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RESEARCH

Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data

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Abstract

Objective To use the rs1229984 variant in the alcohol dehydrogenase 1B gene (*ADH1B*) as an instrument to investigate the causal role of alcohol in cardiovascular disease.

Design Mendelian randomisation meta-analysis of 56 epidemiological studies.

Participants 261 991 individuals of European descent, including 20 259 coronary heart disease cases and 10 164 stroke events. Data were available on *ADH1B* rs1229984 variant, alcohol phenotypes, and cardiovascular biomarkers.

Main outcome measures Odds ratio for coronary heart disease and stroke associated with the *ADH1B* variant in all individuals and by categories of alcohol consumption.

Results Carriers of the A-allele of *ADH1B* rs1229984 consumed 17.2% fewer units of alcohol per week (95% confidence interval 15.6% to 18.9%), had a lower prevalence of binge drinking (odds ratio 0.78 (95% CI 0.73 to 0.84)), and had higher abstention (odds ratio 1.27 (1.21 to 1.34)) than non-carriers. Rs1229984 A-allele carriers had lower systolic blood pressure (–0.88 (–1.19 to –0.56) mm Hg), interleukin-6 levels (–5.2% (–7.8 to –2.4%)), waist circumference (–0.3 (–0.6 to –0.1) cm), and body mass index (–0.17 (–0.24 to –0.10) kg/m^2). Rs1229984 A-allele carriers had lower odds of coronary heart disease (odds ratio 0.90 (0.84 to 0.96)). The protective association of the *ADH1B* rs1229984 A-allele variant remained the same across all categories of alcohol consumption (P=0.83 for heterogeneity). Although no association of rs1229984 was identified with the combined subtypes of stroke, carriers of the A-allele had lower odds of ischaemic stroke (odds ratio 0.83 (0.72 to 0.95)).

Conclusions Individuals with a genetic variant associated with non-drinking and lower alcohol consumption had a more favourable cardiovascular profile and a reduced risk of coronary heart disease than those without the genetic variant. This suggests that reduction of alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health.

Introduction

Alcohol is the fifth leading risk factor for death and disability accounting for 4% of life years lost due to disease.[1] While the harmful effects of alcohol on conditions such as liver cirrhosis, injuries, and cancers of the liver, colorectum, breast, and upper aerodigestive tract have been firmly established,[2] uncertainty remains concerning the potential protective effects of light to moderate alcohol consumption on risk of coronary heart disease and stroke.[3-5] Observational studies have consistently reported that compared with non-drinkers, light to moderate drinking exhibits a reduced cardiovascular risk,[6 7] with the lowest risk found at approximately 12-25 British units per week, while heavier and more hazardous drinking is associated with an increased risk, resulting in the well established U shaped association.[2 8] However, the apparent cardioprotective effect associated with light to moderate drinking could be explained by an elevated cardiovascular risk from underlying poor health in non-drinkers,[9] or confounding by lifestyle or social factors associated with light to moderate drinking.[10]

The most widely proposed mechanism for this purported cardioprotective effect of alcohol is an increase in high density lipoprotein (HDL) cholesterol.[11] However, the causal nature of the association of HDL cholesterol with cardiovascular events is unclear.[12 13] Although an HDL cholesterol raising effect of alcohol has been reported in experimental studies,[11] the small sample size and short follow-up means existing studies may be prone to bias, undermining their validity.

In the absence of a viable randomised trial to confirm or refute the cardioprotective effect of light to moderate alcohol consumption, an alternative approach is to use a genetic variant that serves as a proxy for alcohol consumption. This approach, known as Mendelian randomisation, avoids some of the key limitations of observational studies, since allocation of genetic variants is random with regard to potential confounders, and genotype is not modified by disease (abolishing reverse causality).[14 15] A non-synonymous single nucleotide polymorphism (rs1229984) in the alcohol dehydrogenase 1B gene (*ADH1B*), which encodes the ADH1B enzyme, which provides the primary pathway of alcohol metabolism,[16] has been associated with a flush response to alcohol consumption, lower levels of usual alcohol consumption and blood ethanol levels,[17] as well as a lower risk of alcohol dependence among adult drinkers[18 19] and adolescents,[19] which led to the selection of this single nucleotide polymorphism as a genetic instrument in previous Mendelian randomisation studies that investigated the role of alcohol in high blood pressure and various cancers.[20-23] We present results from an international collaboration that used the *ADH1B* rs1229984 variant as an instrument to investigate the association of alcohol with cardiovascular biomarkers and events in more than 260 000 individuals.

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Supplementary appendix supplied by the author (see http://www.bmj.com/content/349/bmj.g4164?tab=related#datasupp)

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Methods

Formation of the consortium

Given that the rs1229984 genetic variant is not represented in widely available genotyping platforms such as Illumina-metabochip, Illumina-immunochip, or genome-wide association platforms (with the exception of recent platforms), we initially focused on studies genotyped with the IBC Cardiochip array, which contains this single nucleotide polymorphism (SNP). Through contact with the designer of the Institute for Translational Medicine and Therapeutics (ITMAT) Broad Institute CARe consortium (IBC) CardioChip array (B J Keating,[24] coauthor), we contacted all population based studies genotyped on this array. Subsequently, we established contact with a series of genetic study groups with whom we have collaborated in the past and sent them a brief proposal describing the general aims of the study, including de novo genotyping in their studies. A minor subset of studies in European descent population that used this variant in previous publications was also identified and included in the consortium (details available in table S1 in the appendix on bmj.com). In addition, we checked publicly available consortia such as CARDIoGRAMplusC4D (www.cardiogramplusc4d.org) and found the SNP was not included in these consortia.

