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ADH1B polymorphism, alcohol consumption and binge drinking in Slavic Caucasians. Results from the Czech HAPIEE study

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Abstract

Background—Several genetic polymorphisms influence the risk of heavy alcohol consumption but it is not well understood whether the genetic effects are similar in different populations and drinking cultures, nor whether the genetic influences on binge drinking are similar to those seen for alcoholism.

Methods—We have analysed the effect of the Arg47His (rs1229984) variant within the alcohol dehydrogenase (*ADH1B*) gene on a range of drinking related variables in a large Eastern European Slavic population (Czech HAPIEE study), which recruited random samples of men and women aged 45–69 years in six Czech towns (3,016 males and 3,481 females with complete data). Drinking frequency, annual alcohol intake, prevalence of binge drinking (≥100g in men and ≥60g in women at least once a month) and the mean dose of alcohol per occasion were measured by the graduated frequency questionnaire. Alcohol intake in a typical week was used to define heavy drinking (≥350g/week in men and ≥210g in women). Problem drinking (≥2 positive answers on CAGE) and negative consequences of drinking on different aspects of life were also measured.

Results—The frequency of the His47 allele carriers was 11%. Homozygotes in the common allele (Arg47Arg), among both males and females, had significantly higher drinking frequency, and annual and weekly intake of alcohol than His47 carriers. The odds ratio of heavy drinking in Arg47Arg homozygotes vs. His47 carriers was 2.1 (95% confidence intervals 1.1–3.2) in men and 2.2 (1.0–4.7) in women. In females, but not in males, Arg47Arg homozygotes had marginally significantly higher prevalence of binge drinking and mean alcohol dose per drinking session. There was no consistent association with problem drinking and negative consequences of drinking.

Conclusions—The *ADH1B* genotype was associated with the frequency and volume of drinking but its associations with binge drinking and problem drinking were less consistent.

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Conflict of interest
None

Introduction

In western countries, alcohol consumption is common and socially acceptable. A significant proportion of drinkers consume more than the recommended levels and a significant numbers of them develop alcohol dependency. In addition, while moderate alcohol consumption is associated with lower mortality (Ferreira and Willoughby 2008), mainly due to its cardio-protective effects, high levels of alcohol intake are associated with increased mortality (Rehm et al., 2009). It has been estimated that approximately 4% of all global deaths are attributable to alcohol (WHO 2009). The mortality fraction attributable to alcohol is higher in Central and Eastern Europe and in countries of the former Soviet Union (Rehm et al., 2007), most likely because of the hazardous drinking patterns characterized by large amount of alcohol consumed per occasion (binge drinking) (Bobak et al., 2004; Britton and McKee, 2000). Understanding determinants of drinking in different populations with different drinking cultures is therefore essential when designing appropriate public health policy.

Family and twin studies have suggested that genetic variability contributes between 40% and 60% of the variance in ethanol intake and alcohol dependency (Dick and Bierut, 2006). Similarly to other common behaviours and chronic conditions, the genetic influences on alcohol intake and alcohol dependency have a polygenic background. One of the candidate genes, intensively analyzed in the recent years, is the gene for alcohol dehydrogenase 1B (ADH1B) (OMIM acc N. 103720; GeneID: 125). ADH1B is a member of a family of seven alcohol dehydrogenase enzymes that share about 95% sequence identity. It is a key enzyme in the catabolism of ethanol and converts ethanol to acetaldehyde. Within the *ADH1B* gene, the Arg47→His variant (c.143G>A; rs1229984) has a significant impact on the enzyme activity. The $\beta_1\beta_1$ (ArgArg) isozyme, common in Europeans, has a significantly lower activity than the less common $\beta_2\beta_2$ (HisHis)variant which is estimated to produce high levels of acetaldehyde (Peng and Yin, 2009). This less common variant has been found to be associated with lower alcohol intake in both men and women in several populations, probably because the elevated acetaldehyde levels cause unpleasant reactions to alcohol (Wall, 2005). This mechanism is supported by animal model; rats expressing the fast analog of human ADH1B enzyme showed significantly higher blood acetaldehyde levels after ethanol administration (Rivera-Meza et al, 2010).

