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A phenome-wide Mendelian randomization analysis reveals the genetical associations of myocardial infarction, angina pectoris and Alzheimer's disease with lung cancer

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Lung cancer is a complex disease with varying subtypes. The genetic architectures and risk factors that are similar or distinct among these subtypes remain unclear. In this work, Genome-wide association studies (GWAS) conducted by the International Lung Cancer Consortium and transdisciplinary Research in Cancer of the Lung were utilized to illustrate the genetic landscapes of different subtypes of lung cancer. GWAS of 942 phenotypes from UK Biobank and 902 phenotypes from FinnGen Biobank were analyzed to identify the genetic risk factors specific or common to each subtype of lung cancer through two sample Mendelian randomization inverse variance weighting method. Multivariable Mendelian randomization was employed to assess the true causals of lung cancer. We found that lung cancer, small cell lung carcinoma, squamous cell lung cancer and lung adenocarcinoma shared similar, yet varied genetic architectures. Genetic risk loci at 15q25 were identified in all types of lung cancer. Yet, genetic risk loci at 5p15 were observed in squamous cell lung cancer and lung adenocarcinoma, but not in small cell lung carcinoma. Out of 942 phenotypes from UK Biobank, smoking, time spent watching television, age first had sexual intercourse, alcohol usually taken with meal and age at first live birth were common risk factors for all types of lung cancer. Moreover, out of 902 traits in FinnGen Biobank, chronic obstructive pulmonary disease (COPD) was positively associated with small cell lung carcinoma, squamous cell lung cancer and lung adenocarcinoma. Angina pectoris and myocardial infarction were negatively associated with lung cancer, squamous cell lung cancer and lung adenocarcinoma. And Alzheimer's disease was negatively associated with lung cancer, small cell lung carcinoma and squamous cell lung cancer. In further weighted median and weighted mode methods, myocardial infarction, angina pectoris and Alzheimer's disease also had genetical associations with lung cancer or its subtypes. Even, considering factors such as smoking, COPD, and other risk factors together, myocardial infarction, angina pectoris and Alzheimer's disease retained the genetical associations with lung cancer and its subtypes. Overall, in a phenome-wide Mendelian randomization analysis, our results have highlighted both similar and distinct risk factors among different subtypes of lung cancer. Additionally, our findings have provided genetic associations linking myocardial infarction, angina pectoris and Alzheimer's disease with lung cancer or its various subtypes.

Keywords Lung cancer, Myocardial infarction, Angina pectoris, Alzheimer's disease, Mendelian randomization, Genome-wide association studies

Abbreviations

GWAS	Genome-wide association studies
SNPs	Single-nucleotide polymorphisms

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BMI	Body mass index
IEU	Integrative Epidemiology Unit
ILCCO	International Lung Cancer Consortium
TRICL	Transdisciplinary Research in Cancer of the Lung
IVW	Inverse variance weighting
STROBE-MR	The strengthening the reporting of observational studies in epidemiology using Mendelian Randomization
COPD	Chronic obstructive pulmonary disease
OR	Odd ratio
CI	Confidence interval

Lung cancer is one of the most commonly diagnosed cancer, with an incidence of 11.4% worldwide[1–3]. Lung cancer is one of leading cause of cancer related mortality, accounting for about 18% of all cancer-related deaths[4]. Despite improvements of treatments have been made in past few years, the 5-year survival of lung cancer is still less than 20%[5]. Therefore, it is essential to determine the risk factors that could help to decrease the incidence of lung cancer. Smoking is a significant conventional risk factor for lung cancer. Other nontobacco factors include air pollution, occupational exposure, chronic lung disease and infection[5]. However, the observational results can be confounding and biased. Therefore, determining the impacts of those risk factors on lung cancer is urgently needed.

Except for tobacco or nontobacco factors, the heritability of lung cancer is estimated at 18%[6]. Large-scale genome-wide association studies (GWAS) have identified over 400 lung cancer susceptibility single-nucleotide polymorphisms (SNPs), including variants of the CHEK2, TP53 and TERT genes[7–9]. Using these GWAS datasets, Mendelian randomization analysis has been utilized to investigate the genetical associations between smoking and lung cancer[10]. Additionally, consumption of alcohol[11], education[12], age at first birth[13], body mass index (BMI)[10], obesity[14], time spent watching television[15], sleep trait insomnia[16] and membranous nephropathy[17] have all been found to be genetically associated with lung cancer. Furthermore, Mendelian randomization analysis has been used to determine the associations of gut microbiota[18], human serum metabolites[19], circulating inflammatory cytokines[20] and plasma proteins[21] with the development of lung cancer. These findings offer valuable insights into the genetic susceptibility of lung cancer and indicate that Mendelian randomization analysis is a reliable method for identifying risk factors associated with lung cancer.

However, lung cancer is a complex and heterogeneous disease, which includes small cell lung cancer and non-small cell lung cancer[22]. Non-small cell lung cancer accounts for about 85% of all lung cancer and could be further divided into lung adenocarcinoma, lung squamous cell carcinoma and large cell carcinoma[23]. Striking differences in epidemiological and molecular characteristics have been identified among different subtypes of lung cancer[24]. Each subtype of lung cancer also demonstrates different clinical outcomes and drug response[25,26]. Additionally, there is significant heterogeneity in genetic susceptibility loci and risk factors across various histological subtypes of lung cancer[27]. For example, BMI is a risk factor for lung squamous cell carcinoma and for small cell lung cancer, but not for lung adenocarcinoma[14]. These inconsistent findings underscore the complexity of lung cancer and suggest that the relationships between risk factors and lung cancer should be investigated within each pathologic subtype.