We incorporated individual participant data from 261 991 participants of European ancestry from 56 studies (see appendix). All participants provided written, informed consent, and ethical approval was granted by local ethics committees for participating studies. Ethical approval for secondary data analysis was granted by the London School of Hygiene & Tropical Medicine ethics committee (application No 5905).

Alcohol traits

The principal alcohol trait was weekly volume of alcohol in British units (1 British unit is equivalent to 0.57 US units or 10 ml (7.9 g) ethanol), which we derived using questionnaire data from each study (table S2 in the appendix). We additionally assessed the overall drinking status (drinkers *v* non-drinker) of study subjects, the study specific top tertile of alcohol consumption (separately for men and women), and history of binge drinking (for details see supplementary methods 2.1). γ-glutamyltransferase was used as a marker of heavy alcohol consumption.

Clinical outcomes

The primary clinical event was incident and prevalent (including fatal and non-fatal) coronary heart disease. Secondary clinical outcomes were stroke and type 2 diabetes. Stroke included all subtypes and consisted of incident and prevalent (including fatal and non-fatal) cases. In a subsample, information on ischaemic stroke was also available. For type 2 diabetes, we restricted the analysis to prevalent cases with the exception of one nested case-cohort that included incident cases.[25] Precise definitions of outcomes for each study are reported in table S3 of the appendix.

Genotype properties

Genotyping platforms, genotype frequencies, Hardy Weinberg equilibrium P values, and call rates (median of 98.8%) for *ADH1B* rs1229984 (directly genotyped in all studies) are listed in table S1 and figure S1 of the appendix.

Statistical analysis

A standard analysis protocol was applied to each study to produce a consistent dataset. Analyses were conducted using individual participant data in each study and then pooled across studies using meta-analysis. Because of differences in variables collected by each study, not all studies were included in all analyses (fig S2 of appendix). We restricted analyses to individuals of European descent with data for *ADH1B* rs1229984 genotype, age, sex, and any one of the outcomes of interest. All non-normally distributed continuous variables, including units/week of alcohol, were natural log transformed. For these traits, the mean difference on the logarithmic scale was exponentiated to generate the relative difference and then converted to a percentage difference.

We investigated the shape of the association between alcohol consumption (log units/week) and cardiovascular biomarkers and potential confounders in observational analysis among 131 490 individuals from 28 studies. Statistical details are given in supplementary methods 2.2 of the appendix.

For all genetic analyses, we used a dominant model due to the low prevalence of the rs1229984 A-allele (average carriage of rs1229984 A-alleles: 7%): data from carriers of either one or two rare A-alleles were pooled and compared with individuals homozygous for the G-allele (the reference group). We first quantified the effects of rs1229984 A-allele on alcohol traits as well as on lifestyle and social factors to validate our instrument for alcohol consumption. Then, we studied the associations of the rs1229984 A-allele with cardiovascular biomarkers from several pathways that may mediate the effects of alcohol on cardiovascular events. Finally, we evaluated the effects of the rs1229984 A-allele on coronary heart disease, combined subtypes of stroke (as well as ischaemic stroke separately) and type 2 diabetes.

For continuous traits, means and standard deviations were derived for rs1229984 A-allele carriers and non-carriers. For binary traits, log odds ratios and standard errors were estimated for rs1229984 A-allele carriers versus non-carriers. All effect estimates were calculated within each study and then pooled using fixed (default) and random effects meta-analysis. Between study heterogeneity was quantified using I^2.[26]

If the U shaped association between alcohol consumption and cardiovascular events is real, a comparison of event rates in rs1229984 A-allele carriers (associated with a reduction in alcohol consumption from published studies[20]) versus non-carriers will vary across broad categories of alcohol consumption. In light to moderate drinkers (>0 to <21 units/week), *ADH1B* rs1229984 A-allele carriers will be expected to have a higher coronary heart disease event risk, whereas, for heavy drinkers (≥21 units/week) they will be expected to have a lower event risk. Likewise, this stratification by alcohol consumption will also serve to validate the *ADH1B* rs1229984 A-allele variant as a specific instrument for alcohol consumption, as it is expected that in non-drinkers carriage of the rs1229984 A-allele variant will have no effect on cardiovascular traits or events, or a substantially attenuated effect given the known difficulty in correctly classifying long term non-drinkers from self reported questionnaires.[27] Therefore, we repeated the genetic analysis in strata of alcohol intake (none (0 units/week), light to moderate (>0 to <21 units/week), and heavy (≥21 units/week); the strata were selected to represent the U shaped association of alcohol and cardiovascular events from observational studies) and investigated if there was a trend between alcohol categories and the effect of rs1229984 A-allele using meta-regression (see supplementary methods 2.3 of

