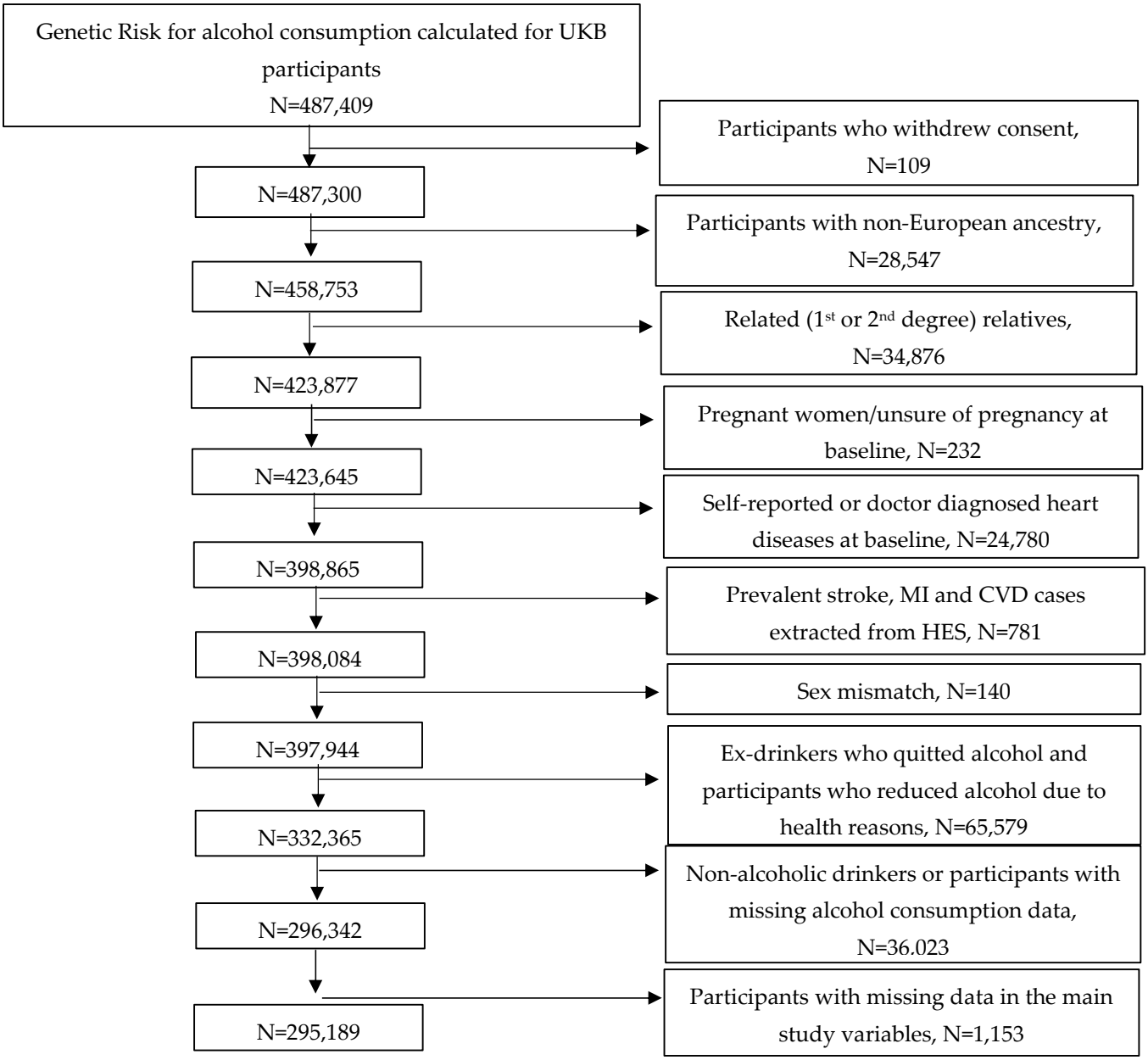

Figure 1. Exclusion flowchart. Exclusion criteria and the final UKB sample size used in the analysis.