In this study, we conducted a phenome-wide Mendelian randomization analysis using GWAS data from UK Biobank and FinnGen Biobank to identify genetic risk factors for lung cancer, small cell lung cancer, lung adenocarcinoma, and lung squamous cell carcinoma. Our results confirmed the genetic associations of smoking, alcohol consumption, and age at first birth with these types of lung cancer. Additionally, our findings revealed for the first time the genetical associations with of myocardial infarction and angina pectoris on lung cancer, lung squamous cell carcinoma, and lung adenocarcinoma, as well as the associations with of Alzheimer's disease on lung cancer, small cell lung cancer, and lung squamous cell carcinoma.

Materials and methods

Selection of lung cancer for outcome

The summary GWAS of lung cancer, small cell lung carcinoma, squamous cell lung cancer and lung adenocarcinoma was publicly available in Integrative Epidemiology Unit (IEU) Open GWAS Project (https://gwas.mrcieu.ac.uk/) with GWAS ID ebi-a-GCST004748, ieu-a-966, ieu-a-985, ieu-a-987, ebi-a-GCST004746, ieu-a-988, ebi-a-GCST004750, ieu-a-967, ieu-a-989, ebi-a-GCST004744, ieu-a-965, ieu-a-984, finn-b-C3_SCLC, finn-b-C3_SCLC_EXALLC, finn-b-C3_LUNG_NONSMALL, finn-b-C3_LUNG_NONSMALL_EXALLC, finn-b-C3_NSCLC_SQUAM, finn-b-C3_NSCLC_SQUAM_EXALLC, finn-b-C3_NSCLC_ADENO and finn-b-C3_NSCLC_ADENO_EXALLC. The consortium, sample size and number of SNPs for each GWAS was provided in Table1. Among them, lung cancer ebi-a-GCST004748, small cell lung carcinoma ebi-a-GCST004746, squamous cell lung cancer ebi-a-GCST004750 and lung adenocarcinoma ebi-a-GCST004744 were derived from James D McKay *et.al* study based on European descent[27]. Lung cancer ieu-a-966, squamous cell lung cancer ieu-a-967 and lung adenocarcinoma ieu-a-965 were obtained from International Lung Cancer Consortium (ILCCO)[7–9]. Lung cancer ieu-a-985, ieu-a-987, small cell lung carcinoma ieu-a-988, squamous cell lung cancer ieu-a-989 and lung adenocarcinoma ieu-a-984 were from Transdisciplinary Research in Cancer of the Lung (TRICL) study[8,28]. Moreover, lung cancer finn-b-C3_SCLC, finn-b-C3_SCLC_EXALLC, non-small cell lung cancer finn-b-C3_LUNG_NONSMALL, finn-b-C3_LUNG_NONSMALL_EXALLC, squamous cell lung cancer finn-b-C3_NSCLC_SQUAM, finn-b-C3_NSCLC_SQUAM_EXALLC and lung adenocarcinoma finn-b-C3_NSCLC_ADENO, finn-b-C3_NSCLC_ADENO_EXALLC were obtained from FinnGen Biobank[29].

GWAS ID	Trait	Consortium	Sample size	Number of SNPs
ebi-a-GCST004748	Lung cancer	NA	85,716	7,857,154
ieu-a-966	Lung cancer	ILCCO	27,209	8,945,893
ieu-a-985	Lung cancer	TRICL	40,453	7,877,791
ieu-a-987	Lung cancer	TRICL	85,449	10,439,018
ebi-a-GCST004746	Small cell lung carcinoma	NA	24,108	7,620,430
ieu-a-988	Small cell lung carcinoma	TRICL	23,371	7,438,318
ebi-a-GCST004750	Squamous cell lung cancer	NA	63,053	7,838,805
ieu-a-967	Squamous cell lung cancer	ILCCO	18,313	8,893,750
ieu-a-989	Squamous cell lung cancer	TRICL	62,467	10,341,529
ebi-a-GCST004744	Lung adenocarcinoma	NA	66,756	7,849,324
ieu-a-965	Lung adenocarcinoma	ILCCO	18,336	8,881,354
ieu-a-984	Lung adenocarcinoma	TRICL	65,864	10,345,176
finn-b-C3_SCLC	Small cell lung cancer	FinnGen	218,792	16,380,466
finn-b-C3_SCLC_EXALLC	Small cell lung cancer (ACE)	FinnGen	174,185	16,380,303
finn-b-C3_LUNG_NONSMALL	Non-small cell lung cancer	FinnGen	218,792	16,380,466
finn-b-C3_LUNG_NONSMALL_EXALLC	Non-small cell lung cancer (ACE)	FinnGen	175,633	16,380,305
finn-b-C3_NSCLC_SQUAM	Squamous cell lung cancer	FinnGen	218,792	16,380,466
finn-b-C3_NSCLC_SQUAM_EXALLC	Squamous cell lung cancer (ACE)	FinnGen	174,369	16,380,303
finn-b-C3_NSCLC_ADENO	Lung adenocarcinoma	FinnGen	218,792	16,380,466
finn-b-C3_NSCLC_ADENO_EXALLC	Lung adenocarcinoma (ACE)	FinnGen	174,576	16,380,303

Table 1. Characteristics of the GWAS for lung cancer. *GWAS* genome-wide as association study, *SNPs* single-nucleotide polymorphisms, *ACE* all cancers excluded, *ILCCO* international lung cancer consortium, *TRICL* transdisciplinary research in cancer of the lung, *ACE* all cancers excluded.

