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$GABA_A$ subunit single nucleotide polymorphisms show sex-specific association to alcohol consumption and mental distress in a Norwegian population-based sample

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ABSTRACT

Little is known about genetic influences on the relationship between alcohol consumption and mental distress in the general population, where the majority report consumption and distress far below diagnostic thresholds. This study investigated single nucleotide polymorphisms (SNPs) from candidate gene studies on alcohol use disorder and depressive disorders, for association with alcohol consumption and with mental distress in a population-based sample from the Cohort of Norway (n = 1978, 49% women). The relationship between alcohol consumption and mental distress was further examined for genotype modification. There was a positive correlation between mental distress and alcohol consumption in men, as well as an association between SNPs and mental distress in men (*GABRG1, GABRA2, DRD2, ANKK1, MTHFR*) and women (*CHRM2, MTHFR*) and between SNPs and alcohol consumption in women (*GABRA2, MTHFR*).

No modification by SNP genotype was found on the relationship between alcohol consumption and mental distress. The association between mental distress and *GABRG1* in men remained significant after correcting for multiple comparisons. The results indicate that alcohol consumption and mental distress are associated in the general population even at levels below clinical thresholds and point to SNPs in genes related to GABAergic signalling for level of mental distress in men.

1. Introduction

Genetic vulnerability for alcohol use disorders (AUD) and depressive disorders (DD) continues to be widely investigated. In addition to the impact on the global burden of disease posed by AUD and DD separately (WHO, 2019), the two conditions co-occur more frequently than by chance, worsening prognosis and treatment outcome (Boden and Fergusson, 2011; Kendler et al., 2003; McHugh and Weiss, 2019). There is less research into genetic influences on alcohol consumption and depressive symptoms in the general population, where symptoms do not normally meet the requirements for clinical diagnosis. Nonetheless, subclinical depressive symptoms incur substantial cost to the individual and society (Cuijpers and Smit, 2008; WHO, 2019) and alcohol consumption may pose a health risk even at low levels (e.g. less than 1 unit/day) (Bagnardi et al., 2013; Rehm and Shield, 2013). Furthermore, recent epidemiological studies suggest a positive correlation between alcohol consumption and depressive symptoms (Gigantesco et al., 2015; Jokela et al., 2020; Mathiesen et al., 2012) which is in turn associated with increased morbidity and mortality (Degerud et al., 2020), highlighting the need for further investigations.

The prevalence and presentation of both alcohol consumption and depressive symptoms are strongly influenced by gender (WHO, 2013). Women are more likely to experience depressive mood (Lépine and Briley, 2011), while men consume more alcohol and have a higher

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prevalence of AUD (Merikangas and Almasy, 2020). Gender specific findings have been documented in relation to AUD and DD in both candidate gene studies (Enoch et al., 2006) and genome wide association studies (GWAS) (Lewis et al., 2010; Shyn et al., 2011). A recent follow-up study on depression GWAS found the majority of gene products to have a sex specific expression (Wu et al., 2021). This supports an earlier study which found that genes contribute to depression risk in a sex specific manner (Zhao et al., 2020).

Alcohol consumption and AUD represent two distinct but related phenotypes (Morozova et al., 2012) which share genetic substrates, demonstrated by a genetic correlation (r_g) of 0.52 (Kranzler et al., 2019). Candidate genes for AUD phenotypes, investigated by use of single nucleotide polymorphisms (SNPs) located in the gene region, are related to alcohol metabolising enzymes, neurotransmitters such as gamma-aminobutyric acid (GABA), glutamate, dopamine, serotonin, endogenous opioids and acetylcholine, as well as stress hormones and brain derived neurotrophic factor (*BDNF*) (Edenberg and Foroud, 2013; Schuckit, 2018). The same genes have been investigated in relation to alcohol consumption (Agrawal et al., 2011), where associations with alcohol metabolizing enzymes such as *ADH1B* have been replicated (Edenberg et al., 2019; Sanchez-Roige et al., 2020). GWA studies report a slight overlap between SNPs related to AUD and those related to alcohol consumption (Kranzler et al., 2019), and some candidate genes have been recognized in recent GWAS, such as dopamine receptor D2 (*DRD2*) and *BDNF* (Evangelou et al., 2019).

Depressive symptoms in the general population are frequently investigated by brief self-report scales capturing mental (or psychological) distress (Degerud et al., 2020; Kessler et al., 2003; Søgaard et al., 2003). There is a high genetic correlation (r_g = 0.82) between brief self-report scales of anxiety and depression symptoms (mental distress) and anxiety disorders and DD, validating self-report scales as screening tools in studies on genetic variance (Gjerde et al., 2011). Candidate genes for depressive symptoms and DD include genes of importance to GABAergic, dopaminergic, serotoninergic and cholinergic transmission, as well as intracellular signalling, stress hormones, folate metabolism and *BDNF* (Fan et al., 2020).

Candidate gene studies on the comorbidity of AUD and DD have reported findings in genes related to GABA (Enoch et al., 2006), *DRD2, MAOA, CHRM2, COMT* (Edwards et al., 2012), *MTHFR* and *BDNF* (McEachin et al., 2008), in addition to an overlap of genes found to be associated with both disorders separately. Only one SNP has been discovered to date in GWA studies (*SEMA3A*, in an African American sample) (Zhou et al., 2017), despite an estimated genetic correlation of 0.56 (Walters et al., 2018).

In the current study, we explored the relationship between 26 candidate gene SNPs, alcohol consumption and mental distress in a multipurpose case-control sample (n = 1978, 49% women) derived from a Norwegian general population sample. We hypothesized that alcohol consumption and mental distress were positively correlated and that this relationship and the effects of SNPs would be gender specific. We then aimed to (1) investigate candidate gene SNPs and their relationship to alcohol consumption and to mental distress, and (2) use findings from aim 1 to explore whether the relationship between alcohol consumption and mental distress differed across SNP genotype.

2. Material and methods

2.1. Sample and study design

The sample consisted of 3439 individuals (44.1% women) drawn from the Cohort of Norway (CONOR), a national compilation of ten large regional population-based surveys. It was carried out by the National Health Screening Service between 1994 and 2003 and included 173 236 individuals in total, with an overall response rate of 58.7% (Naess et al., 2008). Information was gathered from self-report questionnaires, physical examination and blood samples. The current genotyped multipurpose sample consisted of two case categories derived from register data in 2009 on (1) death due to coronary heart disease (CHD) and (2) incidental colon cancer, in addition to age and gender-matched controls (Hoiseth et al., 2013; Jansen et al., 2014). Available data was cross-sectional, apart from inclusion group status representing a longitudinal measurement point. Individuals were excluded from the current study if there was insufficient biological sample quality (n = 458), non-response on drinking frequencies (n = 113), consumption amounts (n = 377) or mental distress (n = 1273), leaving a total number of included participants n = 1978 (49.1% women, 99.7% Caucasian origin). The number of participants varied for each SNP, with a mean of n = 1703.

