Association of alcohol consumption with allergic disease and asthma: a multicenter Mendelian Randomization analysis

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Conflicts of interest

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Abstract

Aims: The aims were to use the rs1229984 variant associated with alcohol consumption as an instrument for alcohol consumption to test the causality of the association of alcohol consumption with hay fever, asthma, allergic sensitization, and serum total IgE.

Design: Observational and Mendelian randomization analyses using genetic variants as unbiased markers of exposure to estimate causal effects, subject to certain assumptions.

Setting: Europe.

Participants: We included a total of 466434 persons aged 15–82 years from 17 population-based studies conducted from 1997–2015.

Measurements: The rs1229984 (*ADH1B*) was genotyped, alcohol consumption, hay fever and asthma were self-reported. Specific and total IgE were measured from serum samples.

Findings: Observational analyses showed that ever-drinking vs. non-drinking, but not amount of alcohol intake, was positively associated with hay fever and inversely associated with asthma but not with allergic sensitization, or serum total IgE. However, Mendelian randomization analyses did not suggest that the observational associations are causal. The causal odds ratio (OR) per genetically assessed unit of alcohol/week was an OR=0.91 (95% confidence interval (CI): 0.81, 1.02; p=0.101) for hay fever, an OR=0.90 (95% CI: 0.79, 1.02; p=0.095) for asthma, an OR=0.97 (95% CI: 0.80, 1.17; p=0.763) for allergic sensitization, and a 4.7% change (95% CI: -5.5%, 14.9%; p=0.366) for total IgE.

Conclusions: Ever-drinking vs. not drinking was in observational analyses positively associated with hay fever, and negatively associated with asthma. However, the Mendelian randomization results were not consistent with these associations being causal.

Keywords: Alcohol, allergic disease, allergic sensitization, asthma, hay fever.

Introduction

Alcohol is a strong immune modulating factor (1, 2). Previous observational studies have shown that moderate and excessive alcohol intake is associated with higher serum levels of total immunoglobulin E (IgE) (3-13). Likewise, alcohol consumption in pregnancy is associated with an increase in cord blood IgE levels from the newborn (14). Some epidemiologic studies have found a positive association between alcohol consumption and allergic sensitization (9, 12) but other studies have not (6, 8, 15). Regarding allergic disease, alcohol consumption was positively associated with the risk of developing perennial allergic rhinitis (16), and alcohol consumption during pregnancy may increase the risk of atopic dermatitis in the offspring (17). In addition, alcohol is a trigger of hypersensitivity reactions and can cause asthma in genetically predisposed individuals (18). The possible mechanisms by which alcohol consumption could affect allergic sensitization and levels of total IgE may include a direct effect of alcohol or its metabolites on lymphocyte subsets with subsequent T helper (Th)1/Th2 cytokine imbalance, or an indirect effect due to alcohol-induced permeability of the gut mucosa to endotoxin of other bacterial products (1, 3, 5, 10, 19).

Causal inference from conventional epidemiologic studies between alcohol consumption and allergic respiratory disease is difficult due to the potential confounding and reverse causation. Mendelian randomization examines causality by using genetic variants, typically single nucleotide polymorphism (SNP), as instruments for exposures. It assumes random allocation of genes from parents to offspring and no direct association between genotype and outcome and will not be associated with the confounding factors that are inherent in conventional observational studies. The enzyme alcohol dehydrogenase (ADH) oxidizes alcohol to acetaldehyde. The more active forms of this enzyme are protective against drinking, because they cause higher levels of acetaldehyde. In European samples, the rs1229984 variant in the *ADH1B* gene is most strongly associated with alcohol phenotypes, and the protective A-allele frequency is approximately 2–5% in

Europeans (20). The rs1229984 has previously been used as instrument for alcohol consumption in Mendelian randomization studies to examine the effect of alcohol consumption in cardiovascular disease (20).