Selection of phenotypes from UK Biobank and FinnGen Biobank as exposure

IEU analysis of UK Biobank (ukb-b) was downloaded from IEU Open GWAS Project (https://gwas.mrcieu.ac.uk/), including 2,514 phenotypes. FinnGen Biobank analysis round 5 was downloaded from https://www.finngen.fi website, including 218,792 samples and 2,803 phenotypes[29]. Three steps were carried out to select instrumental variables used for further Mendelian randomization analysis. First, only SNPs with strong associations (*P* value < 5e−08) were selected. Second, SNPs from UK Biobank and FinnGen Biobank were clumped with linkage-disequilibrium threshold of $R^2 < 0.001$ and 10,000 kilobase distance based on European ancestry reference data[30]. Third, F-statistic for each SNP was determined using the "TwoSampleMR" package, and SNPs with F statistic < 10 was deleted. After those selections, 1170 phenotypes from UK Biobank and 902 phenotypes from FinnGen Biobank with at least on instrument were remained.

Mendelian randomization analysis

Lung cancer, small cell lung carcinoma, squamous cell lung cancer and lung adenocarcinoma were used as outcomes. After harmonizing of the exposure and outcome data, genetical associations of 942 phenotypes from UK Biobank and 902 phenotypes from FinnGen Biobank with lung cancer were investigated by Mendelian randomization analysis. Six methods including Inverse variance weighting (IVW), MR-Egger, weighted median, weighted mode, Wald ratio and Simple mode were used to determine the effects between the exposure and outcome. IVW method combines the Wald ratio estimates of all relevant instrumental variables in a fixed-effect meta-analysis model and provides the consistent primary analysis for causality inference of exposure. IVW method is considered the standard and the strongest Mendelian Randomization method[31,32]. So, IVW method was primary used in the scanning step, and then validated using weighted median and weighted mode methods. MR-Egger and IVW methods were applied to determine the heterogeneity and horizontal pleiotropy in the sensitivity analysis. Mendelian randomization analysis and sensitivity analysis were performed using the "TwoSampleMR" package in R software.

Multivariable Mendelian randomization

Multivariable Mendelian randomization analysis was also performed using the "TwoSampleMR" package in R software, taking three or four risk factors from UK Biobank or FinnGen Biobank together to determine the true causals of lung cancer.

Statistical analysis

All the statistical analyses were performed in R software. P values between 0.05 were considered as statistically significant causal associations between the exposure and outcome. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ were shown.

Reporting guidelines and ethics

This study was designed and assessed according to the strengthening the reporting of observational studies in epidemiology using Mendelian randomization (STROBE-MR) guidelines[33,34] (Supplementary File). All the exposure data and outcome data were publicly available without any applications. And no additional ethics approval was needed. We also provided all the GWAS ID used in this study derived from IEU Open GWAS Project (https://gwas.mrcieu.ac.uk/) to facilitate the reproductivity of Mendelian randomization analysis.

Results

Shared genetic architecture among different subtypes of lung cancer

To illustrate the similarities and variations in genetic architectures among different subtypes of lung cancers, GWAS datasets for lung cancer (ebi-a-GCST004748, ieu-a-966, ieu-a-985, and ieu-a-987), small cell lung carcinoma (ebi-a-GCST004746 and ieu-a-988), squamous cell lung cancer (ebi-a-GCST004750, ieu-a-967, and ieu-a-989), and lung adenocarcinoma (ebi-a-GCST004744, ieu-a-965, and ieu-a-984) were collected from the IEU Open GWAS Project (Table 1). Based on a threshold of P value < 1e−03, 2,183 SNPs were commonly associated with lung cancer in the mentioned GWAS datasets, while 7743 SNPs were commonly associated with small cell lung carcinoma, 2617 SNPs with squamous cell lung cancer, and 1284 SNPs with lung adenocarcinoma (Fig. 1A). Interestingly, common genetic risk loci on 15q25 were identified in all four subtypes of lung cancer (Fig. 1B), totaling 230 genetic risk loci (Fig. 1C). Additionally, genetic risk loci on 5p15 were observed in squamous cell lung cancer and lung adenocarcinoma but not in small cell lung carcinoma (Fig. 1B). Furthermore, genetic risk loci on 6p21 were only found in squamous cell lung cancer, not in lung adenocarcinoma (Fig. 1B). These results highlight that while lung cancer, small cell lung carcinoma, squamous cell lung cancer, and lung adenocarcinoma share some similarities in genetic architecture, there are also variations between them.

Identifications of the shared genetic risks for lung cancer and its subtypes using UK Biobank

Since lung cancer, small cell lung carcinoma, squamous cell lung cancer, and lung adenocarcinoma share similar genetic architectures, we speculated that these types of lung cancer also share genetic risk factors. Using GWAS data from 2514 phenotypes in the UK Biobank as exposure, we conducted a phenome-wide Mendelian randomization analysis to identify shared genetic risk factors for lung cancer and its subtypes. Following standard clumping and data harmonizing, genetical associations of 942 traits from the UK Biobank with lung cancer ebi-a-GCST004748, ieu-a-966, ieu-a-985, and ieu-a-987 were investigated. The IVW method in Mendelian randomization analysis revealed that 52 traits were commonly associated with lung cancer in these datasets (Fig. 2). Among them, tobacco smoking (ukb-b-223) and BMI (ukb-b-2303) were conventional genetic risk factors for lung cancer.

Similarly, using small cell lung carcinoma GWAS datasets (ebi-a-GCST004746 and ieu-a-988) as outcomes, it was found that 79 out of 942 traits in the UK Biobank were commonly associated with the risks of small cell lung carcinoma (Fig. 3). Furthermore, when utilizing squamous cell lung cancer GWAS datasets (ebi-a-GCST004750, ieu-a-967, and ieu-a-989) as outcomes, 58 out of 942 traits in the UK Biobank were commonly associated with the risks of squamous cell lung cancer (Fig. 4). In the case of lung adenocarcinoma, using GWAS datasets (ebi-a-GCST004744, ieu-a-965, and ieu-a-984) as outcomes, it was found that 20 traits were commonly associated with the risks of lung adenocarcinoma (Fig. 5).