2.2. Measures

2.2.1. Depressive symptoms

Depressive symptoms were investigated as a continuous variable measured by the CONOR Mental Health Index (CMHI), a 7-item inventory constructed for the CONOR study based on the General Health Questionnaire (GHQ) (Reid, 1973) and Hopkins Symptoms Checklist (HSCL) (Derogatis et al., 1974). The scale measures mental distress, a frequently used approximation to symptoms of depression and anxiety in general population surveys (Degerud et al., 2020; Kessler et al., 2003; Søgaard et al., 2003).Validation against HSCL-10 and Hospital Anxiety and Depression Scale (HADS), has demonstrated high correlation with both ($r > 0.70$) (Søgaard et al., 2003). The index maps whether participants have, in the past 14 days, felt: (1) Nervous or worried, (2) Anxious, (3) Confident and calm, (4) Irritable, (5) Happy/Optimistic, (6) Down/Depressed, and (7) Lonely. Answers were given on a 4-point scale, 1 = No, 2 = *A* little, 3 = *A* lot, and 4 = Very much. The two positive statements, question 3 and 5, have in previous studies been included in a continuous score in reversed form. However, as the article validating this index highlights, factor analysis performed on the CMHI results in two factors with an eigenvalue above 1, where the positive statements load on a second factor (Søgaard et al., 2003) and as such increase the sources of variance. This finding was replicated in our own study and is in line with the two-factor theory of affect, which also states that negative affect is more dispositional with significant heritability, while positive affect is more situational (Zheng et al., 2016). As reducing heterogeneity in measures of depression has been highlighted as beneficial for genetic analyses (Laurin et al., 2015), we therefore used a novel, abbreviated version of the CMHI based on the five negative questions only, termed CMHI-5.

2.2.2. Alcohol consumption

Alcohol consumption was modelled as a continuous variable 'drinks per day', constructed by multiplication of the reported frequency mean and amount per person, gathered from two survey questions: (1) How often have you consumed alcohol during the past year?, where participants responded in one of nine categories (4–7 times a week, 2–3 times a week, 1 time a week, 2–3 times a month, 1 time a month, a few times last year, have not drunk alcohol the past year, have never drunk alcohol, abstainer), and (2) How many glasses do you usually drink on a drinking occasion? People who responded drinking never or less than monthly were assigned a value of 0 for consumption.

2.2.3. Other variables

The following background and sociodemographic variables were included: age at survey (years, continuous), education (years, continuous), marital status (married or partner, yes/no, categorical), smoking status (yes/ no, categorical), somatic disease (self-reported occurrence of one or more of the following conditions, past or present: angina, myocardial infarction, cerebrovascular incident, asthma, diabetes, yes/no, categorical) and inclusion group (CHD, colon cancer, control, categorical). For inclusion groups, five cases were listed in both case categories, and were included in the CHD-category.

2.3. SNP selection and genotyping

SNP selection had previously been done for the multipurpose sample and comprised of 216 SNPs marking candidate genes of interest in relation to several diseases. Genotyping was performed at the Centre for Integrative Genetics (CIGENE, Aas, Norway), using Sequenom MassARRAY system with iPLEX Gold technology (Sequenom, San Diego, California, US). Samples were automatically discarded if the signal was less than 0.4, and all samples were manually inspected for allele call. The genotyping process has been described elsewhere (Hoiseth et al., 2013; Jansen et al., 2014).

For the current study, SNPs were selected from the available 216 SNPs if they marked a candidate gene which has an association in literature to both AUD and DD, resulting in 26 SNPs in 14 genes (*GABRA2, GABRG1, ANKK1, DRD2, DRD4, DAT1, MAOA, CHRM2, CRHR1, FKBP1, SDHAF3, ADCY1, MTHFR, ADH1B*) (Table 1).

2.4. Statistical analysis

Statistical analyses were conducted using Stata (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). SNPs were analysed for minor allele frequency (MAF) and excluded if less than 5%. Hardy-Weinberg equilibrium (HWE) was investigated using the *hwsnp* and *genhw* Stata commands (Cleves, 2005). SNPs not in HWE were excluded, as this could be due to genotyping error (Chen et al., 2017; Hosking et al., 2004) which was not accessible for further investigation in the current study. Linkage disequilibrium was analysed using Haploview (Barrett et al., 2005), to give information about non-random association of alleles on the same chromosome (Slatkin, 2008). SNPs were dichotomized and analysed following a dominant and a recessive model, assuming the minor allele as effect allele. Analyses were further gender stratified to incorporate gender differences in alcohol consumption, depressive symptoms and SNP effect, to increase statistical power should effect alleles differ in women and men (Magi et al., 2010). Bivariate associations between CMHI-5, drinks per day, background and SNP-variables were examined using χ^2-test for categorical variables, Student's T-test for continuous variables against categorical variables, and linear regression for continuous outcomes. Covariates were included in the regression model to control for confounding. To validate findings and reduce possible effects of population stratification and heteroscedasticity, bootstrapping analyses with bias corrected and accelerated confidence intervals using 10 000 repetitions were applied (Greenwood et al., 2011). Akaike's information criterion (AIC) was used to examine model fit. The relationship between SNPs, alcohol consumption and mental distress was graphed using the Stata command *qtlsnp* (Cleves, 2005) and regression coefficients were further visualized using the Stata command *coefplot* (Jann, 2014). The relationship between drinks per day and CMHI-5 were examined by linear regression across genotypes that were nominally significant when analysed against CMHI-5 and/or drinks per day alone. Regression coefficients for each genotype model within the SNP were then compared with Student's T-test for significance in case of significant association between drinks per day and CMHI-5. Results were corrected for multiple comparisons using Bonferroni correction, where the analysis count included gender stratified analyses of included SNPs to CMHI-5 and drinks per day ($19 \times 2 \times 2 = 76$ analyses), and the gender stratified analyses of CMHI-5 to drinks per day (=2), resulting in a p-value threshold of $0.05/78 = 0.0006$. Power analyses were not conducted before assembly of the multipurpose cohort, and posthoc power estimation using a diagram for SNPs and quantitative traits (Delongchamp et al., 2018) indicates that our study would have 80% power to detect a SNP effect of 0.28, understood as the proportion of variance explained by genotype.