2.3. Blood Pressure and Definition of Hypertension

Supplementary Table S1 lists the UKB data fields used in our analyses. Blood pressure was measured centrally by the UKB [17] and we summarised these details previously. [6] In brief, for every participant, SBP and DBP was each measured twice at the UKB assessment centre by an automated device (Omron HEM-7015IT digital BP monitor) or a manual device when automated readings could not be taken. Where multiple values for blood pressure existed, we used the mean of all available measurements. We adjusted blood pressure for participants taking blood pressure lowering medication by adding 15 mmHg to their SBP and 10 mmHg to their DBP measurements according to Tobin et al [18].

We defined hypertension as stage 1 or stage 2 according to the American Heart Association (AHA) guideline [19]. Stage 1 hypertension includes individuals with SBP between 130-139 mmHg or DBP between 80-89 mmHg [19]. Stage 2 hypertension includes individuals with SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or using blood pressure lowering medications [19].

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2.4. Cardiovascular Diseases

We described definitions and methods for assessment of CVD events in detail previously [15]. In summary, CVD was defined as an episode of stroke, myocardial infarction, or coronary heart disease.

Nonfatal and fatal records of CVD were extracted from Hospital Episode Statistics (HES). We used the International Classification of Diseases 9 and 10 codes provided in **Supplementary Table S2** to extract CVD cases. We used HES recorded episode date as the date of CVD event or death. If the episode date was missing, we used the hospital admission date. For participants with multiple hospital admissions for the same condition, we used the first recorded date.

Prevalent CVD cases were defined as cases diagnosed prior to the UKB baseline assessment date for each participant. These were additionally identified from the UKB self-reported questionnaire at baseline assessment if participants had self-reported diagnosis of CVDs (**Supplementary Table S2**). Incident cases were defined as newly diagnosed cases after the UKB baseline assessment date. Follow-up time for each participant was defined as the time from the UKB baseline assessment until March 31, 2015.

2.5. Assessment of lifestyle factors

Urinary sodium was measured from spot urine samples collected at the UKB baseline assessment centre. [14] Concentration of sodium in the urine was measured by ion-selective electrode analysis using Beckman Coulter AU5400.

We calculated alcohol intake in grams per day (g/day) for each UKB participant based on self-reported alcohol intake from the UKB touchscreen questionnaire at baseline assessment. We used answers from questions on alcohol intake frequency and average weekly intake of red wine, white wine, beer/cider, spirits and fortified wine respectively (**Supplementary Table S1**). Details of our alcohol intake (g/day) calculation were described previously [10]. In brief, for participants with complete responses to the alcohol questions listed above, we multiplied quantity of the average weekly intake of each alcoholic beverage by its standard drink size and reference alcohol content. We then summed up the drink-specific intake based on the reported drinking frequency and converted alcohol consumption to gram per day.

As alcohol consumption was not normally distributed, we transformed alcohol consumption (g/day) on the natural logarithm scale. All subsequent mentions of alcohol consumption in this study refer to transformed alcohol consumption.

Smoking status was recorded based on a UKB self-reported questionnaire [14]. Methods of assessment for sedentary lifestyle was mentioned in our previous publication [6]. We measured the sum of hours per day participant spent sitting (watching TV, driving, and using a computer). Greater values indicated more hours spent sedentary.

To assess participant's dietary intake, we calculated a Dietary Approaches to Stop Hypertension (DASH) score based on methods published elsewhere [6,15]. In brief, DASH score was calculated by using the UKB self-reported food questionnaire at baseline. We scored and ranked the participants based on selected dietary components listed in **Supplementary Table S1** and derived an overall DASH score for each participant.

Townsend deprivation score used UK national census data on car ownership, household overcrowding, owner-occupation, and unemployment for each UK region/area [16]. The UKB assigned each participant a score based on the residence postcode the participant provided at baseline assessment.

2.6. Genotyping, Imputation and Genetic Calculations in the UKB

Genotyping and imputation were conducted centrally by the UKB. Detailed methodologies were provided elsewhere [13,17]. In brief, participants' blood samples were collected at the UKB assessment centre and DNA was extracted and was genotyped using the UKB Axiom Array. Genotype imputation used 3 reference panels including Haplotype Reference Consortium, UK10K, and 1000 Genomes phase 3, and used the IMPUTE4 program.