Interestingly, factors such as pack years adult smoking as proportion of life span exposed to smoking (ukb-b-7460), time spent watching television (ukb-b-5192), age at first sexual intercourse (ukb-b-6591), alcohol consumption during meals (ukb-b-16878), number of cigarettes smoked daily (ukb-b-469), and age at first live birth (ukb-b-12405) were identified as common risk factors for various types of lung cancer, including small cell lung carcinoma, squamous cell lung cancer, and lung adenocarcinoma.

Identifications of the shared genetic risks for lung cancer and its subtypes using FinnGen Biobank

The FinnGen Biobank is a large GWAS dataset that includes 2803 phenotypes. We utilized these phenotypes from the FinnGen Biobank as exposure to identify the genetic risk factors of lung cancer and its subtypes. Following standard clumping and data harmonizing, genetical associations of 902 traits from the FinnGen Biobank with lung cancer and its subtypes were investigated. The IVW method showed that 19 traits out of the 902 traits in the FinnGen Biobank were commonly associated with lung cancer (ebi-a-GCST004748, ieu-a-966, ieu-a-985, and ieu-a-987) (Fig. 6A). Notably, certain heart diseases such as angina pectoris (finn-b-I9_ANGINA) and myocardial infarction (finn-b-I9_MI) were found to have a negative association with lung cancer. Likewise, when using small cell lung carcinoma GWAS datasets (ebi-a-GCST004746 and ieu-a-988) as outcomes, 27 traits from the 902 traits in the FinnGen Biobank were commonly associated with the risks of small cell lung carcinoma (Fig. 6B). In particular, COPD (finn-b-J10_COPD and finn-b-COPD_HOSPITAL) was positively associated with small cell lung carcinoma (Fig. 6B).

Furthermore, out of 902 traits in the FinnGen Biobank, 20 traits were found to be commonly associated with the risks of squamous cell lung cancer (ebi-a-GCST004750, ieu-a-967, and ieu-a-989) (Fig. 7A), while 12 traits were commonly associated with the risks of lung adenocarcinoma (ebi-a-GCST004744, ieu-a-965, and ieu-a-984) (Fig. 7B). Interestingly, COPD (finn-b-COPD_HOSPITAL) was also commonly and positively associated with squamous cell lung cancer and lung adenocarcinoma (Fig. 7A, B). Angina pectoris (finn-b-I9_ANGINA) and myocardial infarction (finn-b-I9_MI) were also commonly and negatively associated with squamous cell lung cancer and lung adenocarcinoma (Fig. 7A, B). However, angina pectoris and myocardial infarction were not genetically associated with small cell lung carcinoma. It is worth noting that there was no common risk factors identified for lung cancer, small cell lung carcinoma, squamous cell lung cancer, and lung adenocarcinoma in the FinnGen Biobank.