Persons sensitized to inhalant allergens as, measured by serum specific immunoglobulin E (IgE), are at risk of developing allergic respiratory disease. Serum specific IgE positivity to inhalant allergens are an accepted objective tests of allergic respiratory disease in clinical assessment and in epidemiological studies. The aims were to use the rs1229984 variant as an instrument for alcohol consumption to test the causality of the association of alcohol consumption with 1) hay fever, 2) asthma, 3) allergic sensitization, and 4) serum total IgE, in a Mendelian randomization meta-analysis of 466434 participants across 17 studies. We examined the effects for ever-drinkers and non-drinkers separately.

Methods

Design

We performed multicenter traditional observational and Mendelian randomization analyses to determine whether alcohol consumption causally affects allergic respiratory disease, and asthma, and estimate the magnitude of the associations.

Study populations

We included 466434 participants (including 98786 cases of hay fever, 53796 cases of asthma, and 6053 cases of allergic sensitization) of self-reported or genetically determined European ancestry aged ≥16 years from the following 17 studies: The British 1958 birth cohort (1958 BC), Copenhagen City Heart Study (CCHS), the Danish Monitoring of trends and determinants in Cardiovascular Diseases (MONICA) Study (the Dan-Monica10 Study), the Allergy98 Study,

Genomics of Overweight Young Adults (GOYA) Males, the Health2006 Study, the Inter99 Study, the Cooperative Health Research in the Region of Augsburg (KORA) Study, the MRC National Survey of Health and Development (NSHD) Study, the 1936 Cohort, the UK Biobank, the Netherlands Epidemiology of Obesity (NEO) Study, the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), the Rotterdam Study, the Studies of Health in Pomerania (SHIP and SHIP TREND), and the DanFunD Study. Further details of these studies are provided in online Supplementary Material and Supplementary Tables S1-S4.

Measures

Genotype

Rs1229984 is located in the alcohol dehydrogenase 1B gene (*ADH1B*). It encodes the ADH1B enzyme that is the main metabolizer of alcohol (20). Due to the low prevalence of the rs1229984 A-allele, we recoded the genetic variant according to a dominant model into major homozygotes (alcohol-increasing genotype) vs. heterozygotes and minor homozygotes combined (alcohol-decreasing genotypes). Description of the method for genotyping within each study is provided in supplementary material. Genotype frequencies and Hardy-Weinberg equilibrium levels are shown in Table S3. The minor allele frequency ranged from 0.008–0.070 across studies. The SNP was directly genotyped in each study, except for the DanFunD study, KORA, the 1936 Cohort, the Rotterdam study, and the NEO study (Supplementary Material).

Hay fever, asthma, allergic sensitization, lung function, and serum total IgE

Data on hay fever and asthma were obtained from interviews or questionnaires according to Supplemental Table S4. Our first choice of definition/diagnosis was lifetime/ever, but if not available we used a diagnosis in the past 12 months or longer (Table S4). Allergic sensitization was

defined by serum specific IgE positivity to at least one of the tested inhalant allergens (Table S4). We used the cut-offs for positivity generally recommended by the manufacturer. Serum total IgE was measured by a number of assays as detailed in Supplementary Material and Table S2 and S4.

Alcohol intake

We used self-reported alcohol status (non-drinker or ever-drinker) and units of alcohol consumed per week (either by interview or questionnaire), reported at the same time or as close as possible to the assesment of allergic respiratory disease (see Supplementary Material).

Statistical analyses

Statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA), STATA, version 12 (StataCorp, College Station, TX, USA), the statistical software R, version 3.3.3 (http://www.r-project.org/), and Quanto, version 1.2 (University of Southern California, US). The p-values are two-tailed, and statistical significance was defined as $P<0.05$. Serum total IgE was log-transformed in the regression analyses to fulfill requirements on normality.