2.5. Ethical considerations

The CONOR study has been conducted in accordance with the World Medical Association Declaration of Helsinki, and all participants provided written informed consent before inclusion (Næss et al., 2008). The genotyping study was approved by the South-East Regional Committees for Medical and Health Research Ethics, and an extension of the approval was granted for the current study in November 2018 (Ref. No. 2009/814 REK South-East B). All data was stored without person identification markers on a secure platform provided by Service for

Table 1
Overview of single nucleotide polymorphisms (SNPs) in the study.

Chr	Gene product[a]	Abbreviation	Related to	SNP	MAF	HWE p-value
1	Methylene tetrahydro- folate reductase	*MTHFR*	Folate metabolism	rs1801133	*T* = 0.288	0.773
1		*MTHFR*	Folate metabolism	rs12121543	*T* = 0.247	0.112
1		*MTHFR*	Folate metabolism	rs6541003	C = 0.375	0.118
17	Corticotropin releasing hormone receptor 1	*CRHR1*	HPA axis, stress	rs1876831	*T* = 0.169	**0.026**
17		*CRHR1*	HPA axis, stress	rs242936	*A* = 0.095	0.704
6	FKBP prolyl isomerase 5	*FKBP5*	HPA-axis, stress	rs1360780	*A* = 0.264	0.964
4	$GABA_A$ receptor subunit α2	*GABRA2*	$GABA_A$ receptor	rs279845	*T* = 0.489	0.824
4		*GABRA2*	$GABA_A$ receptor	rs279836	*T* = 0.444	**0.016**
4	$GABA_A$ receptor subunit γ1	*GABRG1*	$GABA_A$ receptor	rs11736752	*G* = 0.400	0.958
4		*GABRG1*	$GABA_A$ receptor	rs1497571	*G* = 0.500	0.123
7	Cholinergic receptor muscarinic 2	*CHRM2*	Autonomic NS	rs978437	C = 0.349	0.128
7		*CHRM2*	Autonomic NS	rs1455858	*T* = 0.348	0.847
7		*CHRM2*	Autonomic NS	rs1824024	C = 0.347	0.875
11	Ankyrin repeat and kinase domain containing 1	*ANKK1*	Dopamine	rs1800497	*A* = 0.192	0.154
11		*ANKK1*	Dopamine	rs11214598	*T* = 0.319	0.418
11	Dopamine receptor D2	*DRD2*	Dopamine	rs2471857	*A* = 0.162	0.525
11	Dopamine receptor D4	*DRD4*	Dopamine	rs3758653	C = 0.181	**0.005**
11		*DRD4*	Dopamine	rs11246226	*A* = 0.499	0.867
5	Solute Carrier family 6 member 3	*SLC6A3 (DAT1)*	Dopamine	rs11564772	*A* = 0.086	0.229
X	Monoamine oxidase A	*MAOA*	Monoamine degradation	rs1800464	C = 0.032	**<0.001**
7	Succinate dehydrogenase complex assembly factor 3	*SDHAF3*	Metabolism	rs7794886	C = 0.373	0.114
7		*SDHAF3*	Metabolism	rs12670377	*A* = 0.289	0.081
7	Adenylate cyclase 1	*ADCY1*	Intracellular signalling	rs6961503	C = 0.453	**0.033**
7		*ADCY1*	Intracellular signalling	rs11771815	*T* = 0.401	**0.002**
7		*ADCY1*	Intracellular signalling	rs11982719	C = 0.133	0.527
4	Alcohol dehydrogenase 1B	*ADH1B*	Alcohol metabolism	rs1229984	*A* = 0.009	0.067

Note. Abbreviations: Chr= Chromosome. MAF=Minor allele frequency (observed in the current study). HWE= Hardy-Weinberg equilibrium. HPA=hypothalamus-pituitary-adrenal gland. $GABA_A$=gamma-aminobutyric acid type A. NS=nervous system. Statistically significant result highlighted in bold.

[a] Information from https://www.ncbi.nlm.nih.gov/snp

Sensitive Data (TSD) at the University of Oslo, complying with Norwegian privacy regulation.

3. Results

3.1. Study population

All study variables, except for allele distribution, differed between women and men (Table 2, all $p < 0.001$). Mean age was 69.2 years (women) and 67.3 (men). Notably, women consumed less alcohol and scored higher on mental distress than men. Comparison of background variables to alcohol consumption (Table 3) showed that for both women and men, higher age ($p < 0.0001$) and somatic disease ($p < 0.01$) were associated with reduced alcohol consumption, while higher education ($p < 0.0001$ women, $p < 0.01$ men) and smoking ($p < 0.05$ women, $p < 0.01$ men) were associated with increased alcohol consumption. Unmarried women consumed less than those married ($p < 0.05$), while unmarried men consumed more than those married ($p < 0.01$). When comparing background variables to CMHI-5, mental distress was higher in unmarried participants ($p < 0.05$ women, $p < 0.0001$ men), and for women if they were smoking currently ($p < 0.05$) or had a somatic disease ($p < 0.01$). For men, increasing age indicated a reduction in mental distress ($p < 0.05$), while smoking currently displayed a trend towards higher mental distress ($p = 0.058$). Women who were included in the study due to death from CHD reported smaller amounts of alcohol consumption ($p < 0.01$) and higher levels of mental distress ($p < 0.05$) at the time of the survey, while no association was found for men.

3.2. SNP analyses

One SNP was excluded due to MAF < 5%, (rs1229984 *ADH1B*) and six SNPs due to departure from HWE (rs1876831 *CRHR1*, rs279836 *GABRA2*, rs3758653 *DRD4*, rs1800464 *MAOA*, rs6961503 and rs11771815 *ADCY1*), leaving 19 SNPs included in further analyses (Tab.1). Linkage disequilibrium analyses demonstrated a high degree of linkage disequilibrium between rs279836 and rs279845 in *GABRA2* ($r^2 = 0.89$), rs1455858, rs97845 and rs1824024 in *CHRM2* ($r^2 > 0.90$), and rs1800497 in *ANKK1* and rs2471857 in *DRD2* ($r^2 = 0.78$), indicating that these SNPs are located in regions on the chromosome that have a high probability of being inherited as a block and not independently of each other.

Table 2
Characteristics of the sample by gender ($n = 1978$).