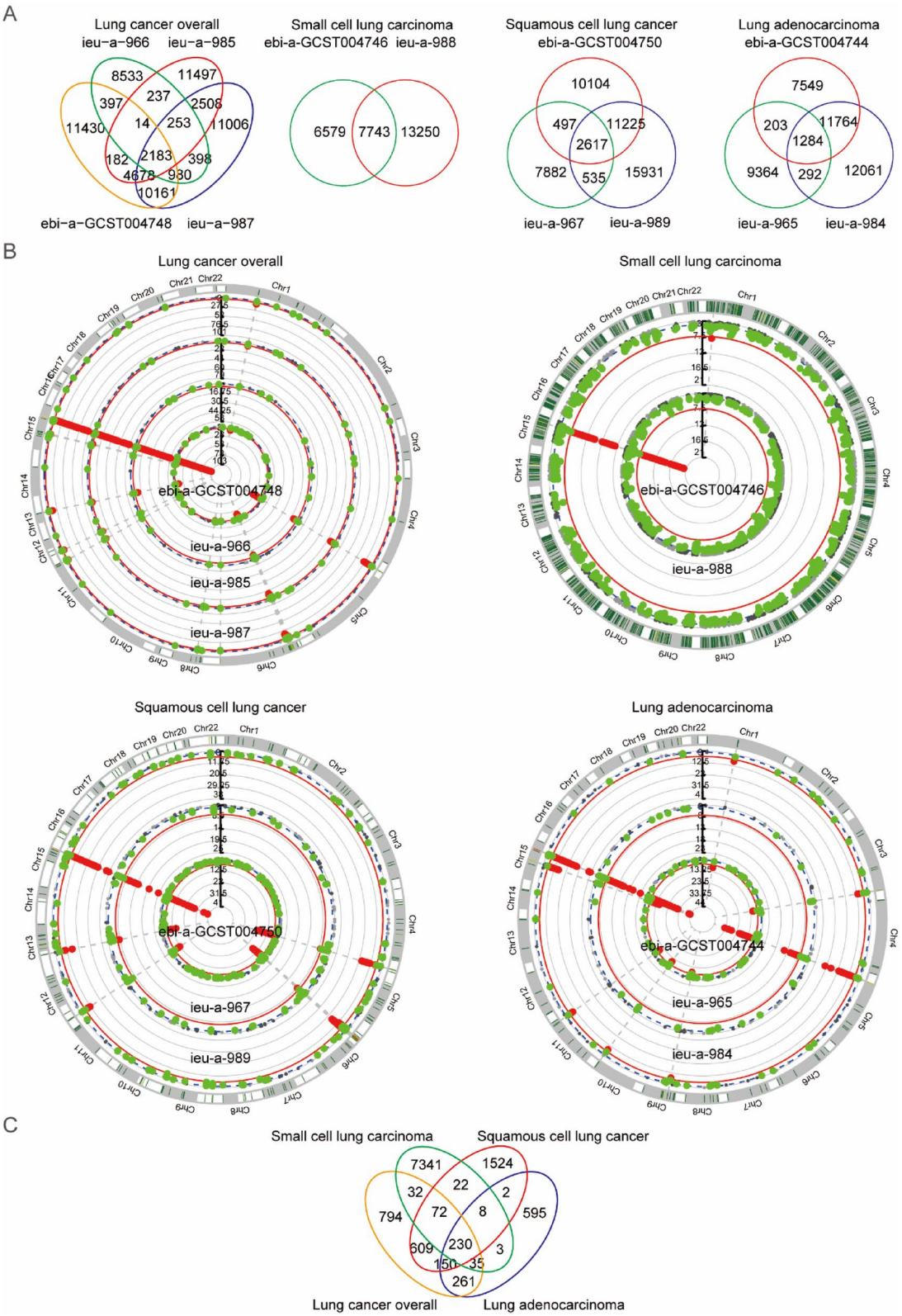

Fig. 1. GWAS meta-analysis of the genetic architectures of lung cancer and its subtypes. (**A**) In ILCCO and TRICL GWAS datasets, common SNPs correlated with lung cancer, small cell lung carcinoma, squamous cell lung cancer or lung adenocarcinoma (*P* value < 1e−03) were showed. (**B**) Manhattan plots illustrated those SNPs in lung cancer, small cell lung carcinoma, squamous cell lung cancer or lung adenocarcinoma as against their respective positions on each chromosome. (**C**) Common SNPs correlated with lung cancer, small cell lung carcinoma, squamous cell lung cancer and lung adenocarcinoma.

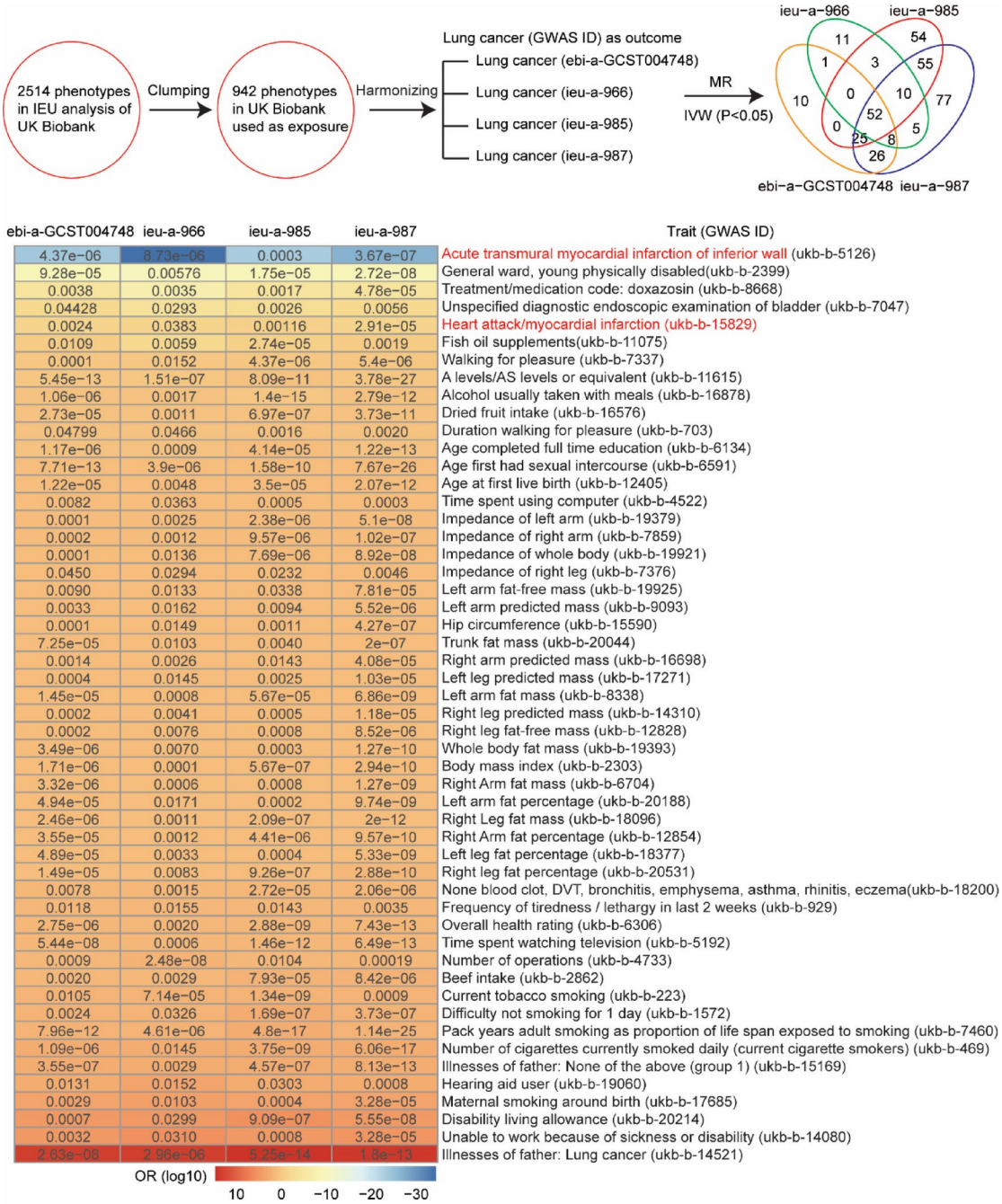

Fig. 2. Genetic risk factors in UK Biobank associated with lung cancer. GWAS of 2514 phenotypes were deposited in UK Biobank. After standard clumping, 942 traits were remained as exposure. The correlations of those 942 traits with lung cancer were determined. The common risk factors in UK Biobank associated with lung cancer (ebi-a-GCST004748, ieu-a-966, ieu-a-985 and ieu-a-987) were illustrated. The odd ratio (OR) and *P* values were determined by IVW method in two sample Mendelian randomization analysis. The number in the heatmap represented the P values and the color represented the OR (log10).