The effect of the *ADH1B* gene on increased alcohol intake and risk of alcoholism has been demonstrated in several populations (Whitfield, 1997), although the effects may be stronger in Asians than in Caucasians (Whitfield, 2002). The genetic influences on alcohol intake have not been extensively studied in Central and Eastern Europe, a region where the burden of ill health caused by alcohol is particularly high. In addition, much of the evidence in Caucasians comes from case-control studies, while studies in large samples of general Caucasian populations are sparse. To fill this gap, we have analysed the Arg47His variant in the *ADH1B* gene variant and its associations with not only alcohol intake but also with binge drinking, problem drinking and negative consequences of drinking in a large sample of the Czech Republic, a country with a predominantly Western Slavic population (Wozniak et al., 2010).

Materials and methods

Study population and study subjects

We used data from the 2002–05 baseline of the Czech part of the multi-centre HAPIEE study (Peasey et al., 2006). The participants, men and women aged 45–69 years in 2002, were randomly selected from population registers of 7 Czech towns (Jihlava, Havirov, Hradec Kralove, Karvina, Kromeriz, Liberec and Usti nad Labem). A total of 8,856

individuals were recruited (response rate 55%); of these, 6,681 provided a DNA sample. The study was approved by the local ethics committees at both Czech National Institute of Public Health and at University College London, and all procedures performed were in accordance with the Helsinki declaration of 1975 (revised 1983) (http://www.wma.net/en/30publications/10policies/b3/index.html). Written informed consent was obtained from each subject.

DNA analysis

DNA was isolated using the standard salting out method (Miller et al., 1988) from the frozen whole EDTA blood. PCR device DYAD and 96-well polycarbonate plates (both MJ Research, Waltham, MA) were used to perform the PCR reaction in a total volume of 25 μL. DNA was amplified under the following conditions: initial denaturation of 96°C for 3 min, followed by 35 cycles of 95°C for 15 sec, annealing temperature of 56.5°C for 30 sec and 72°C for 30 sec. The last amplification step was extended for 3 min at 72°C. Twenty five pmol of oligonucleotides (5′ aca atc ttt tct gaa tct gaa cag ctt ctc and 5′ ttg cca cta acc acg tgg tca tct gcg), together with 0.05 U of Dream Taq DNA polymerase and 0.2 mMol of each dNTP in buffer provided by manufacturer were used for the amplification. A 10 μl of PCR product were digested in a total volume of 25 μl with 1U of the restriction enzyme Hin6I at 37 °C overnight in the buffer provided by the manufacturer. All used chemicals were produced by Fermentas, Burlington, Canada. Restriction fragments were separated on 10% polyacrylamide gel using the MADGE technique (Day and Humphries, 1994). Uncut PCR product of 92 bp represents allele A (His47), restriction fragments of 65 bp and 27 bp allele G (Arg47). One plate (94 samples) was genotyped twice within two weeks with the 100% conformity. From the entire sample, 1.8% (N=121) samples were re-genotyped because of the unclear or missing results. The final achieved genotype call rate (the proportion of samples with valid genotyping result) was 99.6%.

Measurements

Participants completed an extensive questionnaire on medical history, health status, life style, diet and socioeconomic and psychosocial factors, underwent a short examination, including anthropometry, and provided a blood sample.