		Women $n = 972$ (49.1%)	Men $n = 1006$ (50.9%)	p-value
Age at survey (years)	mean (SD)	69.2 (12.2)	67.3 (12.0)	<0.001[a]
Education (years)	mean (SD)	10.1 (2.4)	10.7 (2.9)	<0.001[a]
Married/partner	n (%)	482 (49.6)	730 (72.6)	<0.001[b]
Smoking	n (%)	197 (21.4)	230 (25.0)	<0.001[b]
Somatic disease[c]	n (%)	294 (30.3)	382 (38.1)	<0.001[b]
CMHI-5	mean (SD)	1.31 (0.44)	1.24 (0.38)	<0.001[a]
Drinks per day	mean (SD)	0.12 (0.30)	0.25 (0.64)	<0.001[a]
Inclusion group				
CHD	n (%)	201 (20.7)	314 (31.2)	
Colon cancer	n (%)	275 (28.3)	271 (26.9)	
Controls	n (%)	496 (51.0)	421 (41.9)	<0.001[b]

Abbreviations: SD: Standard Deviation. CMHI-5: CONOR Mental Health Index 5. CHD: Coronary Heart Disease. Missing data (n) from Education: 78; Married/partner: 1; Smoking: 135; Somatic disease:3. [a] Students T-test.
[b] Chi-square test.
[c] Self-reported angina and/or myocardial infarction and/or cerebrovascular incident and/or asthma and/or diabetes, past or present. Statistically significant result highlighted in bold.

3.3. Bivariate analyses

3.3.1. Associations between alcohol consumption and mental distress

The association between drinks per day and CMHI-5 was weak but statistically significant for men (coefficient 0.076 (95% CI 0.033–0.109), $p < 0.0001$) and not women (0.053 (−0.053–0.147), $p = 0.259$) (Fig. 1, Supplementary tab 2b and c).

3.3.2. Associations between SNPs and alcohol consumption

There were nominally significant associations between increased alcohol consumption in women homozygous for the minor allele of rs279845 (*GABRA2*), rs12121543(*MTHFR*) and rs6541003 (*MTHFR*) (Fig. 2, Supplementary Tables 1 and 2a). No SNPs were associated with alcohol intake in men (Fig. 2, SupplementaryTable 1).

3.3.3. Associations between SNPs and mental distress

There were nominally significant associations between mental distress and the dominant models of rs978437, rs1824024, rs1455858 (*CHRM2)* and rs6541003 (*MTHFR*) (Fig. 3, Supplementary Tables 1 & 2b) in women. In men, there were significant associations with the recessive model of rs11736752 (*GABRG1)* and nominally significant associations with the dominant models of rs279845 (*GABRA2*), rs1800497 (*ANKK1*), rs11736752 (*GABRG1*), rs2471857 (*DRD2*), and the recessive models of rs1497571(*GABRG1)* and rs6541003 (*MTHFR*) (Fig. 3, Supplementary Tables 1 & 2c).

3.4. Modification by SNP genotype on alcohol consumption's association to mental distress

When analysing regression coefficients from linear regression models on alcohol consumption and mental distress separately for each nominally significant SNP-model, we found no modification by genotype in men or women (Supplementary Fig. 1).

3.5. Effects of correction for multiple comparisons, bootstrapping and adjustments for covariates

When correcting for multiple comparisons using Bonferroni-threshold ($p = 0.0006$), only the association between mental distress and the recessive model rs11736752 (*GABRG1*) and the association between drinks per day and mental distress in men remained significant. Adjustment for covariates attenuated the association between alcohol consumption and mental distress in men (Fig. 1, Supplementary Table 2c), which remained nominally significant. Bootstrapped regression analyses confirmed the validity of associations between all SNPs with mental distress and with alcohol consumption in crude analyses (Fig. 4, supplementary Table 2), apart from alcohol consumption's association with rs12121543 (*MTHFR*) in women (Fig. 4a). Adjustment for covariates associated with mental distress or alcohol consumption failed to reproduce the association with alcohol consumption for rs6541003 (*MTHFR*) in women (Fig. 4).

4. Discussion

We report three main findings from this general population study. First, we found a significant association between alcohol consumption and mental distress in men, where increased alcohol intake was related to a higher level of mental distress. No association was detected in women. Second, we found that men homozygous for the minor allele in rs11736752 (*GABRG1*) reported a higher level of mental distress, which was significant after correction for multiple testing and higher than the mean of the male sample (nominally significant). Several other SNPs displayed nominally significant associations with higher level of mental distress in men (*GABRA2, ANKK1, DRD2, MTHFR*), and women

Table 3
Descriptive statistics compared to CONOR Mental Health Index-5 (CMHI-5) and Drinks per day in women and men ($n = 1978$).

	Women $n = 972$ (49.1%)				
Variable		Drinks per day	p-value	CMHI-5	p-value
Age (years)	B (95% CI)	−0.006 (−0.007- −0.004)	**<0.0001**[a]	0.001 (−0.001–0.004)	0.204[a]
Education (years)	B (95% CI)	0.036 (0.028–0.044)	**<0.0001**[a]	0.026 (0.012–0.040)	0.527[a]
Married/partner					
Yes	Mean (SD)	0.14 (0.33)		1.28 (0.40)	
No	Mean (SD)	0.09 (0.26)	**0.014** [b]	1.34 (0.45)	**0.028** [b]
Smoking					
Yes	Mean (SD)	0.22 (0.48)		1.38 (0.49)	
No	Mean (SD)	0.08 (0.21)	**<0.0001** [b]	1.29 (0.41)	**0.012** [b]
Somatic disease[c]					
Yes	Mean (SD)	0.07 (0.23)		1.38 (0.48)	
No	Mean (SD)	0.14 (0.33)	**0.001** [b]	1.29 (0.41)	**0.004** [b]
Inclusion group					
CHD	Mean (SD)	0.05 (0.22)		1.37 (0.50)	
Colon cancer	Mean (SD)	0.12 (0.25)		1.27 (0.38)	
Control	Mean (SD)	0.14 (0.35)	**0.004** [b]	1.32 (0.43)	**0.038** [b]
	Men $n = 1006$ (50.9%)				
Age (years)	B (95% CI)	−0.011 (−0.015- −0.008)	**<0.0001**[a]	−0.002 (−0.004- −0.001)	**0.012**[a]
Education (years)	B (95% CI)	0.026 (0.012–0.040)	**<0.001**[a]	0.000 (−0.008–0.008)	0.993 [a]
Married/partner					
Yes	Mean (SD)	0.21 (0.40)		1.20 (0.34)	
No	Mean (SD)	0.35 (1.03)	**0.002** [b]	1.32 (0.46)	**<0.0001** [b]
Smoking					
Yes	Mean (SD)	0.35 (0.93)		1.28 (0.45)	
No	Mean (SD)	0.20 (0.51)	**0.003** [b]	1.22 (36)	0.058 [b]
Somatic disease[c]					
Yes	Mean (SD)	0.17 (0.39)		1.25 (0.40)	
No	Mean (SD)	0.29 (0.75)	**0.003** [b]	1.23 (0.37)	0.557 [b]
Inclusion group					
CHD	Mean (SD)	0.21 (0.78)		1.22 (0.35)	
Colon cancer	Mean (SD)	0.30 (0.66)		1.22 (0.34)	
Control	Mean (SD)	0.24 (0.48)	0.177 [b]	1.26 (0.42)	0.207 [b]

Abbreviations: CMHI-5: CONOR Mental Health Index. SD: Standard Deviation. CHD: Coronary Heart Disease. Missing data (n) from Education: 78; Married/partner: 1; Smoking: 135; Somatic disease: 3. [a] Simple linear regression [b] Student's T-test.
[c] Self-reported angina and/or myocardial infarction and/or cerebrovascular incident and/or asthma and/or diabetes, past or present. Statistically significant result highlighted in bold.