Genetical associations of myocardial infarction and angina pectoris with lung cancer, squamous cell lung cancer and lung adenocarcinoma subtypes

In the UK Biobank, our analysis showed a negative association between myocardial infarction (ukb-b-15829) and lung cancer (Fig. 2). Angina (ukb-b-8650 and ukb-b-8468) as well as myocardial infarction (ukb-b-15829) were also negatively associated with squamous cell lung cancer (Fig. 4). Specifically, acute transmural myocardial infarction of the inferior wall (ukb-b-5126) was found to be most negatively associated with squamous cell lung cancer and lung adenocarcinoma (Figs. 4 and 5). Our analysis in both the UK Biobank and FinnGen Biobank suggested genetical associations of myocardial infarction and angina pectoris with lung cancer, squamous cell lung cancer, and lung adenocarcinoma using the Mendelian randomization IVW method.

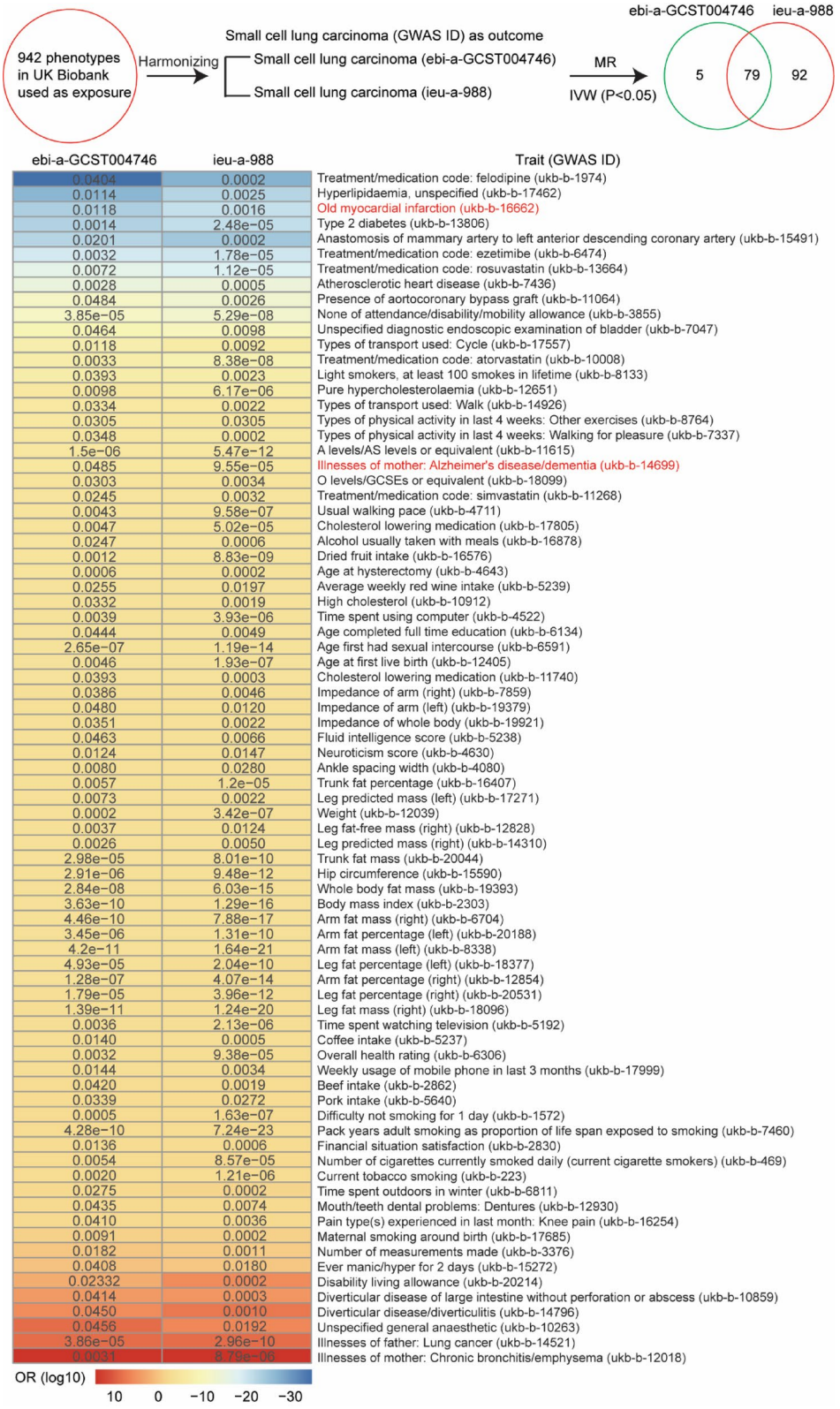

Fig. 3. Genetic risk factors in UK Biobank associated with small cell lung carcinoma. The correlations of 942 traits from UK Biobank with small cell lung carcinoma were determined. The common risk factors in UK Biobank associated with small cell lung carcinoma (ebi-a-GCST004746 and ieu-a-988) were illustrated. The OR and *P* values were determined by IVW method in two sample Mendelian randomization analysis. The number in the heatmap represented the P values and the color represented the OR (log10).