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appendix for further details). The same stratified analysis was conducted for potential confounders, to investigate if confounding was reintroduced by stratifying by alcohol.[28] For units/week of alcohol consumption (our main alcohol phenotype), we also performed a subgroup analysis according to the type of alcohol questionnaire (according to whether consumption questions asked separately for beverage type (such as beer, wine, spirits) *v* all beverages combined). Exploratory subgroup analyses were undertaken to assess the impact of study characteristics included sex, mean age, geographical region, Hardy Weinberg equilibrium, genotype platform, year of DNA extraction, and, whether the study contributed to observational analysis.

In order to investigate potential residual confounding by population stratification, we adjusted for principal components derived from IBC CardioChip array[24] in studies with available data (see supplementary methods 2.4 for further details). To evaluate confounding by linkage disequilibrium between rs1229984 with single nucleotide polymorphisms associated with cardiovascular risk factors in genome-wide association studies[29] that could distort associations of rs1229984, we used the Whitehall-II cohort[30] (including both IBC CardioChip[24] and MetaboChip[31] platforms).

In the current manuscript, we did not conduct an instrumental variable analysis to estimate causal effects since the available methods assume a linear association between the exposure and the outcome, which may not hold for alcohol and cardiovascular disease.

Analyses were conducted in Stata v13.0 (StataCorp, Texas, USA). All P values reported are two sided.

Results

We approached 59 studies, of which 56 were included in this collaboration. Of the three excluded studies, two (INTERHEART and INTERSTROKE) declined to participate because of overlap with existing projects, and a third (CoLaus) was excluded as the rs1229984 genetic variant was not directly genotyped.

Of the 261 991 participants in our analysis, 48% were women, and the mean age per study was 58 years (range 26-75 years) (table S4 of appendix). The median number of alcohol units consumed in each study is shown in table S4. There were 20 259 coronary heart disease events, 10 164 stroke cases (4339 ischaemic strokes) and 14 549 type 2 diabetes cases (table S5). Means and distributions for continuous traits in all studies are presented in tables S6-S8. The observational analysis between alcohol and cardiovascular risk factors is reported in the supplementary results section and figures S2 and S3 of the appendix.

Genetic association analysis

ADH1B and alcohol consumption

Carriers of the rs1229984 A-allele consumed fewer units of alcohol per week (−17.2% units/week (95% confidence interval −18.9% to −15.6%)) and had lower odds of being in the top third of drinking volume (odds ratio 0.70 (0.68 to 0.73)) compared with non-carriers. Rs1229984 A-allele carriers also had lower odds of binge drinking (odds ratio 0.78 (0.73 to 0.84)), increased odds of being self reported abstainers (odds ratio 1.27 (1.21 to 1.34)) and lower levels of γ-glutamyltransferase (−1.8% (−3.4% to −0.3%)) (table 1⇓).

The association of the rs1229984 A-allele with alcohol volume remained unaltered when stratified by age, gender, geographical region, Hardy Weinberg Equilibrium P value, and whether the alcohol questionnaire used was beverage specific (fig S4 of appendix), or after exclusion of samples with a proportion of A-allele carriers >10% (approximately >5% minor allele frequency; data available on request). A meta-regression analysis of the mean alcohol volume (on the log scale) in rs1229984 A-allele carriers compared with non-carriers that takes into account the uncertainty around the mean suggested a constant proportional effect of the of *ADH1B* rs1229984 variant on alcohol volume (fig S5). This was also supported by the finding that in our samples the standard deviations for carriers and non-carriers were very similar (fig S6).

ADH1B and cardiovascular biomarkers

Carriers of the rs1229984 A-allele had lower systolic blood pressure (−0.88 (−1.19 to −0.56) mm Hg) compared with non-carriers. Concordant with this, rs1229984 A-allele carriers also had lower odds of hypertension (104 570 cases; odds ratio 0.94 (0.91 to 0.98)). Rs1229984 A-allele carriers had lower levels of interleukin-6 (−5.2% (−7.8% to −2.4%)), C reactive protein (−3.4% (−5.7% to −1.1%)), body mass index (−0.17 (−0.24 to −0.10) kg/m^2), and waist circumference (−0.34 (−0.58 to −0.10) cm). Rs1229984 A-allele carriers also had lower non-HDL cholesterol concentrations (−0.03 (−0.05 to −0.01) mmol/L) (table 2⇓).

When the effect of the *ADH1B* rs1229984 A-allele on these cardiovascular traits was stratified by alcohol consumption, a differential effect was observed. Among heavy drinkers (≥21 units/week), carriers of the rs1229984 A-allele, who on average consume 17.2% less alcohol than non-carriers, showed a more pronounced reduction in these cardiovascular traits than that observed in light to moderate drinkers and non-drinkers (fig 1⇓). In contrast, the effect of rs1229984 on these cardiovascular traits did not differ systematically according to exploratory subgroup analyses by laboratory procedures or study characteristics (P>0.05 for 52 of 58 comparisons; fig S7 of appendix).