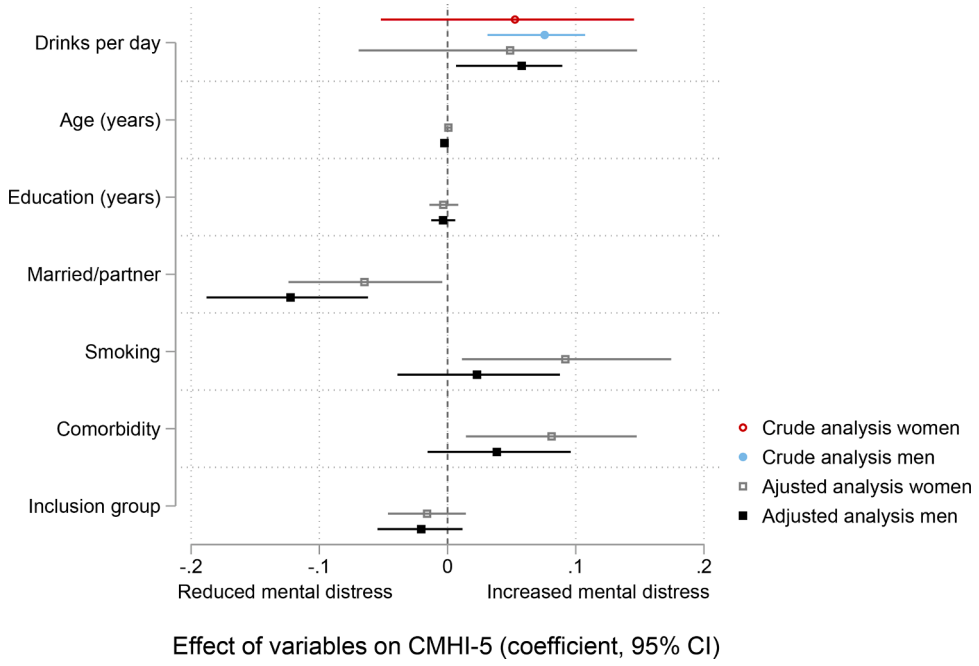

Fig. 1. Relationship between alcohol consumption and mental distress in women and men. Illustrates the coefficients of drinks per day on CMHI-5 in crude and adjusted analyses. It further displays the coefficients of included covariates in the adjusted analysis. Demographic variables included in adjusted analyses only. Confidence interval (CI) represented by 95% bias corrected and accelerated bootstrapped CI. CIs not including zero indicate significant results.

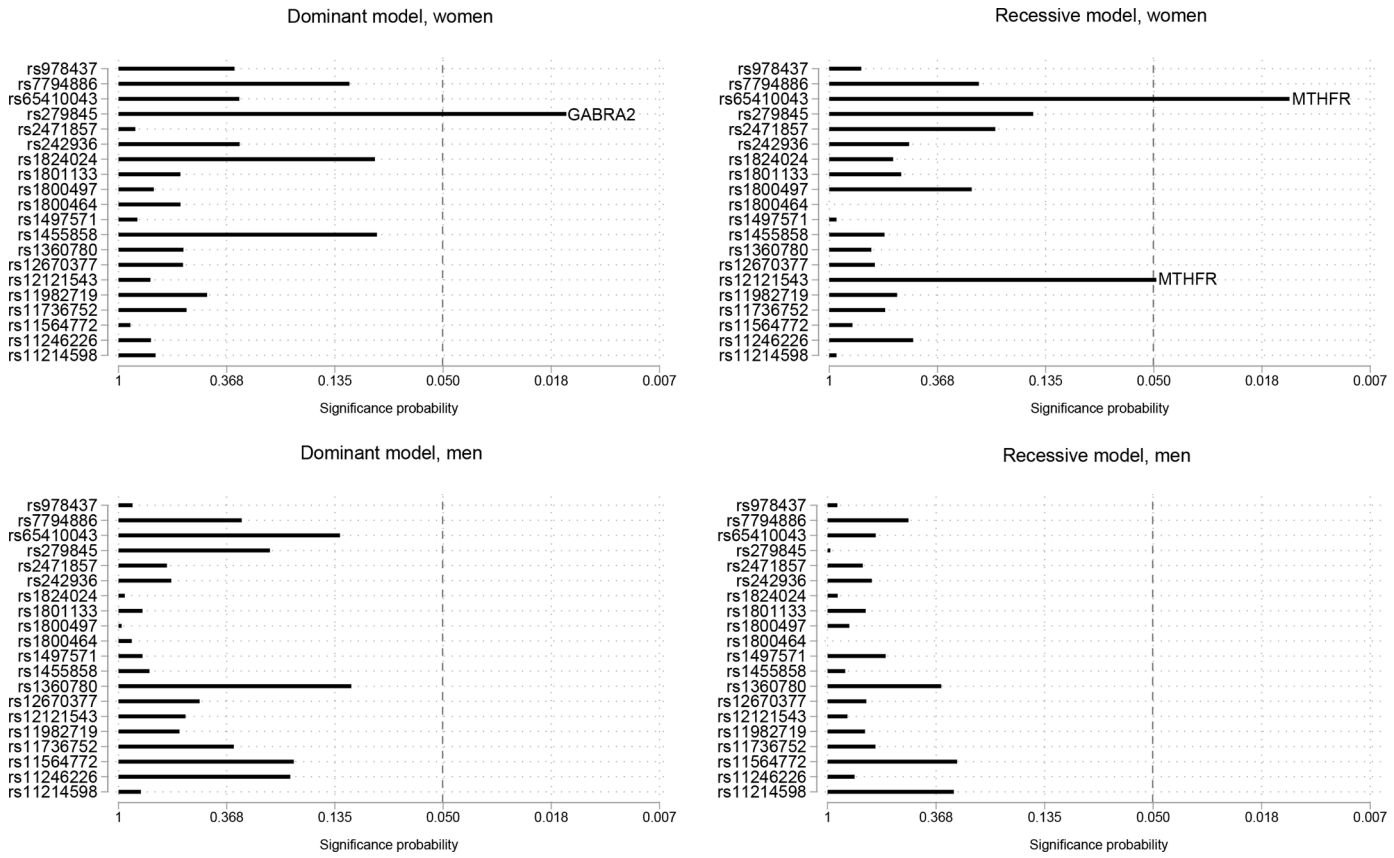

Fig. 2. SNP analysis of 'drinks per day' in women and men. Included SNPs in the study and their statistical association to 'drinks per day' in women and men. Dotted reference line=nominal significance threshold at $p = 0.05$. Bonferroni corrected significance threshold at $p = 0.0006$, reference line not visible in figures. Model defined according to minor allele.