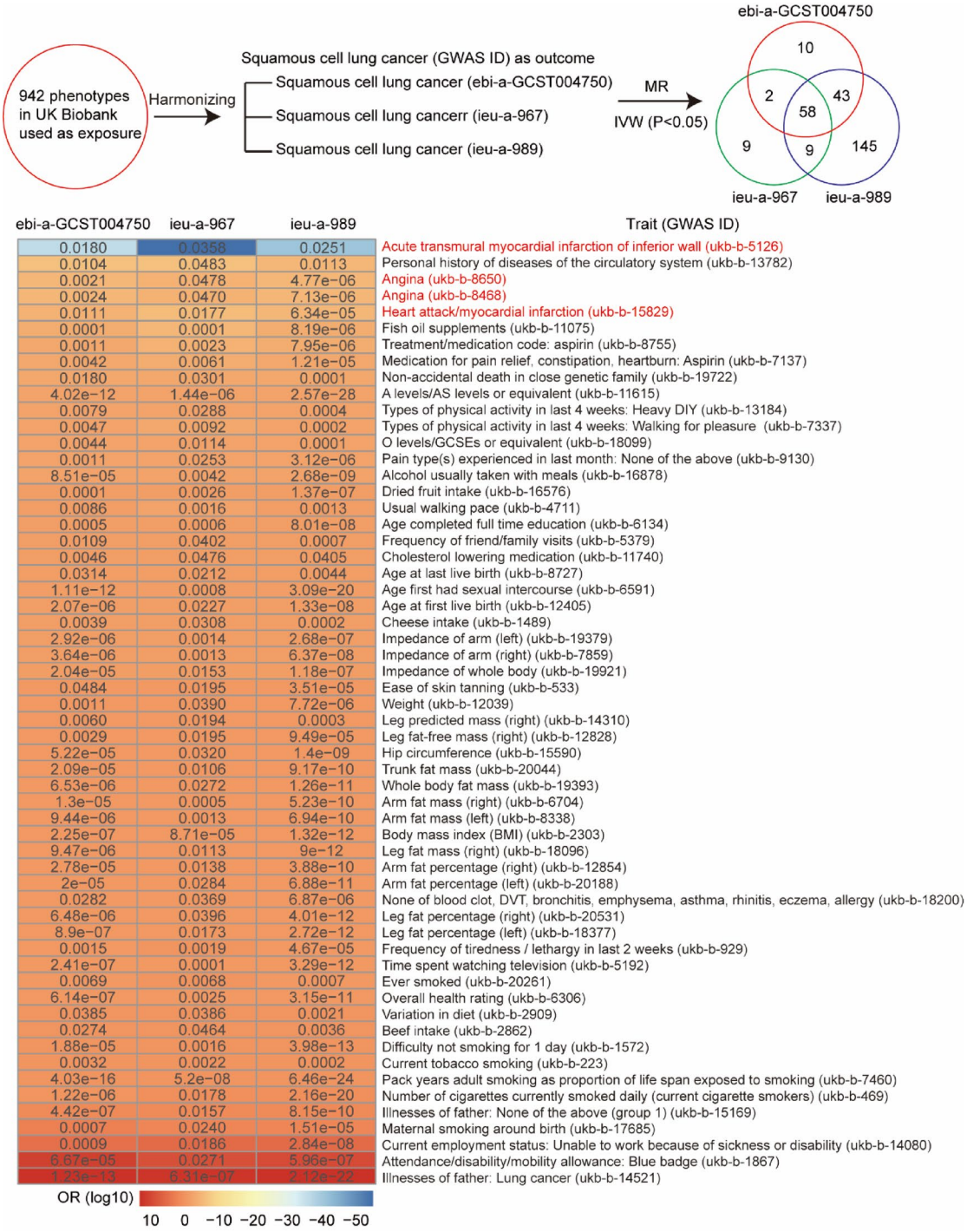

Fig. 4. Genetic risk factors in UK Biobank associated with squamous cell lung cancer. The correlations of 942 traits from UK Biobank with squamous cell lung cancer were determined. The common risk factors in UK Biobank associated with squamous cell lung cancer (ebi-a-GCST004750, ieu-a-967 and ieu-a-989) were illustrated.

Except for the IVW method, the ME Egger method, Simple mode, weighted median, and weighted mode methods were used to determine the genetic risk factors for lung cancer and its subtypes in the UK Biobank and FinnGen Biobank. All of these methods showed similar negative correlations between myocardial infarction (finn-b-I9_MI) and lung cancer (ebi-a-GCST004748, ieu-a-966, ieu-a-985, and ieu-a-987), squamous cell lung cancer (ebi-a-GCST004750, ieu-a-967, and ieu-a-989), and lung adenocarcinoma (ebi-a-GCST004744, ieu-a-965, and ieu-a-984) as shown in scatter plots (Fig. 8A). Similarly, angina pectoris (finn-b-I9_ANGINA) also displayed similar negative correlations with lung cancer, squamous cell lung cancer, and lung adenocarcinoma in scatter plots (Fig. 8B).