With an assumed protective allele frequency of 2% for the rs1229984 genotype, we calculated the required number of cases and controls among ever-drinkers in Quanto 1.2 (University of Southern California, US) for a range of effect sizes prior to the study. For example, with a power of 0.80 we would need approximately 6000 and 18000 ever-drinkers with and without hay fever, respectively, to detect an odds ratio of 0.85 and 14000 and 42000 ever-drinkers with and without hay fever, respectively, to detect an odds ratio of 0.90 among carriers of the protective allele compared to non-carriers. Likewise, for the natural logarithm of serum total IgE (mean=3.4 and standard deviation=1.5) as outcome, we would need approximately 40000 ever-drinkers to detect an R^2=0.0002/ß=-0.10 for carriers vs. non-carriers of the protective allele. The sample size needed to

estimate an effect on, e.g., hay fever per genetically determined drink of alcohol with a power of 0.8, type 1 error rate og 0.05, variance in amount of alcohol explained by the SNP of 0.0045, and an OR=1.3 of hay fever per standard deviation of amount of alcohol, was calculated to be N=293025 (21).

The study was performed as a multicenter meta-analysis. We provided the study representatives with an invitation to contribute to the study, an analysis protocol, and a Stata-script to be used in the analyses. The study results were combined in random effects meta-analyses. Participants with missing value in one or more variables were excluded. Analyses were performed in all participants and in strata defined by alcohol status. The main analyses were performed in ever-drinkers. The analyses were adjusted for age, gender, and genetic principal components if available (British 1958 Birth Cohort, the NEO study, and the UK Biobank).

First, observational analyses of the associations of alcohol status and intake with hay fever, asthma, allergic sensitization, and serum total IgE were assessed by logistic and linear regression analyses. Second, Mendelian randomization analyses were performed. The associations of the alcohol-associated SNP and alcohol status, alcohol intake, hay fever, asthma, allergic sensitization, and serum total IgE were assessed using linear and logistic regression. The estimates from each study were meta-analyzed using the 'metan' command in Stata. Heterogeneity was examined by the I^2 statistic. The instrumental variable (IV) analyses were performed by the "MendelianRandomization" package in R using the inverse variance-weighted method ("mr_ivw"), similar to the ratio method for a single IV. These were performed regardless of statistical significance to show the size of the estimates.

Since the primary definition of hay fever in the UK Biobank also included eczema, we performed additional analyses using different definitions (See Supplementary). A part of the UK Biobank Study, the UK Biobank Lung Exome Variant Evaluation (UK BiLEVE) study, was

sampled according to lung function and smoking status, and we performed sensitivity analyses excluding this study (See Supplementary). Analyses including UK Biobank data and 1958 BC where the alcohol genotype was directly genotyped, and adjustments were made for principal components are shown in Supplementary Figures S1–S5.

Results

Descriptive statistics for each of the study populations are shown in Table 1 and Supplementary Table S1. Minor allele frequencies and Hardy Weinberg Equilibrium p-values are shown in Supplementary Table S3. There was a statistically significant positive association between the rs1229984 genotype (major homozygotes vs. minor homozygotes and heterozygotes) and higher alcohol intake (logarithmically transformed) (Figure 1).

Observational analysis

Ever-drinking, but not alcohol intake, was positively associated with hay fever. Ever-drinking, but not alcohol intake, was inversely associated with asthma (Figure 2). The observed associations of ever-drinking with hay fever and asthma, respectively, were rather consistent across studies (Supplementary Figures S6–S7). For alcohol intake and hay fever and asthma, there was some heterogeneity across studies (Supplementary Figures S10–S11). Ever-drinking and alcohol intake were positively, though ever-drinking statistically non-significantly, associated with allergic sensitization (Figure 2), with low heterogeneity across studies (Supplementary Figures S8 and S12). The number of participants in the analyses of allergic sensitization was substantially lower (N=19443–21213, Figure 2) than for hay fever and asthma. Intake of alcohol, but not ever-drinking, was significantly associated with increasing serum total IgE and log(total IgE) (Figure 3).

Mendelian randomization analysis

The rs1229984 genotype associated with higher alcohol intake (major homozygotes vs. minor homozygotes and heterozygotes) was not significantly associated with hay fever, asthma, allergic sensitization, or log(total IgE) in ever- or non-drinkers (Supplementary Figure S2–S5).