(*CHRM2, MTHFR*), and with alcohol consumption in women (*GABRA2, MTHFR*). Lastly, we found no evidence of modification of genotype on the relationship between alcohol consumption and mental distress.

This study confirms gender differences in depressive symptoms and alcohol consumption and also finds evidence for a positive relationship between alcohol consumption and mental distress in men. This is in line with previous epidemiological findings (Gigantesco et al., 2015; Jokela et al., 2020; Mathiesen et al., 2012) and emphasizes the need for public health awareness regarding this relationship. There were gender differences in the impact of background variables on both alcohol consumption and mental distress. For women, alcohol consumption was not associated with mental distress, whereas smoking currently was associated with both mental distress and alcohol consumption. For men, being a current smoker predicted higher alcohol consumption and showed only a trend towards association with higher levels of mental distress. The association between smoking and mental distress in women and not men has previously been found in a study conducted on a sample with a similar age distribution (Choi and DiNitto, 2011). This suggests a need for attention to this particular association among women. Marital status influenced alcohol consumption in opposite directions by gender, where women reported higher intake and men lower intake if they were married/had a partner. This is in contrast to previous research which shows a reduction in alcohol consumption for women who are married (Liang and Chikritzhs, 2012; Prescott and Kendler, 2001), and it might indicate social aspects of alcohol consumption in partnerships, causing a regression to the mean between drinking patterns for women and men. Consistently with earlier literature (Grundström et al., 2021), not having a partner/being married was associated with higher levels of mental distress regardless of gender.

Our data further displayed a similar percent above cut-off (7.3%) of mental distress as that reported in other studies on the Norwegian population, a cut-off which indicates a clinical diagnosis of depression or anxiety (Degerud et al., 2020; Ormstad et al., 2016; Søgaard et al., 2003), but lower alcohol consumption levels than a larger study drawn partly from the original CONOR study (Degerud et al., 2020). Other descriptive variables did not differ substantially from other studies conducted on similar data, except for a lower percentage of married women and current smokers (Søgaard et al., 2015).

Our main SNP finding was a novel association between increased mental distress and men homozygous for the minor allele in rs11736752. This SNP is located in an intron of the *GABRG1* gene on chromosome 4, which codes for the γ1-subunit of the $GABA_A$-receptor. While there are no earlier studies reporting either negative or positive findings on this particular SNP, it is of particular interest as the γ1-subunit is primarily expressed in central and lateral parts of the amygdala, contributing to inhibitory transmission and extinction of conditioned fear, which is postulated to play a role in anxiety (Esmaeili et al., 2009). There were also nominally significant results for the other SNPs on chromosome 4 tagging *GABRG1* and *GABRA2. GABRA2* codes for the α2-subunit of the $GABA_A$-receptor, which is involved in regulation of anxiolytic effects (Engin et al., 2012; Gonzalez-Nunez, 2015). There is, furthermore, a biological relationship between the α2 and γ1 subunits, as they are found in the same $GABA_A$-receptor complex as mentioned above, although the α2-subunit is more widely expressed in the hippocampus, striatum, and olfactory bulb (Engin et al., 2012; Möhler, 2012). A *GABRA2* haplotype has previously been associated with anxiety in people diagnosed with problematic alcohol use in a Finnish sample (Enoch et al., 2006). However, a later study failed to detect an association between *GABRA2* and anxiety spectrum disorders (Pham et al., 2009). SNPs in *GABRA2* and *GABRG1* have previously been found to