Although we observed that rs1229984 A-allele carriers had higher triglyceride levels (1.6% (0.7% to 2.6%)), this effect was not modified by alcohol categories (fig 1⇓).

There was no overall difference between rs1229984 A-allele carriers and non-carriers in HDL cholesterol concentration (−0.004 (−0.012 to 0.003) mmol/L). However, an association between rs1229984 A-allele carriage with HDL cholesterol was observed in the highest category of alcohol consumption, but in the opposite direction to that expected from observational findings (0.04 (0.02 to 0.06) mmol/L; fig S8 of appendix). (That is, the log-linear association of HDL cholesterol with alcohol consumption from observational studies (fig S3) would suggest that a reduction in alcohol consumption, as observed for carriers of the rs1229984 A-allele, should associate with a reduction in HDL cholesterol levels.) In subgroup analysis by laboratory procedures and major study characteristics, we observed that rs1229984 A-allele carriers from northern Europe had lower levels of HDL cholesterol (−0.04 (−0.05 to −0.02) mmol/L). Since this geographical specificity could reflect residual population stratification in samples outside northern Europe, we adjusted for principal components in a subset of individuals not from northern Europe. The unadjusted model for the association between rs1229984 A-allele and HDL cholesterol (0.02 difference in standard deviation (95% confidence interval −0.02 to 0.06)) did not differ from the model adjusted for population structure (0.01 difference in standard deviation

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(−0.03 to 0.05)) (fig S8). Similar null results were observed for apolipoprotein A1 (table S9 of appendix).

Rs1229984 A-allele carriage was not associated with carotid intima medial thickness, electrocardiographic measures of left ventricular hypertrophy, fibrinogen, von Willebrand factor, factor VII, fasting blood glucose, N-terminal of the prohormone brain natriuretic peptide, or lipoprotein(a) overall (table S9 of appendix). For these traits, similar null results were observed when stratified for alcohol consumption or by other exploratory subgroups (P>0.05 for 47 of 48 comparisons, data available on request), with the exception of fasting glucose and lipoprotein(a), where the strength of association was more pronounced in heavy drinkers compared with other alcohol categories (P values for heterogeneity 0.05 and 0.01, respectively) (fig S9).

ADH1B and lifestyle factors

Carriage of the rs1229984 A-allele was not associated with physical activity, but showed higher odds of ever smoking (odds ratio 1.06 (95% confidence interval 1.02 to 1.09)). However, the association with ever smoking was in the opposite direction to that seen in observational analysis, and no association was observed for other quantitative measures of tobacco exposure such as cigarettes per day, pack years, or cotinine levels. Rs1229984 A-allele carriers showed higher total years in education (0.04 difference in standard deviation (95% confidence interval 0.01 to 0.08)). No differential effect of *ADH1B* on any of the lifestyle factors was identified on stratifying by alcohol intake (making it unlikely that stratifying by alcohol introduced bias) or by other exploratory subgroups (P>0.05 for all comparisons) (figs S10 and S11 of appendix).

ADH1B and cardiovascular events

Rs1229984 A-allele carriage showed reduced odds of coronary heart disease (odds ratio 0.90 (95% confidence interval 0.84 to 0.96, I^2=17%)) (fig 2⇓ and fig S12 of appendix). In studies with ≥1000 coronary heart disease events (four studies with 8374 coronary heart disease events), the odds ratio for coronary heart disease was 0.81 (0.72 to 0.91, I^2=0%) (table S10). When analysis was restricted to non-drinkers the association was null (odds ratio 0.98 (0.88 to 1.10)), while among drinkers (>0 units/week alcohol), carriers of the rs1229984 A-allele had reduced odds of coronary heart disease (odds ratio 0.86 (0.78 to 0.94)). This is consistent with the assumption that the associations ascribed to the *ADH1B* variant are mainly due to alcohol consumption. Further subdivision of the drinkers category into light (>0 to <7 units/week), moderate (≥7 to <21 units/week), and heavy (≥21 units/week) showed the same protective effect of the variant across all alcohol categories (P value for heterogeneity=0.83; fig 2⇓), suggesting that there was no difference between rs1229984 A-allele carriers and non-carriers in coronary heart disease risk across alcohol consumption levels among individuals who drank.

Although there was no association of the rs1229984 A-allele with the combined stroke subtypes (odds ratio 0.98 (0.90 to 1.07)) (fig 3⇓), when the analysis was limited to ischaemic stroke subtype, rs1229984 A-allele carriers had lower odds of ischaemic stroke (odds ratio 0.83 (0.72 to 0.95)) (fig S13 of appendix). No association between rs1229984 A-allele with type2 diabetes was observed (odds ratio 1.02 (0.95 to 1.09)) (fig 3⇓).

Random effect estimates for associations of *ADH1B* with all outcomes were similar to those from fixed effect models (figs S4-14 of appendix).

Adjustment for population structure did not alter the rs1229984 A-allele associations (figs S15-16). The gene variant was not in linkage disequilibrium with previously reported loci from genome-wide association studies for any cardiovascular trait (table S11).