The estimate for the first stage regression (SNP-exposure) among ever-drinkers (calculated in the UK Biobank data) was β=1.324 (standard error (SE)=0.086, N=292158) units of alcohol for alcohol-increasing genotype vs. alcohol-decreasing genotypes. The estimates for the second stage regressions (SNP-outcome) were as follows: hay fever β= -0.130 (SE=0.079); asthma β= -0.144 (SE=0.086); allergic sensitization β= -0.038 (SE=0.128); and log(total IgE) β=0.062 (SE=0.069).

There was no clear evidence that genetically assessed intake of alcohol was associated with risk of hay fever, asthma, or allergic sensitization. The causal estimates, per unit of alcohol consumed, were an OR=0.907 (95% CI: 0.806,1.019; p=0.101) for hay fever, an OR=0.897 (95% CI: 0.790, 1.019; p=0.095) for asthma, and an OR=0.971 (95% CI: 0.804, 1.174; p=0.763) for allergic sensitization.

Genetically assessed higher alcohol intake was not associated with total IgE (Figure 3). The causal estimate of log(total IgE) for ever-drinkers was β=0.047 (95% CI: -0.055, 0.149; p=0.366) per unit of alcohol, which reflects an approximate 4.7% change (95% CI: -5.5%, 14.9%; p=0.366) in total IgE per unit of alcohol consumed (Figure 3).

Analyses including UK Biobank data and 1958 BC where the alcohol genotype was directly genotyped, and adjustments were made for principal components (Supplementary Figures S1–S5) let to similar conclusions.

The primary definition of hay fever in UK Biobank suggested an OR=0.987 (95% CI: 0.952, 1.023, p=0.474, N=394883) for ever-drinkers with alcohol increasing genotype. Using self-

reported hay fever medication as alternative definition of hay fever (see Supplementary Material) suggested an OR=0.977 (95% CI: 0.876, 1.089, p=0.671, N=394883). Using self-reported hay fever classified as serious illness as alternative definitions of hay fever suggested an OR=1.011 (95% CI: 0.934, 1.093, p=0.793, N=394883). Hay fever in UK Biobank without the UK Biobank Lung Exome Variant Evaluation (UK BiLEVE) study (22) (see Supplementary Material) suggested an OR= 0.984 (95% CI: 0.947, 1.022, p=0.398, N=351833).

Asthma in the UK Biobank without BiLEVE suggested an OR=0.989 (95% CI: 0.939, 1.041, p=0.666, N=351833), whereas asthma in the entire UK Biobank suggested an OR= 0.995 (95% CI: 0.949, 1.044, p=0.845, N=394883) for the alcohol increasing genotype.

Discussion

We found that ever-drinking was observationally positively associated with hay fever and inversely associated with asthma, but there was no clear evidence of association with allergic sensitization or total IgE, and in Mendelian randomisation analyses, genetically assessed intake of alcohol was not associated with hay fever, asthma, allergic sensitization, or serum total IgE, suggesting that the observational associations are not causal.

Oldenburg et al found that alcohol feeding decreased airway hyper-responsiveness and allergic airway inflammation in allergic mice, suggesting that there may be an important role for alcohol in the modulation of asthma (23). Few studies have examined the possible bronchodilator effect of alcohol in humans (24, 25). Ayres et al found that intake of 40 ml of sherry was consistent with an increase in peak expiratory flow rate in 19 patients with asthma but not in 16 controls (25). This bronchodilation was more marked in patients with peak flow rate less than 50% of the predicted rate. Lieberoth et al found that alcohol intake was associated with incident asthma in adults with a U-shaped association where the lowest risk of asthma was observed in the group

with a moderate intake of alcohol (26). There is evidence that acetaldehyde increases histamine release from mast cells in both animal and human studies (10). In Japanese populations, in which a genetic variant causing high levels of acetaldehyde is very common, alcohol is in these genetically predisposed individuals accompanied by bronchoconstriction and flushing (alcohol-induced asthma and Oriental flushing) following alcohol intake. Whether the alcohol-induced Th2-skewing of the human immune response is mediated trough acetaldehyde is not fully known.