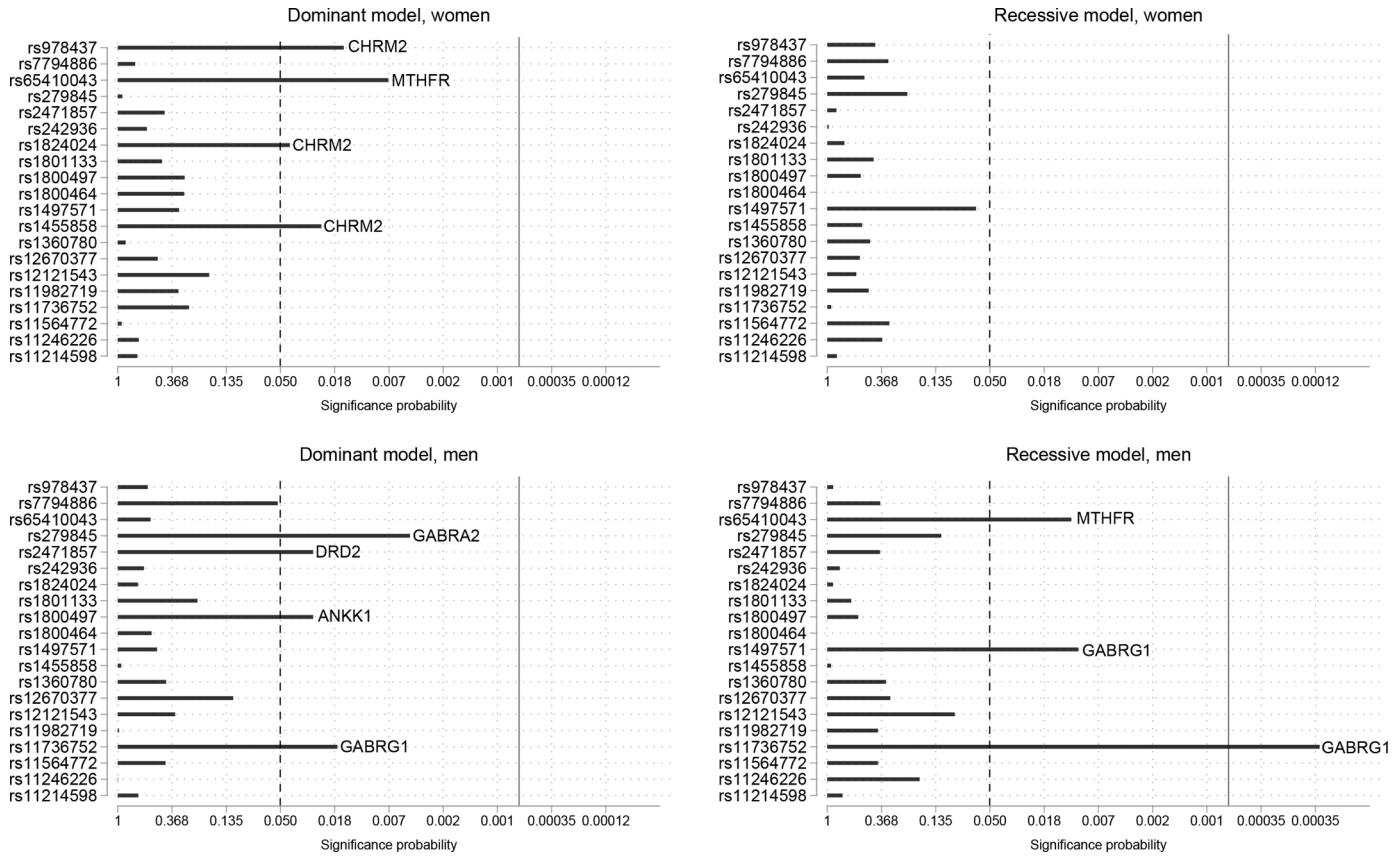

Fig. 3. SNP analysis of CONOR Mental Health Index-5 (CMHI-5) in women and men. Included SNPs and their statistical association to CMHI-5 in women and men. Dotted reference line = nominal significance threshold at $p = 0.05$. Solid reference line=Bonferroni corrected significance threshold at $p = 0.0006$. Model defined according to minor allele.

have a high degree of linkage disequilibrium (Drgon et al., 2006; Ittiwut et al., 2008), which could indicate that the SNPs report the same signal. However, in our data the linkage disequilibrium between the SNPs in GABRG1 and GABRA2 was only moderate ($r^2 < 0.27$) and thus could represent independent signals. In total, our data suggests that genetic variation on chromosome 4 related to *GABRG1* and *GABRA2* has a role in the regulation of mental distress.

Our finding of higher levels of mental distress associated with the minor allele in the dominant model of rs1800497 (*ANKK1*) constitutes a novel replication in a Norwegian population sample, with results following the pattern of other studies where the minor allele (commonly depicted as A1) has a dominant effect on depression risk (Avinun et al., 2020; Hayden et al., 2010). Biological explanations behind the association have not been established but could involve alterations in post-synaptic D2-receptor binding in striatal regions (Savitz et al., 2013). Of note, one study documented an association between *ANKK1* and depression in men only (Roetker et al., 2012). The *ANKK1* SNP displayed a high degree of linkage disequilibrium to rs2471857 (*DRD2*) in our study ($r^2 = 0.78$), and as such likely indicate the same association with mental distress for both SNPs. However, rs2471857 has previously been investigated in relation to mood and depression, without finding any associations with emotion-processing, reward processing (Peciña et al., 2013) or depressive symptoms (Nyman et al., 2011). SNPs in both *ANKK1* and *DRD2* have been replicated in a recent GWAS on depression (Howard et al., 2019).

The association between the minor allele in rs6541003 (*MTHFR*) and mental distress in men has not previously been reported. Other *MTHFR* polymorphisms have been associated with a reduction in MTHFR enzyme activity, which is a critical step in folate and homocysteine metabolism which has been associated with both depression and anxiety (Wan et al., 2018).

In women, increased mental distress was reported for those who were homozygous for major alleles in the three SNPs of *CHRM2*. This constitutes a novel replication in a Norwegian sample, as these same SNPs have previously been associated with increased risk for both AUD and affective disorders in a sample of African American participants but without finding associations with European American participants in the same sample (Luo et al., 2005). One of the SNPs, rs1824024, has been associated previously with both AUD and DD, but without evidence of sex differences (Wang et al., 2004). An earlier study did find an association between SNPs in *CHRM2* and DD in women (Comings et al., 2002), but this study sample only consisted of women.

SNPs were associated with alcohol consumption only in women, where homozygosity for A allele in rs278945 (*GABRA2*) was associated with increased alcohol intake compared to the mean. The rs279845 A allele has previously been associated with alcohol dependency and EEG changes (Edenberg et al., 2004), the T allele with lower negative alcohol effect scores connected to a higher risk of alcohol dependency (Uhart et al., 2013) and to quantitative measures of AUD (Lind et al., 2008). The discrepancies between studies in finding the effect allele to be *A* or *T* could stem from the use of different DNA-strands as reference strands.

Our findings of an association between alcohol consumption and the recessive model of rs6541003 (*MTHFR*) is novel. However, we did not find any replication of rs18001133, which is the most investigated SNP in *MTHFR* when it comes to risk for AUD. This accords with a recent meta-analysis which found no evidence for genetic risk of AUD conveyed by this SNP (Rai and Kumar, 2021).

Despite a relationship between alcohol consumption and mental distress in men, where several SNPs were related to mental distress, there was no evidence of modification by genotype on the relationship