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UKB calculated genetic principal components and kinship coefficients centrally. These were used to account for population stratification and to identify related individuals. [13]

2.7. GRS for Alcohol Consumption

We calculated a GRS for alcohol consumption based on 105 published SNPs (**Supplementary Table S3)** associated with alcohol consumption in Europeans [10,11]. We illustrated the SNP selection process in **Figure 2**. To summarise, we took SNPs identified from two large-scale GWAS meta-analyses on alcohol consumption. [10,11] Collectively within 145 SNPs, we first removed 6 duplicates. Then, we assessed the linkage disequilibrium (LD) among the remaining SNPs using LDlink [20] and PLINK version 1.9 [21]. We defined SNP pairs with R^2>0.1 as dependent SNPs. Using LDlink and plink, we identified 34 correlated SNP pairs. Within each SNP pair, we removed the SNP with the weaker association with alcohol consumption indicated by a larger *P* value. As a result of these exclusions, 105 SNPs (**Supplementary Table S3**) remained for the alcohol GRS calculation.

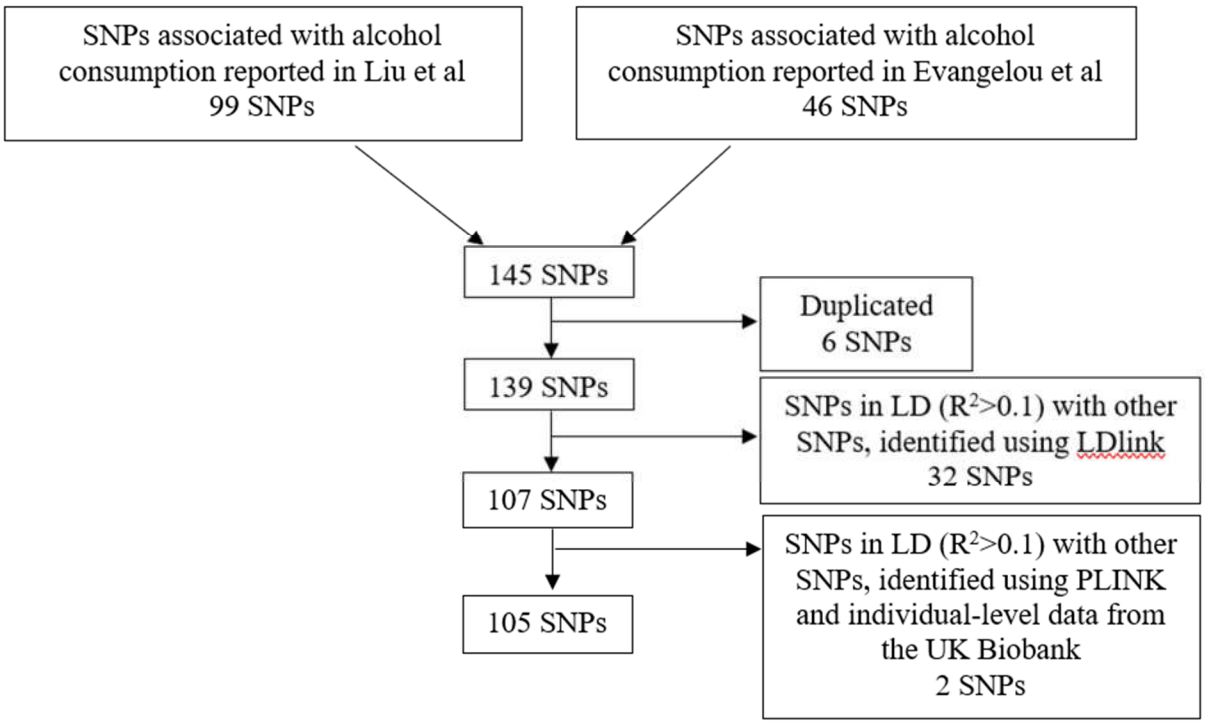

Figure 2. SNPs selection flowchart for alcohol consumption genetic risk score. Flowchart detailing the SNPs selection process prior to being used in the calculation of alcohol consumption genetic risk score for UK Biobank participants. We took SNPs identified for alcohol consumption in Liu et al[11] (99 SNPs) and Evangelou et al. [12] (46 SNPs). We first removed duplicates. We then assessed LD (R^2>0.1) among the SNPs and identified LD pairs by using the LDmatrix function in LDlink[19]. Within each pair, we removed the SNP with the weaker association to alcohol consumption indicated by a larger *P* value (32 SNPs removed). The remaining SNPs went through an extra layer of LD pruning by using PLINK version 1.9 [20] and individual-level data of the UK Biobank (2 SNPs removed). In the end, 105 SNPs were selected to calculate the alcohol genetic risk score. SNP, single nucleotide polymorphism; LD, linkage disequilibrium.