A study by Siu et al found that light to moderate alcohol drinkers had better lung function than abstainers did. This was independent of smoking and evident lung or heart disease suggesting that drinking moderate amounts of alcohol may benefit lung function (27). Frantz et al found that alcohol and heavy drinking in particular had a negative effect on lung function in smokers (28). However, Sparrow et al found that alcohol consumption was not associated with baseline or follow-up levels of FEV1 or FVC in 1,067 men (29).

Several cross-sectional studies have reported a positive association between alcohol intake and allergic sensitization (9, 11, 12). However, Assing et al found no association between alcohol intake and skin prick test positivity among 1668 students (8). The association between alcohol intake and incident allergic sensitization in cohort studies is even more controversial (6, 15). In a study of 5870 women aged 20–29 years, Bendtsen et al (16) found that self- reported alcohol consumption was positively associated with the risk of developing perennial allergic rhinitis but not seasonal allergic rhinitis. The association of moderate and excessive alcohol intake with higher serum levels of total IgE is more consistent (4-6, 9, 12, 13). A high consumption of alcohol may also increase IgE sensitization to cross-reactive carbohydrate determinants, and specific IgE results should be interpreted with caution in heavy alcohol drinkers (30). In addition, experimental alcohol administration to rodents induces an increase of serum IgE concentrations (19). Moreover, cessation of alcohol consumption in heavy drinkers is shortly followed by a decrease of serum IgE

concentrations (4, 13). In a Mendelian Randomization study of 111,408 persons from the general population, Nordestgaard et al found that genetically assessed higher alcohol intake was positively associated with total IgE (but not with allergic disease) (31).

In accordance with previous studies, we found that the rs1229984 was strongly associated with drinking status and alcohol intake which shows that rs1229984 is well-suited as a genetic instrument of alcohol intake (20). We used a standardized analytical protocol to increase reliability and robustness of the findings. To avoid confounding by population stratification, we included Europeans only and adjusted for population structure using principal components when possible. Since this covered most of the participants, we regard confounding by stratification to be of minor concern. We used objective markers of allergic sensitization, serum total IgE and lung function which may be more reliable than self-reported measures in certain situations. Using Mendelian randomization has several shortcomings, e.g., the observational analysis of ever versus never drinkers cannot be mimicked using this approach. Since the genotype explains only a small part of the variation in alcohol consumption, Mendelian randomization has lower power that traditional observational studies for comparable study sizes, i.e. Mendelian randomization studies need very large samples to be adequately powered. A limitation of the study is the use of mostly self-reported hay fever and asthma rather than clinical diagnoses or measurements. A non-differential misclassification of a binary outcome is likely to attenuate associations towards the null. We also defined alcohol consumption from self-report but the validity compared with alternative measurements has previously been found to be reasonable (32). The hay fever variable in the UK Biobank included eczema. Therefore, we assessed two additional hay fever variables from the UK Biobank with similar results which indicates that the misclassification did not substantially bias our results. The main weaknesses of the additional hay fever variables were the fact that one was measured at follow-up in 2015 and in a subgroup only, limiting the available sample size; and the

other was based on self-reported medication rather than a doctor-diagnosed hay fever. Of note, alcohol intake did not distinguish between, e.g., beer and wine. We may have lacked power to show a similar association between alcohol and serum total IgE. It would be of interest to also study extreme exposure to alcohol, as seen in alcoholics. However, such individuals would also differ more substantially from the rest of the population with regard to potential confounders such as genetics of alcohol dependence and socioeconomic factors. The present study focused on the exposure levels in the normal range and in a population-based setting. It is important to acknowledge that the present study does not investigate effects of exposure to alcohol in childhood, before use of alcohol, and thus only relates to cases of asthma/hay fever that develop after start of alcohol use. However, it is increasingly being recognized that many cases of hay fever and asthma have their onset in adolescence or later in adulthood. Moreover, a factor that exacerbate or influence duration of a disease could also increase the prevalence of disease.