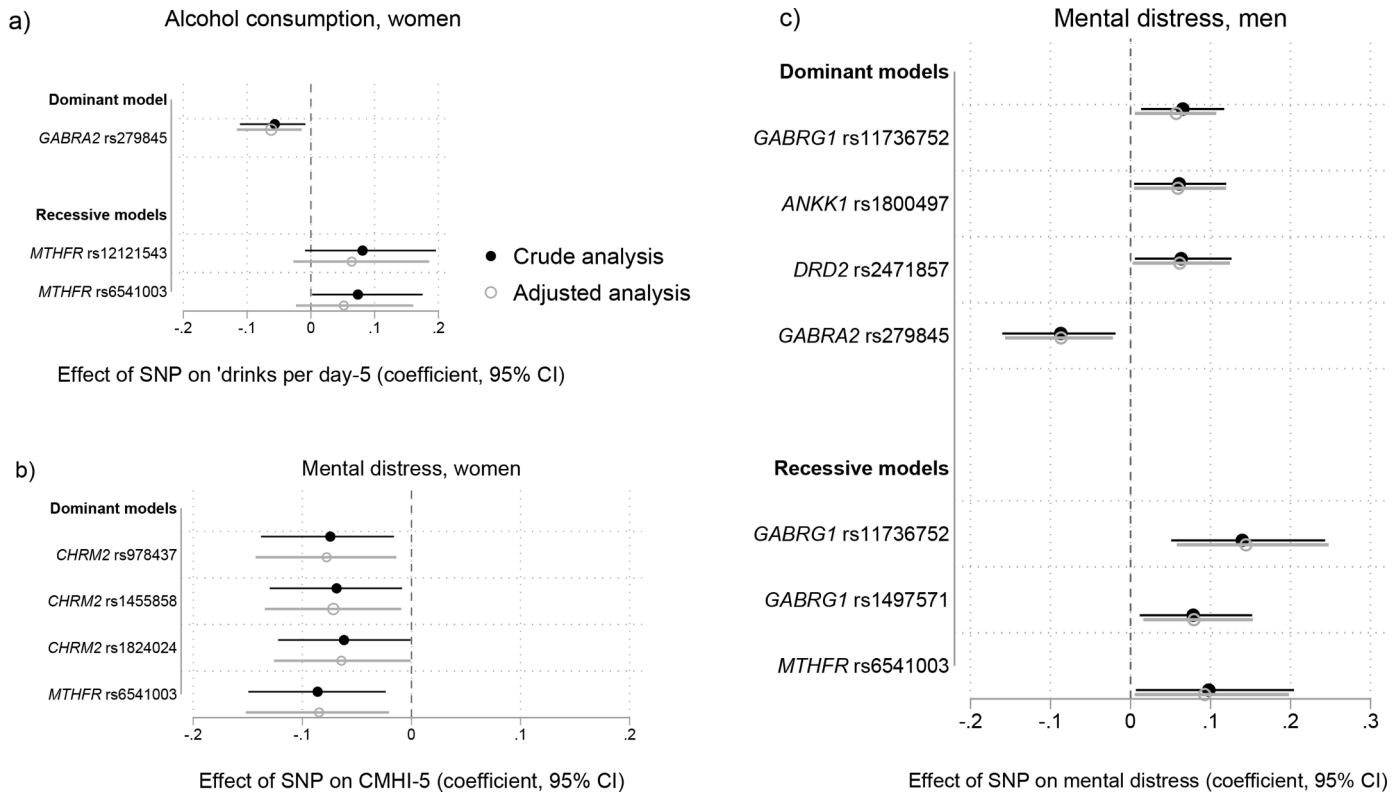

Fig. 4. Associations between SNPs and alcohol consumption or drinks per day, in women and men. Visualises regression coefficients for the association between SNP and (a) 'drinks per day' in women and (b) CMHI-5 in women and (c) CMHI-5 in men. Crude analysis indicated by circle, adjusted analyses by open circle. SNPs adjusted for: (a, b) age, education, marital status, smoking, somatic disease, inclusion group. (b) 'drinks per day', age, marital status, additional adjustment for education (recessive model rs11736752 *GABRG1*); somatic disease (*MTHFR*). Lines from point estimate indicating 95% bias corrected and accelerated confidence interval (10.000 repetitions). CIs not including zero indicate significant results.

between alcohol consumption and mental distress in men. In women, where the association between alcohol consumption and mental distress was not significant overall, there were no alterations in this relationship when testing the nominally significant SNP models.

This study has important limitations. First, the data was derived from an existing multipurpose case-control sample drawn from general population survey data, leaving our analyses prone to selection bias and increased morbidity and mean age compared to the CONOR sample. Women who were included due to death by CHD did report significantly less alcohol consumption and higher mental distress at the time of the survey. However, no other differences were found in men for mental distress and drinks per day and none regarding SNP distribution for women and men so this should not bias our main positive finding of an association between mental distress and alcohol consumption in men. However, it could reduce variation and thus power to detect the same association in women. Second, self-reports on alcohol consumption are associated with a high probability of underreporting, as people with high alcohol consumption are less likely to report accurate measures or any value (Boniface et al., 2014), causing both reporting and selection bias. In our data specifically, married women were less inclined to report their average alcohol consumption and were thus underrepresented in the ensuing analyses. This could further affect our study's power to detect associations with alcohol consumption in women. There could also be selection bias due to mental distress, as people with high levels of mental distress are less likely to complete questionnaires, and higher levels of both alcohol consumption and mental distress were found to be a moderate predictor of non-response in a Norwegian health survey (Torvik et al., 2012). Third, the SNPs investigated in the current study were limited to previously selected candidate gene markers which did not include for instance SNPs in *BDNF* and *5-HTTLPR,* nor recent GWAS SNPs. In addition, the candidate gene approach has been criticized for failure to replicate findings and false positives (Border et al., 2019; Bosker et al., 2011) and recent GWAS findings which have been replicated report few of the SNPs found in candidate gene studies (exceptions include *DRD2* and *ANKK1*) (Howard et al., 2019). Still, candidate gene studies can be cost-efficient (Patnala et al., 2013) when GWAS data are not attainable due to availability of biological material or costs. Fourth, as the actual effect size of each SNP was much lower than would be required to have 80% power (0.28), our study is underpowered and at risk of type 2 errors, particularly influencing the probability of detecting genotype modification. Finally, our data did not include information on sleep quality, physical- or psychological trauma, which can represent confounders to mental distress and alcohol consumption.

This study reports novel SNP findings and replications linked to both alcohol consumption and mental distress. Lack of previous positive and negative findings can have several causes of which false positives are of particular importance. Furthermore, publication bias, where negative findings have not been published, could also reduce the availability of research on specific SNPs (Munafò et al., 2004). Other causes can be heterogeneity of phenotypic measures. Correcting for multiple comparisons increases confidence in our main finding of *GABRG1* and mental distress in men, as well as bootstrapping confidence intervals to validate associations between nominally significant SNPs and depression and alcohol consumption. In addition, the differences in mental distress detected in our study between genotypes where the mean score is below clinical thresholds (cut-off for diagnosis) but which nonetheless reports the same trend as case-control studies on depression (as in the case for *ANKK1*), support recent GWA studies which find evidence for investigating the genetic architecture of depression by means of broad phenotypes based on symptoms rather than diagnoses (Howard et al., 2019; Okbay et al., 2016).

In conclusion, this study reports a positive association between

mental distress and alcohol consumption in men. It further proposes that genetic variation in $GABA_A$-receptor γ1-subunit could be related to increased mental distress in men, which is a novel finding warranting further investigation. Lastly, it provides replication in a Norwegian population sample of association between mental distress and SNPs in *GABRA2* and *ANKK1* in men and *CHRM2* in women as well as an association of *GABRA2* with alcohol consumption in women.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2021.114257.

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