To calculate the GRS for each UKB participant, we sought the effect estimates for the 105 alcohol SNPs from the alcohol GWAS meta-analysis study by Liu et al. [11] To avoid sample overlap with the UKB data, we specifically extracted the effect estimates from the summary statistics provided by Liu et al. [11]excluding UKB and 23andMe. We also checked that this summary statistics dataset used the same genome build assembly (GRCh37) as the UKB genotype data [13]. To calculate the GRS, we multiplied the effect estimates by the number of risk alleles each UKB participant carries on the alcohol SNPs. The products

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were then summed across all SNPs to produce an overall weighted risk score for each participant. We standardised the weighted GRS for further analysis.

2.8. Statistical Analysis

We assessed the variance in alcohol consumption explained by GRS using the adjusted R^2 estimate from a linear regression model regressing alcohol consumption over the GRS. To assess the predictability of the GRS at different alcohol consumption levels, we compared percentage variation in alcohol consumption explained by the GRS across alcohol consumption quintiles comprising of 5 equal groups.

We investigated the association of the GRS with SBP, DBP, Stage 1-, Stage 2 hypertension, and incident CVDs. We used linear regression for SBP and DBP, logistic regression for Stage 1- and Stage 2 hypertension and performed survival analysis using Cox proportional hazards (PH) regression that takes follow-up time into account for incident CVD traits. In our survival analyses, individuals who were lost to follow-up, died of diseases not under study, or did not develop diseases of interest at the end of the follow-up were censored. We assessed the PH assumption for every Cox model using statistical tests that used Schoenfeld residuals against follow-up time. When *P* value for the PH assumption global test was <0.05 i.e., the overall PH assumption was violated, we examined which specific covariate violated the PH assumption in the model. For time-varying continuous covariate(s), we added interaction terms with follow-up time split into groups.

We tested two statistical models in all analyses. We adjusted model 1 for age, $age^{2,}$ and sex. In model 2, we additionally adjusted for major known cardiovascular and genetic confounders including smoking status, DASH diet, Townsend deprivation score, sedentary lifestyle, and genetic principal components. We adjusted analyses for interaction between alcohol GRS and urinary sodium where the interaction term was statistically significant.

2.9. Power Calculation

We calculated statistical power for associations of alcohol GRS with hypertension and CVDs using Quanto, version 1.2.4. [22] Using a two-sided significance threshold of 0.05 and a range of number of cases and effect estimates from 0.9-1.3, we obtained estimation of statistical power for our analyses.

2.10. Software and Packages

We calculated alcohol GRS by using PLINK version 1.9. [21] We conducted all statistical analyses in R studio (R version: 3.5.1). We used the 'survival' package for survival analysis.

3. Results

We included 295,189 UKB participants in the current analysis after applying the exclusion criteria (**Figure 1**). At baseline (**Table 1**), participants had a mean age of 56.3 years at recruitment. Approximately 54.5% of the sample were female (N=161,020). Stage 1 hypertension was present among 23.1% of the sample (N=68,284; 23.5% male *vs*. 22.8% female) while stage 2 hypertension was present in 52% of the sample (N=153,474; 59.4% male *vs*. 45.8% female). The median follow-up time for composite CVD and stroke were 6.1 years and 7.1 years respectively. During follow-up time, 8,688 participants (2.9%) developed CVD and 1,857 (0.6%) developed stroke.

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Table 1. Baseline characteristics and incident events of cardiovascular diseases for participants of the UK Biobank, by sex.