In conclusion, observational analyses found that ever-drinking vs. non-drinking was positively associated with hay fever and inversely with asthma but not with allergic sensitization, and serum total IgE. In contrast, genetic predisposition to consume more alcohol did not affect risk of hay fever, asthma, allergic sensitization, or serum levels of total IgE. The discrepancy of results between observational and Mendelian randomization analyses could be due to potential residual confounding, e.g., by socioeconomic factors or lifestyle factors. Our results challenge the concept of a risk-increasing effect of alcohol consumption on allergic disease and asthma.

Ethics

All the included studies were approved by local ethics committees, and all participants gave their informed consent.

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Author contributions

All authors were involved in the conception and design of the study or the collection and processing of samples. TS conducted data analyses and wrote the initial manuscript. All authors were involved in critical appraisal and revision of the manuscript, and all authors approved the final version.

Conflicts of interest

Lies Lahousse reports expert consultation for Boehringer Ingelheim GmbH and Novartis, grants from AstraZeneca and Chiesi, grants and non-financial support from European Respiratory Society and Belgian Respiratory Society, all outside the submitted work. The remaining authors declare that they have no conflicts of interest.

Table 1. Overview of collaborating studies

Study name	**Year**	**N**	**Age**, median (IQR)	**% males**	**Place**
1936-cohort (33)	1976–77	592	60.5 (60.2, 60.8)	47.3	Copenhagen, Denmark
Monica10 (33)	1993–94	2262	52.0 (42.1, 61.9)	49.7	Glostrup, Copenhagen, Denmark
Allergy98 (33)	1997–98	1148	38.0 (28.7, 51.3)	45.6	Western Copenhagen, Denmark
Inter99 (33)	1999–01	4880	45.1 (40.0, 50.2)	49.0	Copenhagen area, Denmark
Health2006 (34)	2006–08	2818	50.0 (40.0, 60.0)	45.0	Copenhagen area, Denmark
DanFunD (35)	2012–15	7093	54 (44, 63)	46.3	Copenhagen area, Denmark
GOYA Males (36)	1992–94	790	46 (41, 53)	100	Copenhagen area, Denmark
1958 BC (37)	2000	2420	42 (42, 42)	52.1	England, Scotland and Wales
KORA (38)	1997–98	1255	49.0 (39.0, 59.0)	49.1	Augsburg, Germany
NEO (39)	2008–12	5557	57.0 (51.0, 61.0)	48.3	Leiden, Netherlands
NSHD (40)	1999	2675	53 (53, 53)	49.9	England, Scotland and Wales
Prosper (41)	1997–99	5504	75.0 (72.4, 77.9)	48.3	Scotland, Ireland, Netherlands
UK Biobank (42)	2006–10	407767	58 (51, 63)	46.0	United Kingdom
Rotterdam (43)	1990–93	7977	62.5 (58.2, 70.5)	43.0	Rotterdam, Netherlands
SHIP (44)	1997–01	3725	50.0 (36.0, 62.0)	48.7	West Pomerania, Germany
SHIP TREND (45)	2008–12	986	50.0 (40.0, 61.0)	43.8	West Pomerania, Germany
CCH (46)	1991–94	8985	60.5 (47.8, 70.3)	44.3	Copenhagen area, Denmark

Abbreviations: Allergy98, Copenhagen Allergy study; 1958 BC, British 1958 Birth Cohort; CCH, Copenhagen City Heart Study; GOYA, Genomics of extremely Overweight Young Adults; Inter99, Intervention 1999; IQR, interquartile range; KORA, Cooperative Health Research in the Region of Augsburg; NEO, Netherlands Epidemiology of Obesity; NSHD, National Survey of Health and Development; SHIP, Study of Health in Pomerania.