Discussion

Principal findings of study

In this large scale Mendelian randomisation analysis, we showed that carriers of the rs1229984 A-allele had lower levels of alcohol consumption and exhibited lower levels of blood pressure, inflammatory biomarkers, adiposity measures, and non-HDL cholesterol, and reduced odds of developing coronary heart disease, compared with non-carriers of this allele. In contrast to previous observational and experimental studies, our study showed that individuals with a genetic predisposition to consume less alcohol had lower, not higher, odds of developing coronary heart disease regardless of whether they were light, moderate, or heavy drinkers. Moreover, *ADH1B* genotype was not associated with type 2 diabetes, HDL cholesterol level, or coagulation markers.

The rs1229984 A-allele showed very strong association with non-drinking and amount of alcohol consumed. The fact that our analyses suggested a constant proportional effect of the rs1229984 A-allele on alcohol volume across a wide range of alcohol volume from the included studies supports the notion that social pressure in heavier drinking cultures is unlikely to override the effect of the genetic variant on alcohol consumption.[20] It is important to note that the rs1229984 A-allele was a proxy for all types of self reported drinking behaviour including volume, being in the top third of drinkers per study, binge drinking, and abstention, and it also showed association with levels of the liver enzyme γ-glutamyltransferase (an objective marker of heavy alcohol intake). This confirms that rs1229984 was suitable as a non-specific genetic proxy of alcohol consumption in the mendelian randomisation analysis. Our findings are therefore not specific to one particular type of alcohol behaviour, but reflect a combination of different patterns of alcohol exposures, which are nevertheless directionally concordant (that is, the A-allele resulted in lower alcohol consumption).

For the cardiovascular traits that showed association on overall with the rs1229984 A-allele, null or substantially reduced associations were observed in non-drinkers and more pronounced associations in heavy drinkers when compared with light to moderate drinkers. This is as expected under the assumption that the effect of this genetic variant is only explained by exposure to alcohol.

From the U shaped association seen in observational studies, we would expect that for drinkers below the nadir (12-25 units/week), a reduction of 17.2% in alcohol consumption (corresponding to rs1229984 A-allele carriage) would lead to a small increase in the risk of coronary heart disease, whereas for those with alcohol consumption above the nadir, a similar reduction in alcohol consumption would lead to a decrease in coronary heart disease risk. Contrary to these expectations, however, we found that individuals below the nadir with a genetic predisposition to consume less alcohol had lower odds of developing coronary heart disease at all categories of alcohol consumption (fig 2⇓), bringing the hypothesised cardioprotective effect of alcohol into question.

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Strengths and weaknesses of the study

Major strengths of this international collaboration are the large sample size, availability of detailed alcohol phenotypic data and a comprehensive repertoire of cardiovascular risk factors and major cardiovascular events. The process by which studies were recruited into the collaboration, including mainly unpublished data, means that findings are unlikely to suffer from publication bias. The use of a standardised analytical protocol further increases reliability of the findings.

The lack of association of the *ADH1B* rs1229984 A-allele with HDL cholesterol levels was unexpected. In principle, failure to detect an association with HDL cholesterol could have arisen from lack of power. However, this is unlikely as rs1229984 was associated with traits (such as C reactive protein or interleukin 6) for which alcohol consumption had a less powerful effect and where the sample size for genetic analysis was several times smaller than for HDL cholesterol (fig S2 of appendix). Our extensive subgroup and in silico analyses also suggested it was unlikely that laboratory technique, type of alcohol questionnaire used in the studies, or confounding by linkage disequilibrium could explain the overall null effect. We did find an association of rs1229984 A-allele carriage with HDL cholesterol in the subset of northern European studies. Although this suggests the lack of association in non-northern European studies may arise from population stratification, adjustment for population structure using principal components analysis did not reveal an association, making this an unlikely explanation.

We also did not identify associations of the rs1229984 A-allele with coagulation markers, type 2 diabetes, and the combined subtypes of stroke. With regard to coagulation markers, these results seem more robust for fibrinogen, as confirmed by subgroup analysis. For factor VII and von Willebrand factor, reduced sample size limited our ability to exclude a small effect.

Although we observed an overall null association of the rs1229984 A-allele with type 2 diabetes and blood glucose concentration, a stratified analysis by alcohol consumption showed that, among heavy drinkers, carriers of the rs1229984 A-allele had lower levels of glucose and a directionally consistent relationship with type 2 diabetes. It is interesting that we did not observe a stronger protective association of coronary heart disease in heavy drinkers for carriers of the *ADH1B* variant, as we observed for cardiovascular risk factors. This is likely to reflect reduced power due to the low number of coronary heart disease events in the heavy drinking stratum. The relatively small number of stroke events is an important limitation, as well as the use of combined stroke subtypes, which could have obscured some differential associations of alcohol by pathological or aetiological subtype, as suggested by recent overviews from observational studies.[7] In this context it is interesting to note than in a subset of studies, we found the rs1229984 A-allele associated with reduced odds of ischaemic stroke, but this requires replication.