	Overall (N=295,189)	Males (N=134,169)	Females (N=161,020)
Age at recruitment, mean (SD), years	56.3 (8)	56.4 (8.1)	56.2 (7.9)
Males, N (%)	134,169 (45.5)	NA	NA
Smoking, N (%)			
Current	30,388 (10.3)	16,341 (12.2)	14,047 (8.7)
Past	148,209 (50.2)	70,575 (52.6)	77,634 (48.2)
Never	116,592 (39.5)	47,253 (35.2)	69,339 (43.1)
Healthy diet score (DASH), mean (SD)	2.7 (1)	2.4 (1)	2.9 (1)
Sedentary lifestyle, median [IQR], hours/day	4 [3-6]	5 [3-6]	4 [3-5]
SBP*, median [IQR], mmHg	138.5 [125.5-153.5]	142 [130-156]	135 [122-150.5]
DBP*, mean (SD), mmHg	84.2 (11.2)	86.5 (11)	82.2 (11)
Stage 1 Hypertension†, N (%)	68,284 (23.1)	31,492 (23.5)	36,792 (22.8)
Stage 2 Hypertension‡, N (%)	153,474 (52)	79,680 (59.4)	73,794 (45.8)
Townsend Deprivation Index, median [IQR]	-2.4 [-3.8- (-)0.06]	-2.4 [-3.8- (-)0.02]	-2.4 [-3.8- (-)0.1]
Urinary sodium, median [IQR]¶	68 [42.7-102.8]	81.9 [53.4-117.5]	57.6 [36.5-88.3]
Composite cardiovascular disease, N (%)	8,688 (2.9)	5,808 (4.3)	2,880 (1.8)
Stroke, N (%)	1,857 (0.6)	1,048 (0.8)	809 (0.5)

SBP, systolic blood pressure; DBP, diastolic blood pressure; DASH, Dietary approaches to stop hypertension; NA, not available. *SBP and DBP adjusted for blood pressure lowering medication.[19] †Stage 1 hypertension defined as SBP 130-139 mmHg or DBP 80-89 mmHg.[20] ‡ Stage 2 hypertension defined as SBP ≥140mmHg and/or DBP ≥90 mmHg or using blood pressure lowering medication.[20] ¶Urinary sodium had missing values and so the baseline statistics for urinary sodium were calculated based on an overall sample size of N=286,806, men N=130,894 and women N=155,912.

One standard deviation (SD) addition of alcohol GRS resulted in 0.12-fold increase in alcohol consumption (natural logarithm transformed equivalent to an increase in alcohol consumption by 1.13g/day; **Figure 3A**). GRS explained ~1% of the variation in alcohol consumption. Alcohol GRS corresponded to a larger prediction of alcohol consumption (measured by the explained variance) among heavy drinkers (adjusted R^2=0.431%; **Figure 3A)** compared with light drinkers (adjusted R^2=0.004%; **Figure 3B**).