Figure 1.
Random effects meta-analysis of the associations between the rs1229984 genotype (major homozygotes vs. minor homozygotes and heterozygotes) and the logarithm transformed alcohol intake (see heterogeneity in Supplementary Figure 1). Abbreviations: Allergy98, Copenhagen Allergy study; 1958 BC, British 1958 Birth Cohort; CCH, Copenhagen City Heart Study; Inter99, Intervention 1999; NEO, Netherlands Epidemiology of Obesity; NSHD, National Survey of Health and Development; SHIP, Study of Health in Pomerania.

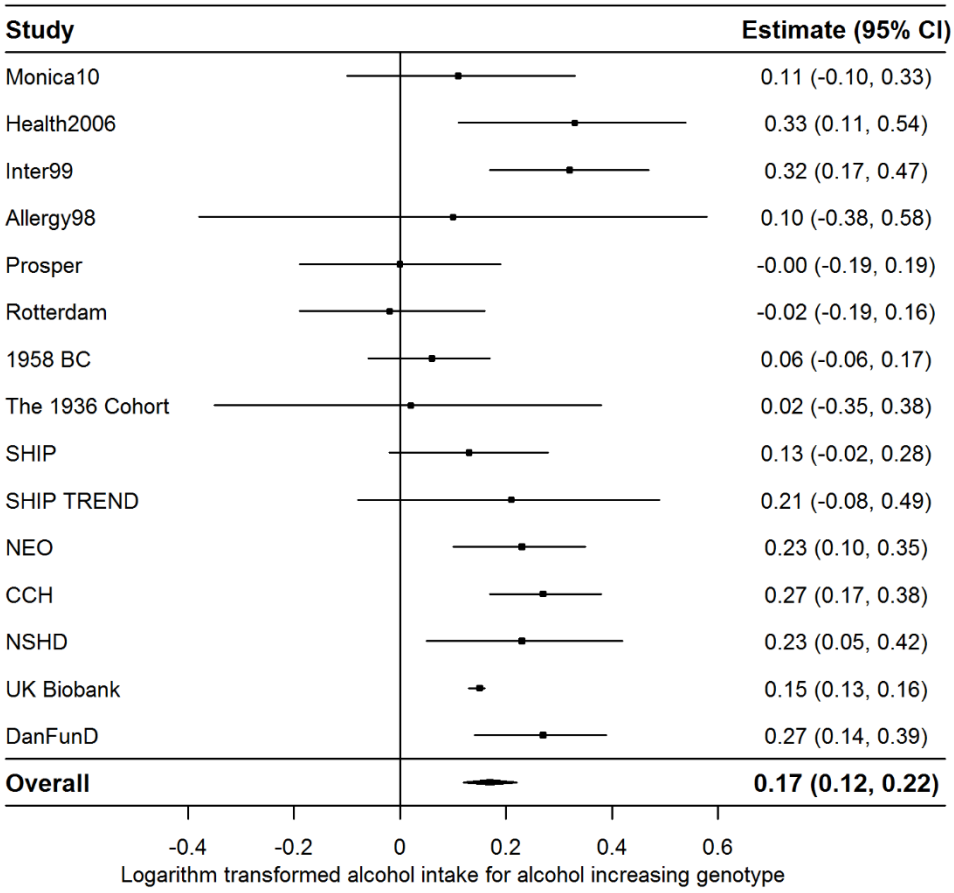


Figure 2.
Random effects meta-analyses of observational and instrumental variable estimates of the sex- and age-adjusted associations of alcohol status and -intake and genetically assessed alcohol intake, respectively, and hay fever, asthma, and allergic sensitization (see heterogeneity in Supplementary Figure 2–4 and 6–8). Numbers in the instrumental variable analyses refer to SNP-exposure and SNP-outcome associations, respectively. Abbreviations: CI, confidence interval.