Alcohol consumption in the last year was ascertained by structured questionnaire, completed in an interview or self-completed and checked by a trained nurse. Several alcohol measures were derived from the graduated frequency questionnaire (GFQ) (Rehm, 1998), containing nine mutually exclusive categories of frequency (ranging from “never” to “daily/almost daily”) and six mutually exclusive categories of amounts of ethanol consumed per single occasion, expressed in local units (0.5 l of beer, 0.2 l of wine and 0.05 l of spirits), ranging from “less than one” to “10 and above”. Total annual consumption of alcohol was calculated from the frequency and amounts consumed; 100 ml of beer, wine and spirit was assumed to contain 4 g, 10 g, or 36 g of ethanol, respectively. Persons were classified into 5 categories of drinking frequency and into 5 categories of annual alcohol intake (with lower cut-off points of annual intake for women than for men, see tables 2 and 3). The GFQ data were also used to estimate the prevalence of occasional and regular binge drinking defined as drinking ≥100 g (men) or ≥60 g (women) of ethanol in one session at least once a month and at least once a week, respectively. Participants also reported their intake of beer, wine and spirits during a typical week; this information was used to define heavy drinking (≥350g per week in men and ≥210g of ethanol per week in women, roughly corresponding to weekly consumption of ≥35 and ≥21 UK units of alcohol, respectively).

Statistical analyses

The statistical analyses are based on participants with valid data on both the *ADH1B* genotype and alcohol intake (6497 individuals), and include non-drinkers. The Hardy-Weinberg test was applied for the confirmation of the independent segregation of the *ADH1B* alleles. Since most indicators of alcohol consumption are not normally distributed, and are therefore not suitable for linear regression, we have used the following approach. First, the outcome variables were categorised or dichotomised, and were analysed by chi-square test (comparing distribution of alcohol intake categories between ArgArg homozygotes and His-allele carriers) and logistic regression (for dichotomised outcomes). Second, we used non-parametric methods (Spearman correlation and Kruskal-Wallis test) for continuous variables and for variables with a large number of categories. Finally, we used logistic regression to examine the influence of potential confounding variables, such as age and socioeconomic characteristics. However, since the adjustment for covariates did not change the odds ratios, confirming that the Mendelian randomisation approach provides unconfounded effect estimates, we present bivariate results. All analyses were conducted using the STATA statistical software (version 11, College Station, TX).

Results

Valid data on *ADH1B* genotype and drinking characteristics were available on 3016 men and 3481 women. Of these, 89% of men and women were homozygous for the common Arg47 allele; 10.7% had one minor His47 allele, and 0.3% were homozygous in the His47 allele (table 1). Minor allele frequency was 5.5%. The Hardy-Weinberg test confirmed the independent segregation of the individual *ADH1B* alleles ($p = 0.75$ for the entire population, $p = 0.73$ for males and $p = 0.92$ for females). No sex differences in genotype frequencies were observed ($p = 0.49$).

The *ADH1B* genotype was not associated with age, smoking or educational level in neither sex (tables 2 and 3). In men, the *ADH1B* polymorphism was associated with drinking frequency, annual and weekly alcohol intake (table 2). The median weekly intake was 30 g higher in Arg47Arg homozygotes than in His47 carriers. Most remaining alcohol intake indices, except binge drinking, showed lower levels for His47 carriers but the differences were not statistically significant. In women, the associations of Arg47Arg genotype with most drinking measures appeared somewhat stronger than in men, and this genotype was also associated with binge drinking and with high mean dose of alcohol per occasion, albeit at borderline significance levels (table 3).

Table 4 shows the odds ratios of dichotomised alcohol consumption measures by the *ADH1B* genotype. Only heavy alcohol consumption was clearly associated with *ADH1B* in both genders, with homozygotes in the common allele (Arg/Arg) being about twice more likely to be heavy drinkers, compared with carriers of the rare allele. In men, none of the other variables was significantly associated with the *ADH1B* genotype; in women, consuming 60g or more per day at least once a week was significantly related to the ADH1B His47 allele.

The analyses presented in tables 2–4 were based on categorised or dichotomised variables. Since this approach can lead to loss of statistical power, we additionally analysed the original continuous variables or variables with the maximum number of categories using the non-parametric Spearman correlation, and we also assessed whether the strength of the associations differed between the full samples (which included non-drinkers) and samples restricted to current drinkers. These analyses are shown in table 5. Several observations are noteworthy. First, most associations seemed slightly more statistically significant than in tables 2 and 3, confirming the assumption that this type of analysis is statistically more

efficient (although we are aware that statistical significance alone is not a perfect guide). Second, the association of the *ADH1B* polymorphism with drinking frequency and the annual and weekly alcohol intake appeared slightly more pronounced in women than in men (although there were no statistically significant interactions with gender). Finally, the associations of the *ADH1B* polymorphism with alcohol intake variables seem marginally stronger among drinkers than in the full sample but the two sets of analyses were generally similar.