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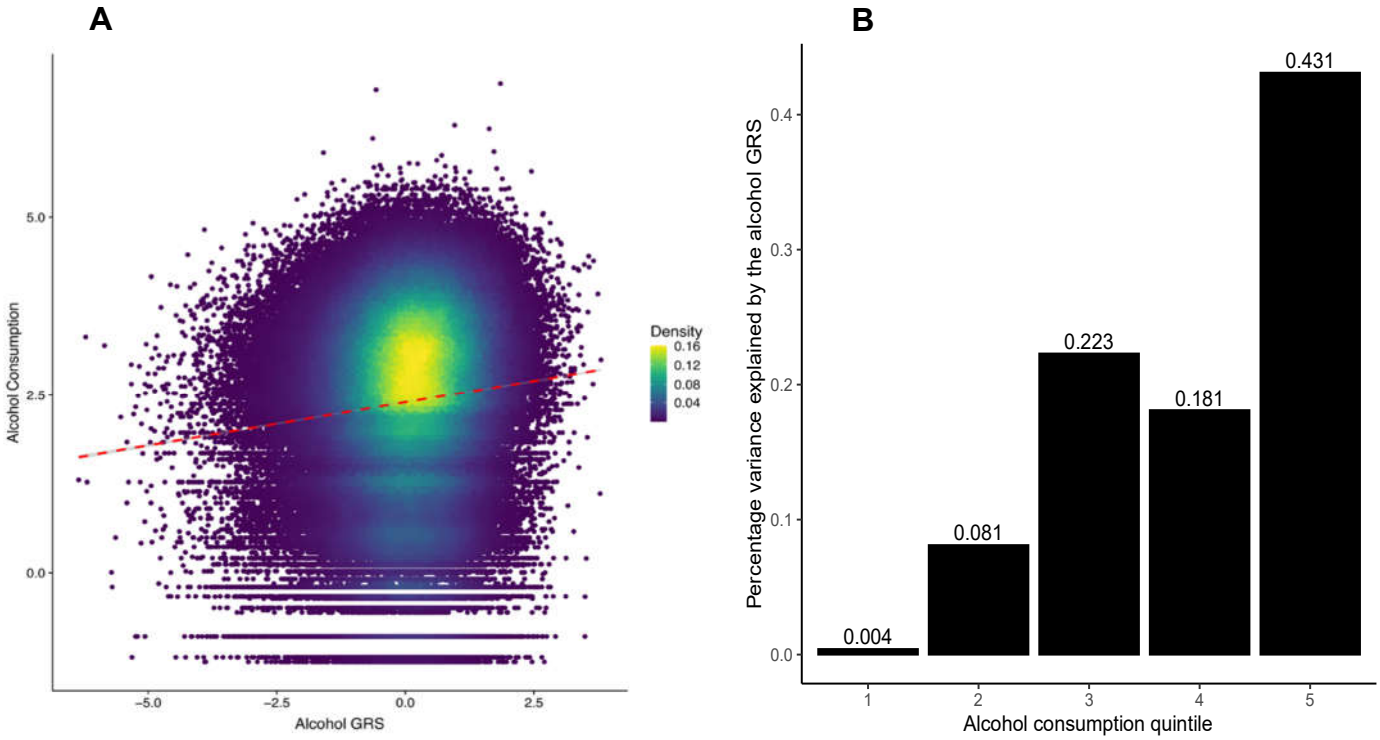

Figure 3. Relationship between alcohol genetic risk score (GRS) and alcohol consumption. Alcohol consumption values have been natural logarithm transformed. (**A**) Linear regression of alcohol consumption over alcohol GRS. Effect estimate=0.12, *P* value<$2x10^{-16}$. Adjusted R^2=0.92%. The red dotted line the gradient of the fitted regression line. (**B**) Percentage variation in alcohol consumption explained by the alcohol GRS within alcohol consumption quintiles. Percentage of explained variation was assessed using the adjusted R^2 estimate from regressing alcohol consumption over the GRS. Alcohol consumption quintile 1 includes participants with alcohol consumption level ranging from 0.287 to 3.648 g/day; Quintile 2=3.651-10.667 g/day; Quintile 3=10.671-17.857 g/day; Quintile 4=17.859-31.328 g/day; Quintile 5=31.330-964.533 g/day.

Within the whole UKB sample (N=295,189), we observed association of the GRS with SBP (β=0.24 mmHg; 95% CI=0.17-0.31; *P*=2.73×10^{-11}), DBP (β=0.13 mmHg; 95% CI=0.09-0.17; *P*=8.56×10^{-11}), Stage 2 hypertension (Odds ratio=1.02; 95% CI=1.01-1.03; *P*=1.92×10^{-8}) and with stroke (Hazard Ratio= 1.06; 95% CI=1.01-1.11; *P*=0.01). We observed a statistically significant interaction between alcohol GRS and urinary sodium on Stage 2 hypertension ($P_{interaction}$=0.03) and CVD ($P_{interaction}$=0.03) (**Table 2**). In participants with high urinary sodium excretion, alcohol GRS showed enhanced the effect of on hypertension and CVD (**Figure 4**).

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Table 2. Interactive effect between alcohol GRS and urinary sodium for blood pressure, hypertension, and incident CVDs.