One of the advantages of a mendelian randomisation study is that this design is less prone to some of the biases of observational studies. In contrast to observational analyses that have shown associations of alcohol with physical activity and different measures of smoking,[32] rs1229984 A-allele was not associated with physical activity or any of the more precise measures of smoking exposure (cigarettes/day, pack years, or cotinine level). However, an association was observed with the binary ever/never smoking trait, but this was in the opposite direction to the association with coronary heart disease and is therefore unlikely to explain the association of rs1229984 A-allele with a reduced risk of coronary heart disease. There was also some evidence for a difference in years of education, and, while the size of the effect was small, this requires further investigation.

Strengths and weaknesses in relation to other studies

Our findings compare with findings from studies in east Asians, using the rs671 genetic variant of the aldehyde dehydrogenase 2 gene (*ALDH2*), that have also shown associations of alcohol with blood pressure, body mass index, and non-HDL cholesterol levels.[21 22] However, the association with coronary heart disease events remains unclear since the association of *ALDH2* with coronary heart disease has been analysed only in small studies.[21 22] In contrast to our findings, *ALDH2* rs671 has shown an association with HDL cholesterol levels in individuals of Asian ancestry.[21] In Europeans the *ALDH2* rs671 variant is monomorphic and cannot be used for mendelian randomisation, and previous studies have therefore used the *ADH1B* genotype to investigate the effect of alcohol on cardiovascular disease.[20-34] Our results not only replicate findings of *ADH1B* on blood pressure and body mass index from smaller data collections, but expand the number of cardiovascular traits and include major vascular events. Given our large sample size, we are able to identify associations with other cardiovascular traits (non-HDL cholesterol, interleukin 6, and C reactive protein), and most notably we are able to detect for the first time an association with coronary heart disease.

One feature in common to both *ALDH2* and *AHD1B* for mendelian randomisation is the use of genetic variants within loci that encode alcohol metabolising enzymes. In both examples, genetic variation results in altered exposure to acetaldehyde, a metabolite of alcohol that causes unpleasant symptoms, thought to be responsible for the different drinking behaviour in individuals who possess the alleles.[35] Thus, a simple interpretation of a mendelian randomisation analysis using a genetic variant in an alcohol metabolising enzyme is that it is akin to a long term randomised trial of more versus less alcohol exposure.

Meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions

These data show that individuals of European descent with a genetic predisposition to consume less alcohol had a reduced risk of coronary heart disease and ischaemic stroke, and lower levels of several established and emerging risk factors for cardiovascular disease. These findings suggest that reductions of alcohol consumption, even for light to moderate drinkers, may be beneficial for cardiovascular health. Our results therefore challenge the concept of a cardioprotective effect associated with light to moderate alcohol consumption reported in observational studies and suggest that this effect may have been due to residual confounding or selection bias.

Unanswered questions and future research

Although the association of the *ADH1B* variant with coronary heart disease is compatible with being null in non-drinkers and a more pronounced association is seen in drinkers, future access to large scale population studies such as UK Biobank and China Kadoorie Biobank Study will help to minimise potential measurement error in alcohol exposure and provide sufficiently large numbers of coronary heart disease events to enable replication of our findings, in particular the analysis stratified

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by alcohol status, but will also allow a more detailed examination of stroke subtypes.

Members of the InterAct Consortium and IMPROVE study group are listed in the supplementary appendix.

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What is already known on this topic

Observational studies suggest that consuming alcohol in heavy amounts is deleterious for cardiovascular health, whereas light to moderate consumption may be protective

However, findings for light to moderate drinkers could be due to unaccounted bias

What this study adds

Use of a genetic approach in an analysis of over 260 000 participants showed that carriers of a variant in the alcohol dehydrogenase 1B gene (*ADH1B*) associated with less alcohol consumption were found to have a reduced risk of coronary heart disease, and this was maintained at all levels of alcohol consumption

Under the principles of mendelian randomisation, these findings suggest that reduction of alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health

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At each clinic visit, a medical history was obtained with a focus on cardiovascular content, and participants underwent a physical examination including measurement of height and weight from which BMI was calculated; **HAPIEE**: This study was supported by Wellcome Trust 'Determinants of Cardiovascular Diseases in Eastern Europe: A multi-centre cohort study' [grants 064947/Z/01/Z; and 081081/Z/06/Z]; the MacArthur Foundation 'MacArthur Initiative on Social Upheaval and Health' [grant 712058]; the National Institute on Ageing 'Health disparities and aging in societies in transition (the HAPIEE study)' [grant 1R01 AG23522]; and a project from the Ministry of Health, Czech Republic, for the development of the research organization No. 00023001 (IKEM, Prague, Czech Republic). 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development of subclinical cardiovascular disease. A total of 6814 women and men between the age of 45 and 84 year were recruited for the first examination between 2000 and 2002. Participants were recruited in six US cities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St. Paul, MN). This study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants. This cohort was genotyped as part of the National Heart Lung and Blood Institute's (NHLBI) Candidate Gene Association Resource (CARe) (Musunuru, K., Lettre, G., Young, T., Farlow, D.N., Pirruccello, J.P., Ejebe, K.G., Keating, B.J., Yang, Q., Chen, M.H., Lapchyk, N. et al. Candidate gene association resource (CARe): design, methods, and proof of concept. Circ. Cardiovasc. 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A listing of WHI investigators can be found at https://cleo.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Prof