Discussion

This study, in a large Slavic Caucasian general population sample of middle aged and older adults, confirmed the effect of the Arg47His variant within the *ADH1B* gene on alcohol intake. However, the effects on binge drinking were weak and inconsistent, and we found no association with problem drinking and negative consequences of drinking. Within the *ADH1B* gene, there are several SNPs with different degree of linkage disequilibrium but the genetic effects on alcohol intake of all of them are thought to be mediated through the Arg47His polymorphism (Choi et al. 2005). The population frequency of the rs1229984 SNP is known for almost 200 populations worldwide, and the frequency of the His allele differs considerably between different ethnic groups (Li et al., 2007, Borinskaya et al. 2009). In East Asian populations, the frequency of the “minor” His47 allele often exceeds 80% while in Western Europeans the frequency is commonly below 5%.

The “protective” effect of the *ADH1B* His47 allele against alcoholism, especially in East Asia (or in persons of Indian and Chinese origin) has been known for some time (Higuchi 1994, Osier et al. 1999, Tan et al. 2010). Despite the pronounced geographic and ethnic variations in the allele frequency, there is a good consistency in findings regarding the association between alcohol dependence and *ADH1B* Arg47His variant, although the association may be weaker in Caucasians than in Asians (Whitfield, 2002).

The low frequency of the *ADH1B* His47 allele in Caucasian populations underlines the importance of well powered studies. For example, a Danish study of 1250 subjects proved too small to detect an effect of *ADH1B* polymorphism on alcohol consumption (Husemoen et al. 2008). Similarly, the low frequency of the His47 allele carriers in a Dutch population sample precluded identification of genetic predispositions to alcoholism in a study of 1754 individuals (van Beek et al. 2010). It is only large studies that have confirmed the association between *ADH1B* and alcohol consumption in Caucasians. A study of 4,500 Australians reported a significant association of *ADH1B* with alcohol intake and a borderline association with alcohol dependence (Macgregor et al., 2009). A study of 9,080 males and females from Copenhagen found that the Arg47Arg homozygotes drank more alcohol and had a higher prevalence of daily drinking, heavy drinking and excessive drinking, and had a higher risk of developing alcoholism (Tolstrup et al., 2008). Finally, a large study of 7,410 pregnant women in England found that carriers of the His47 allele consumed less alcohol before pregnancy, were less likely to engage in binge drinking during pregnancy, and were more likely to have abstained in the first trimester of gestation (Zuccolo et al., 2009).

Our results were, in general, consistent with these three large Caucasian studies. We have also found a relationship with drinking frequency and overall drinking intake. We did not find an association of *ADH1B* genotype with the CAGE questionnaire score nor with negative consequences of drinking, both of which are thought to reflect problem drinking and potential risk of alcoholism. This lack of association may perhaps be related to the subjective nature of these self-reported scales, which may be prone to under-reporting.

Interestingly, we did not find any association between *ADH1B* and binge drinking, either less frequent (monthly) or relatively frequent (weekly) in men. Given the relatively high prevalence of binge drinking in men, and given its association with other alcohol consumption categories as well as with factors strongly associated with alcohol intake (such as hypertension [unpublished results from the HAPIEE study]), the lack of association with binge drinking was surprising, especially since we did find a borderline association with binge drinking at least once a month in women, consistent with the finding in the ALSPAC females study (Zuccolo et al., 2009). It is plausible, however, that while genetic factors influence the volume and frequency of drinking and the risk of alcoholism, drinking patterns may be much more culturally determined than drinking *per se*. Male binge drinking in Eastern Europe differs from female drinking (Bobrova et al., 2010), possibly due to long-term cultural patterns. This may help explaining the lack of association with binge drinking in men.