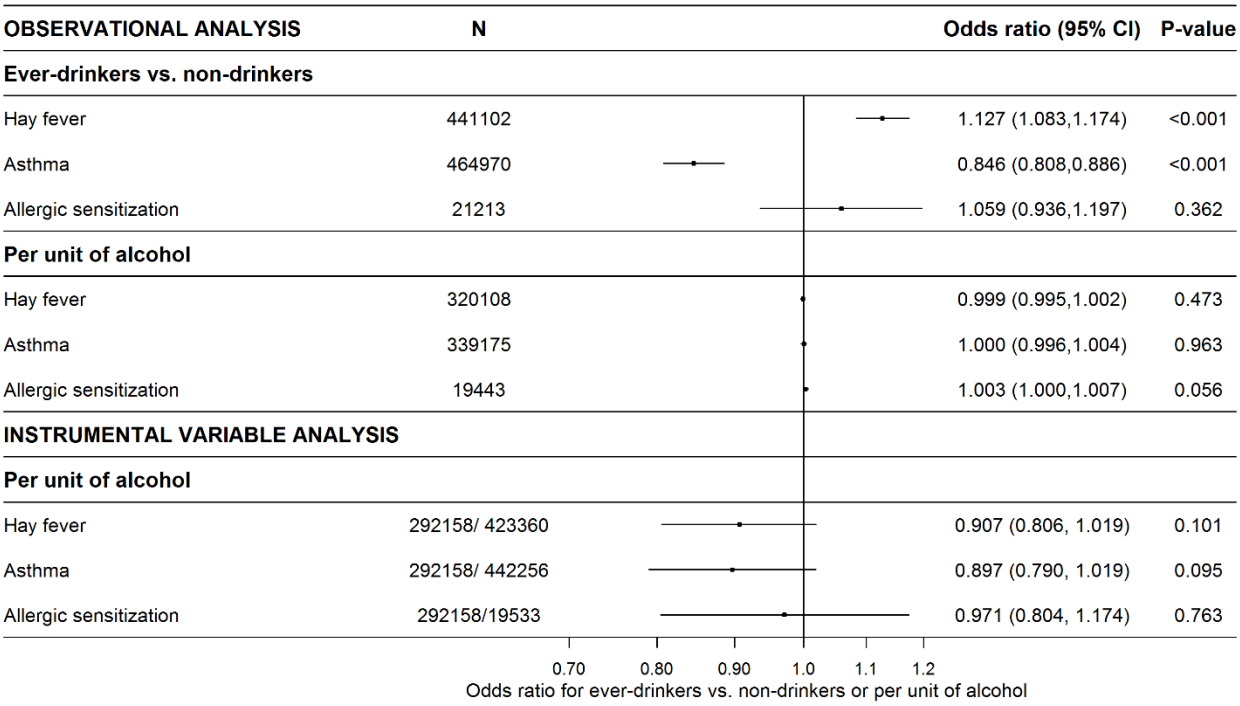
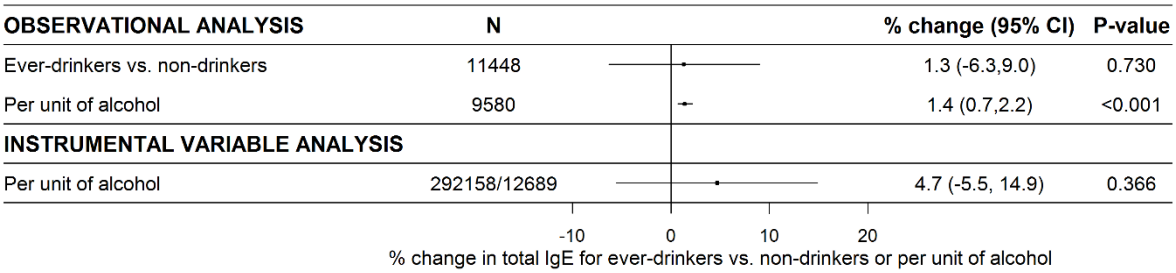


Figure 3.
Random effects meta-analyses of observational and instrumental variable estimates of the sex- and age-adjusted and sex-stratified associations of alcohol status and -intake and genetically assessed alcohol intake, respectively, and serum total IgE (see heterogeneity in Supplementary Figure 5 and 9). Numbers in the instrumental variable analyses refer to SNP-exposure and SNP-outcome associations, respectively. Abbreviations: CI, confidence interval; IgE, immunoglobulin E.



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