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Data sharing statement: No additional data available

Transparency declaration: The lead authors, MVH, CED, and JPC (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Tables

Table 1| Pooled estimates of association between genetic variant ADH1B rs1229984 (A-allele carriers v non-carriers) and measures of alcohol consumption. (Summary effect estimates are derived from fixed effects meta-analysis)

Alcohol consumption measure	No of studies, cases/individuals	Effect estimate (95% CI)	P value	I^2 value (%)
Log transformed data*		**% difference**		
Intake volume (units/week†)	46, NA/218 969	−17.22 (−18.86 to −15.55)	5.5×10^{-76}	64
γ-glutamyltransferase level (U/L)	15, NA/97 755	−1.84 (−3.40 to −0.26)	0.028	36
Categorical data		**Odds ratio**		
Top tertile of alcohol intake	45, 69 229/222 332	0.70 (0.68 to 0.73)	9.8×10^{-67}	60
Binge drinker‡	21, 22 198/131 290	0.78 (0.73 to 0.84)	1.4×10^{-12}	47
Alcohol abstainer‡	32, 24 482/189 854	1.27 (1.21 to 1.34)	2.6×10^{-19}	73

NA = not applicable.

*Non-normally distributed variables were natural log transformed and mean differences on the log scale were converted to percentage differences.

†Alcohol units in British units; 1 UK unit = 0.57 US units or 10 mL (7.9 g) ethanol.

‡For definitions of binge drinker and alcohol abstainer, see table S2 in appendix.

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Table 2| Pooled estimates of association between genetic variant ADH1B rs1229984 (A-allele carriers v non-carriers) and cardiovascular biomarkers in all participants. (Summary effect estimates are derived from fixed effects meta-analysis and are reported as mean differences unless stated otherwise)

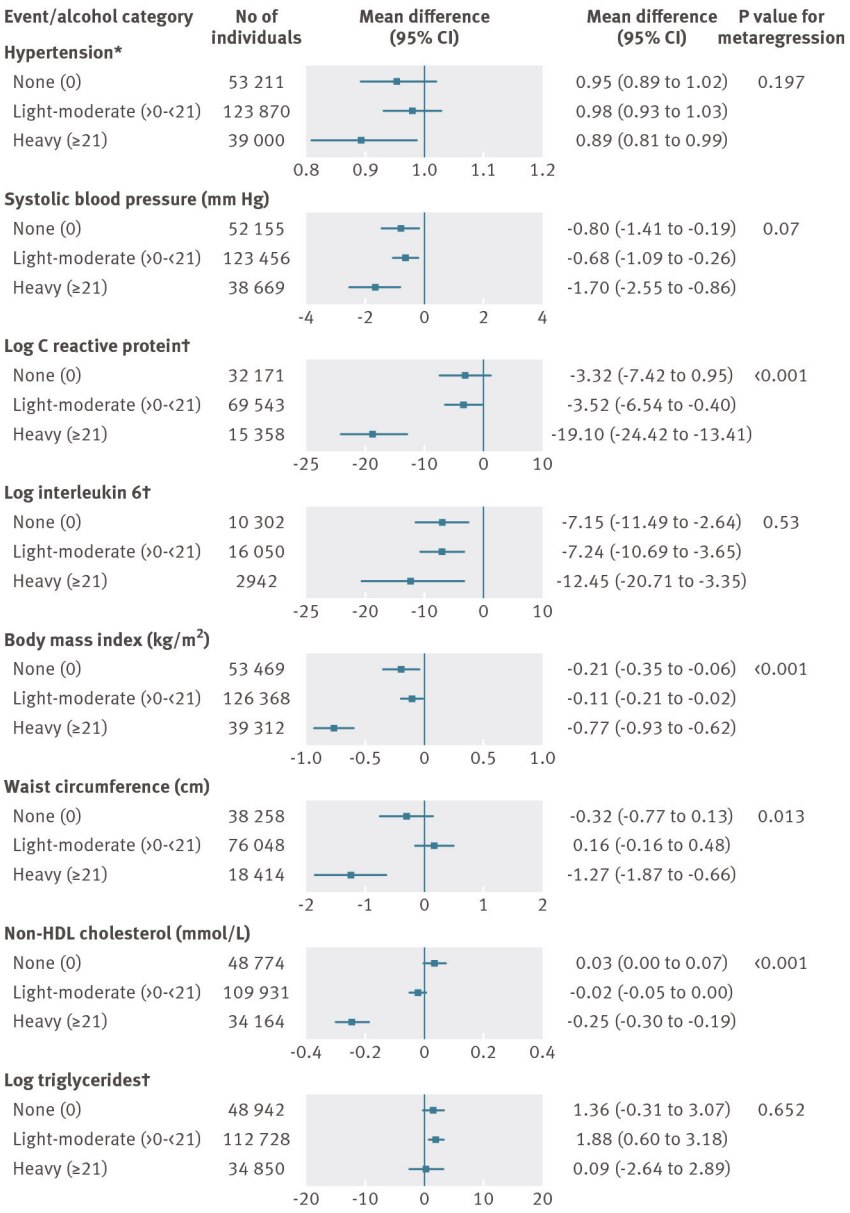
Biomarker	No of studies, individuals	Effect estimate (95% CI)	P value	I^2 value (%)
Systolic blood pressure (mm Hg)	48, 227 559	−0.88 (−1.19 to −0.56)	4.1×10^{-8}	26
Anthropometric measures:				
Body mass index (weight (kg)/(height (m)^2))	51, 232 570	−0.17 (−0.24 to −0.10)	3.4×10^{-6}	52
Waist circumference (cm)	42, 140 923	−0.34 (−0.58 to −0.10)	6.2×10^{-3}	41
Inflammation:				
Log transformed interleukin 6 (% difference)*	17, 30 950	−5.15 (−7.82 to −2.40)	2.90×10^{-4}	33
Log transformed C reactive protein (% difference)*	42, 124 498	−3.40 (−5.68 to −1.05)	4.60×10^{-3}	1
Lipids:				
Non-HDL cholesterol (mmol/L)	46, 202 794	−0.03 (−0.05 to −0.01)	5.10×10^{-3}	25
Log transformed triglycerides (% difference)*	46, 205 824	1.61 (0.66 to 2.57)	8.90×10^{-4}	36
HDL cholesterol (mmol/L)	46, 203 440	−0.004 (−0.012 to 0.003)	0.259	54