Studies of genetic influences on alcohol consumption in Central and Eastern Europe are sparse, and most of them reported only the genotype frequencies. Making meaningful comparison of our results to other studies in the region is therefore difficult. The frequency of the His47 carriers in the neighbouring Polish, German and Hungarian populations have been reported to be 11%, 10% and 18%, respectively (Lilla et al. 2005, Cichoz-Lach et al. 2010, Toth et al. 2010), which is similar to our results and significantly higher than in western European populations. Unfortunately, these studies were not primarily focused on the associations between *ADH1B* and with alcohol intake. Nevertheless, a German study found an association between *ADH1B* polymorphism and alcoholism (defined as >20 g/day); in a Polish case-control study the ArgArg genotype was more frequent in alcohol dependent men than among controls (Cichoz-Lach et al. 2010); and *ADH1B* Arg47Arg homozygotes in Hungary had higher drinking prevalence (Toth et al. 2010).

In conclusion, this large study in a general population sample confirms the important role of the common Arg47His polymorphism within the *ADH1B* gene in the determination of the alcohol intake both in males and females of Slavic origin. The *ADH1B* Arg47His variant was also associated with binge drinking in women, but we failed to detect such an association in males. It will be interesting to assess the genetic influences on drinking patterns in populations with more extreme levels of hazardous drinking, such as Russia.

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Table 1

Distribution of the *ADH1B* genotypes by sex.

***ADH1B* genotype**	**Men N (%)**	**Women N (%)**	**Total N (%)**
Arg/Arg	2695 (89.4)	3104 (89.2)	5799 (89.3)
Arg/His	313 (10.4)	367 (10.5)	680 (10.5)
His/His	8 (0.3)	10 (0.3)	18 (0.3)
Total	3016 (100)	3481 (100)	6497 (100)

Table 2

Socio-demographic variables, alcohol intake and problem drinking in men by *ADH1B* genotype.

	All	ADH1B		p-value
		ArgArg	His carriers	
No. of subjects	3016	2695	321	
Mean age, years (SD)	58.3 (7.1)	58.3 (7.2)	58.3 (6.8)	0.847
Smoking (%)	25.9	25.9	25.9	0.999
University educ. (%)	18.1	17.7	21.7	0.169
Drinking frequency (%)				
Never	6.0	6.1	5.3	
<1/month	17.2	16.6	22.4	
1–3/months	17.4	17.4	17.5	0.052
1–4/week	36.8	37.0	35.8	
5+/week	22.6	23.0	19.0	
Annual intake of alcohol (g)				
None	6.0	6.0	5.2	
<3000 g	46.0	45.4	50.6	
3000–5999 g	14.4	14.4	14.1	0.073
6000–11999 g	15.8	15.7	16.6	
12000g+	18.0	18.6	13.5	
Weekly alcohol intake (g)				
None	13.8	13.2	19.2	
<100g	28.6	28.2	31.9	<0.001
100–249g	31.7	31.6	32.5	
250g+	25.9	27.0	16.4	
Weekly alcohol intake (g) Median (IQR) *	120 (40, 256)	126 (40,268)	96 (40, 200)	<0.001
Binge, ≥60g ≥1/month (%)	36.7	37.1	33.0	0.151
Binge, ≥100g ≥1/month (%)	16.9	16.9	17.1	0.923
Mean dose ≥60g per occasion	18.6	19.0	15.9	0.181
CAGE 2+ (%)	9.5	9.7	7.6	0.232
Negative consequences (%)	9.1	9.1	8.8	0.867

* IQR = interquartile range; statistical significance tested by Kruskal-Wallis rank test.

Table 3

Socio-demographic variables, alcohol intake and problem drinking in women by *AHD1B* genotype.