	N non-cases/ N cases	Effect estimates*	95% CI	*P* value for GRS	Interaction *P* value	PH†
SBP	286,806	0.25	0.18,0.32	3.12×10^{-12}	0.052	NR
DBP	286,806	0.14	0.10,0.19	3.50×10^{-12}	0.33	NR
Stage 1 Hypertension	71,322/66,395	1.01	1.00,1,02	0.10	0.32	NR
Stage 2 Hypertension	137,717/149,089	1.02	1.02,1.03	9.78×10^{-9}	0.03	NR
Stroke	285,012/1,794	1.06	1.01,1.11	0.02	0.72	0.23
Composite CVD	278,418/8,388	1.01	0.99,1.03	0.37	0.03	0.45

N, sample size; OR/HR, odds ratio/hazards ratio; GRS, genetic risk score; CI, confidence interval; PH, proportional hazard; SBP, systolic blood pressure; NR, not relevant; DBP, diastolic blood pressure; CVD, cardiovascular diseases. The effect estimates, 95% CI and *P* for GRS correspond to the effect of alcohol GRS on the outcome. We used multiple linear regression for SBP and DBP, multiple logistic regression for Stage 1- and Stage 2 hypertension (OR) and Cox proportional hazard model for CVDs (HR). All models presented were fitted with an interaction between alcohol GRS and urinary sodium along with model 2 adjustments. The interaction effect size/OR/HR and interaction *P* shows the interaction effect size and *P* value for the interaction between alcohol GRS and urinary sodium in the model. Alcohol GRS and urinary sodium values were centred around the mean. *Effect estimates for Stage 1- and Stage 2 hypertension are presented as odds ratio. Effect estimates for stroke and composite CVD are presented as hazard ratio. †This is the overall PH assumption *P* value for Cox proportional hazard model derived from statistical tests that used Schoenfeld residuals against follow-up time.

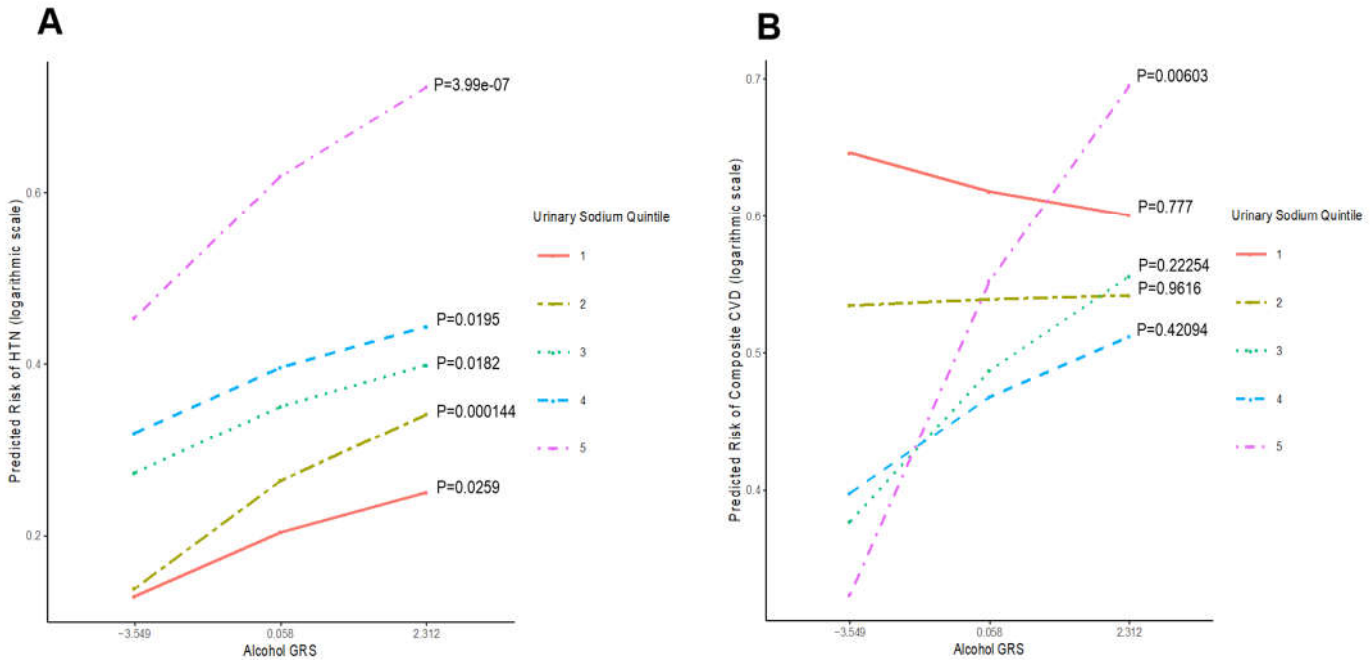

Figure 4. Effect of alcohol genetic risk score (GRS) on hypertension and cardiovascular disease across urinary sodium excretion quintiles. We predicted (A) SBP and (B) DBP at each alcohol consumption quintile for 3 values of the GRS (x-axis): -3.549, 0.058, 2.312. They are the median of alcohol GRS quintile 1, 3 and 5 respectively.