*Non-normally distributed variables were natural log transformed and mean differences on the log scale were converted to percentage differences.

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Figures

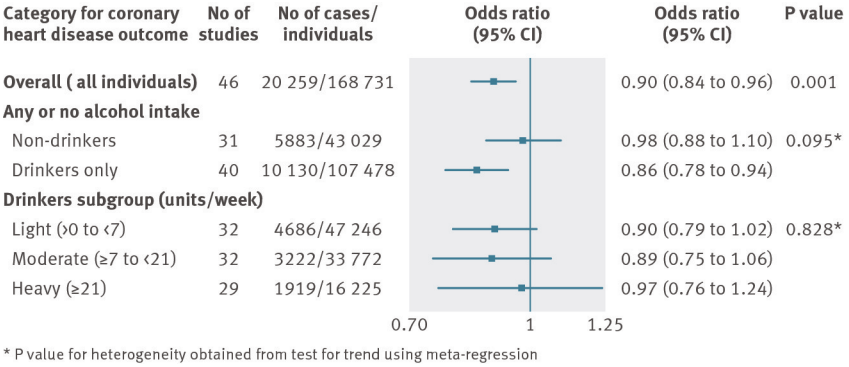


* For hypertension, plotted values are odds ratio (95% CI); † for natural log transformed traits, plotted values are the percentage difference (95% CI) in the geometric mean; for all other traits, plotted values are mean difference (95% CI). Alcohol units are UK units (1 UK unit=10 mL (7.9 g) ethanol = 0.57 US units). P values for heterogeneity represent tests for trend derived from meta-regression (see supplementary methods 2.3)

Fig 1 Meta-analysis pooled estimates of the association between *ADH1B* rs1229984 (A-allele carriers *v* non-carriers) and cardiovascular disease biomarkers showing association on crude analysis, stratified by alcohol intake

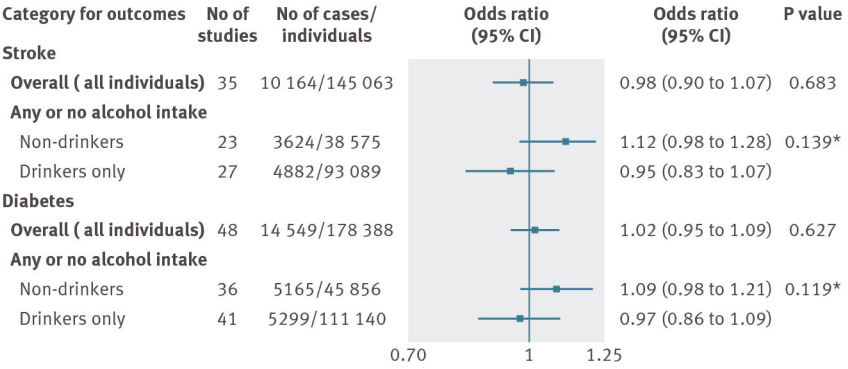
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* P value for heterogeneity obtained from test for trend using meta-regression

Fig 2 Meta-analysis pooled estimates of the association between *ADH1B* rs1229984 (A-allele carriers *v* non-carriers) and coronary heart disease overall, and stratified by alcohol intake



*P value for heterogeneity obtained from test for trend using meta-regression

Fig 3 Meta-analysis pooled estimates of the association between *ADH1B* rs1229984 (A-allele carriers *v* non-carriers) and stroke (combined subtypes) and type 2 diabetes overall, and stratified by alcohol intake

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