	All	ADH1B		p-value
		ArgArg	His carriers	
No. of subjects	3481	3104	377	
Mean age, years (SD)	57.4 (7.1)	57.4 (7.1)	57.3 (7.3)	0.716
Smoking (%)	20.2	19.2	22.0	0.340
University educ. (%)	9.9	10.0	9.7	0.444
Drinking frequency (%)				
Never	16.6	16.2	19.4	
<1/month	34.0	33.1	42.2	
1–3/months	24.0	24.5	20.2	<0.001
1–4/week	21.0	21.7	15.1	
5+/week	4.3	4.5	3.2	
Annual intake of alcohol (g)				
None	16.6	16.2	19.4	
<1000 g	54.4	53.6	60.7	
1000–2999 g	16.5	17.0	11.9	0.002
3000–5999 g	6.7	7.0	4.5	
6000g+	5.9	6.2	3.5	
Weekly alcohol intake (g)				
None	47.6	46.2	58.7	
<100g	38.4	39.3	31.5	<0.001
100–249g	11.8	12.2	8.7	
250g+	2.2	2.4	1.1	
Weekly alcohol intake (g) Median (IQR) *	10 (0, 50)	12 (0,56)	0 (0, 40)	<0.001
Binge, ≥60g ≥1/month (%)	9.6	9.9	6.9	0.060
Binge, ≥100g ≥1/month (%)	3.0	3.1	1.9	0.172
Mean dose ≥60g per occasion	5.7	6.0	3.5	0.047
CAGE 2+ (%)	2.1	2.2	1.3	0.284
Negative consequences (%)	3.6	3.7	2.6	0.301

* IQR = interquartile range; statistical significance tested by Kruskal-Wallis rank test.

Table 4

Odds ratios (95% confidence intervals) for binary measures of alcohol intake and drinking consequences by ADH1B genotype (ArgArg vs. His carriers).

	Men	Women
Heavy drinking (≥350g/week in men and ≥210g/week in women)	2.14 (1.14–3.21)	2.18 (1.01–4.70)
Daily drinking	1.28 (0.95–1.71)	1.43 (0.78–2.60)
≥60g/day at least once a month	1.20 (0.94–1.53)	1.49 (0.98–2.25)
≥60g/day at least once a week	1.27 (0.92–1.76)	8.48 (1.17–61.3)
≥100g/day at least once a month	0.98 (0.72–1.34)	1.71 (0.79–3.70)
≥100g/day at least once a week	1.22 (0.72–2.07)	No cases
Problem drinking (CAGE 2+)	1.30 (0.84–2.01)	1.64 (0.66–4.10)
Negative consequences of drinking	1.04 (0.68–1.59)	1.44 (0.72–2.86)

Table 5

Spearman rank correlation coefficients for continuous measures of alcohol intake by *ADH1B* genotype (ArgArg, ArgHis and HisHis carriers), for all participants, and for those who reported any alcohol intake in the last year.

		Men		All women	
		Coeff.	**p-value**	**Coeff.**	**p-value**
Drinking frequency (9 categories)	All	−0.038	0.036	−0.070	<0.001
	Drinkers	−0.048	0.011	−0.077	<0.001
Annual alcohol intake (continuous)	All	−0.040	0.029	−0.074	<0.001
	Drinkers	−0.049	0.009	−0.083	<0.001
Weekly alcohol intake (continuous)	All	−0.078	<0.001	−0.075	<0.001
	Drinkers	−0.088	<0.001	−0.081	<0.001
Mean dose per occasion (continuous)	All	−0.032	0.084	−0.044	0.009
	Drinkers	−0.040	0.034	−0.040	0.032
Frequency of drinking ≥60g (9 categories)	All	−0.032	0.086	−0.052	0.003
	Drinkers	−0.038	0.045	−0.052	0.006
CAGE questionnaire (5 categories)	All	−0.037	0.041	−0.038	0.026
	Drinkers	−0.038	0.042	−0.038	0.043
Negative consequences (9 categories)	All	−0.003	0.895	−0.019	0.298
	Drinkers	−0.002	0.917	−0.017	0.373