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4. Discussion

In this large-scale longitudinal study, we used data from 295,189 alcohol drinkers and provided insight into the interplay between genetic factors, alcohol consumption, urinary sodium on blood pressure and cardiovascular outcomes. We found that urinary sodium excretion modifies the effect of genetic factors on stage 2 hypertension and risk of CVD.

Observational studies have demonstrated association of alcohol consumption (drinks per day) with blood pressure[23] and CVD [24]. Similarly genetic epidemiological studies [25] [26] [27] focusing on genetic variants (rs671/rs1229984) within the aldehyde/alcohol dehydrogenase (*ALDH2*/*ADH1B*) gene demonstrated that individuals carrying the risk allele for alcohol consumption had higher risk of hypertension[25] [26] [27] and CVD [25] compared to non-carriers. Our results additionally capture variation in genetic underpinning of alcohol consumption and shows that gradient increase in blood pressure and CVD due to genetic risk can be altered by changing lifestyle including changes in the sodium intake. We showed that higher GRS remains associated with higher blood pressure at all levels of urinary sodium. However, at lower vs. higher level of urinary sodium, GRS makes a smaller difference in blood pressure.

The large sample size of the UKB in addition to its rich phenotyping provides optimal statistical power to investigate the relationship between genetic factors and complex outcomes. The use of individual-level data allowed us to investigate the effect of potential confounders and perform subgroup analyses. Additionally, our GRS for alcohol consumption was created based on a total of 105 SNPs identified from two largest-scale GWAS meta-analysis studies for alcohol consumption thus far. [10,11] This is the largest number of SNPs identified for alcohol consumption so far and allowed us to capture more variation in alcohol consumption compared to previous studies that used limited number of SNPs in their analyses. Such number of SNPs although the largest currently available yet captures less than 1% of the total variation in alcohol consumption. [11] Future large-scale GWAS would be helpful to increase the number of SNPs identified for alcohol consumption. It should also be considered that alcohol consumption is assessed using a self-reported questionnaire in the UKB and thus bias due to underreporting or over-reporting may be present. Furthermore, the UKB is a recently established study and thus has a short follow-up time to study endpoints that might have affected statistical power to investigate survival data.

5. Conclusion

Our study showed that the effect of GRS on hypertension and CVD was substantially greater among participants with a higher amount of urinary sodium excretion. Our study highlights the interactive effect of lifestyle habits in modifying the risk posed by genetic factors on hypertension and CVDs. Our current findings emphasize the role of reduction in sodium intake as well as alcohol consumption to decrease blood pressure and risk of CVD and inform health policies in terms of dietary sodium and alcohol consumption.

Supplemental Materials: Supplemental Materials.pdf

Acknowledgments and Sources of Funding: R.P. holds a fellowship supported by Rutherford Fund from Medical Research Council (MR/R0265051/1 and MR/R0265051/2). X.J. was supported by Rutherford Fund from Medical Research Council MR/R0265051/2. UKB genotyping was supported by the British Heart Foundation (grant SP/13/2/30111) for Large-scale comprehensive genotyping of UKB for cardiometabolic traits and diseases: UK CardioMetabolic Consortium. P.E. is Director of the Medical Research Council Centre for Environment and Health and acknowledges support from the Medical Research Council and Public Health England (MR/L01341X/1 & MR/S019669/1). P.E. also acknowledges support from the National Institute of Health Research Imperial Biomedical Research Centre. P.E. is a UK Dementia Research Institute professor, UK Dementia Research Institute at Imperial College London. The DRI receives funding from UK Dementia Research Institute Ltd funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK. P.E. is associate director of Health Data Research UK- London funded by a consortium led by the

UK Medical Research Council. This work used the computing resources of the UK MEDical BIOinformatics partnership (UK MED-BIO) which is supported by the Medical Research Council (MR/L01632X/1).

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