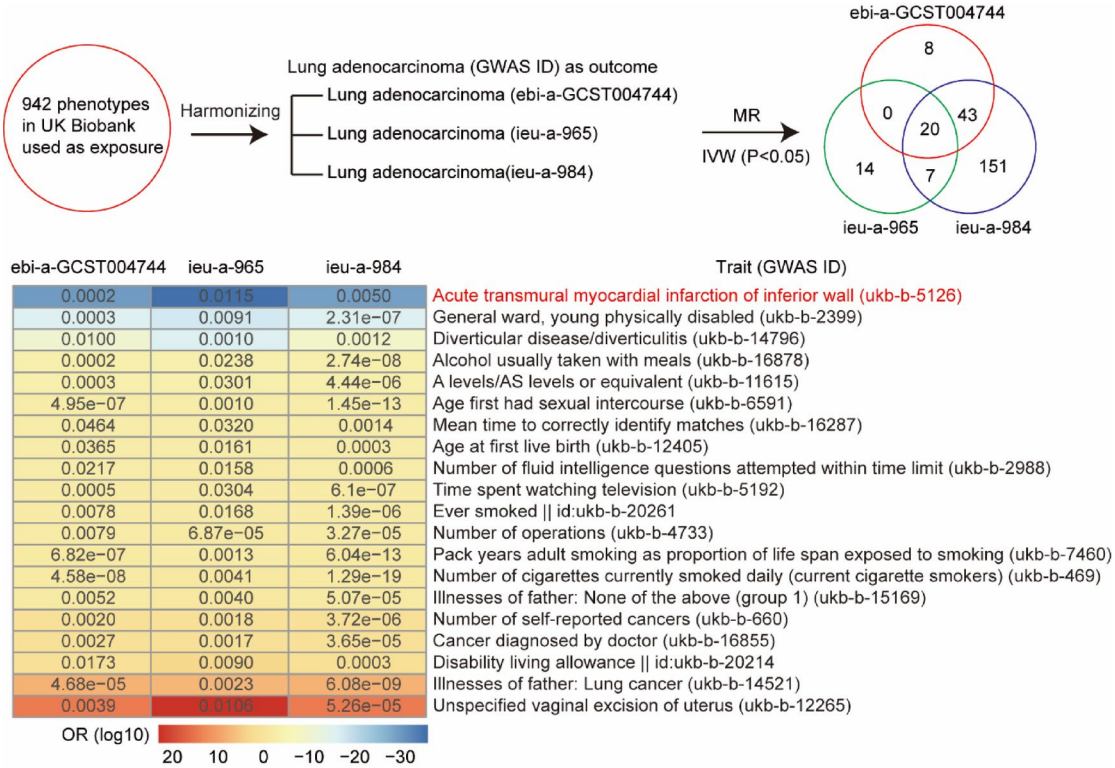

Fig. 5. Genetic risk factors in UK Biobank associated with lung adenocarcinoma. The correlations of 942 traits from UK Biobank with lung adenocarcinoma were determined. The common risk factors in UK Biobank associated with lung adenocarcinoma (ebi-a-GCST004744, ieu-a-965 and ieu-a-984) were illustrated.

The detailed results of weighted median and weighted mode methods in the associations of myocardial infarction with lung cancer, small cell lung carcinoma and lung adenocarcinoma were further showed. Myocardial infarction (finn-b-I9_MI) was negatively correlated with lung cancer (ebi-a-GCST004748, ieu-a-966, ieu-a-985 and ieu-a-987), squamous cell lung cancer (ebi-a-GCST004750, ieu-a-967 and ieu-a-989) and lung adenocarcinoma (ebi-a-GCST004744 and ieu-a-984) in the Mendelian randomization weighted median method (Fig. 8C). Furthermore, myocardial infarction (finn-b-I9_MI) was negatively correlated with lung cancer (ebi-a-GCST004748, ieu-a-966, ieu-a-985 and ieu-a-987), squamous cell lung cancer (ieu-a-967) and lung adenocarcinoma (ebi-a-GCST004744 and ieu-a-984) in the weighted mode method (Fig. 8C). Similarly, angina pectoris (finn-b-I9_ANGINA) was negatively correlated with lung cancer (ebi-a-GCST004748, ieu-a-966, ieu-a-985 and ieu-a-987), squamous cell lung cancer (ebi-a-GCST004750, ieu-a-967 and ieu-a-989) and lung adenocarcinoma (ebi-a-GCST004744 and ieu-a-984) in weighted median method (Fig. 8D). And angina pectoris (finn-b-I9_ANGINA) was negatively correlated with lung cancer (ebi-a-GCST004748, ieu-a-966, ieu-a-985 and ieu-a-987), squamous cell lung cancer (ieu-a-967) and lung adenocarcinoma (ebi-a-GCST004744 and ieu-a-984) in weighted mode method (Fig. 8D).

Using angina and myocardial infarction from the UK Biobank as exposure, and lung cancer from the FinnGen Biobank as outcome, we further elucidated the associations of angina and myocardial infarction with lung cancer, particularly small cell lung carcinoma and lung adenocarcinoma. Angina (ukb-b-8650 and ukb-b-8468) showed a negative association with non-small cell lung cancer (finn-b-C3_LUNG_NONSMALL_EXALLC and finn-b-C3_LUNG_NONSMALL) and squamous cell lung cancer (finn-b-C3_NSCLC_SQUAM_EXALLC) in the Mendelian randomization IVW method (Fig. 9A). Additionally, angina pectoris (ukb-b-15686) was negatively associated with squamous cell lung cancer (finn-b-C3_NSCLC_SQUAM and finn-b-C3_NSCLC_SQUAM_EXALLC) in the Mendelian randomization IVW method (Fig. 9A). These associations between angina (ukb-b-8650 and ukb-b-8468) and non-small cell lung cancer, as well as squamous cell lung cancer, were further demonstrated in scatter plots using Mendelian randomization IVW, ME Egger, Simple mode, weighted median, and weighted mode methods (Fig. 9B). However, myocardial infarction (ukb-b-15829) did not show any significant association with lung cancer or squamous cell lung cancer in the FinnGen Biobank (Fig. 9A).

Genetical associations of Alzheimer's disease with small cell lung carcinoma

Lung cancer, small cell lung carcinoma, squamous cell lung cancer, and lung adenocarcinoma share similar genetic architectures, such as 15q25 (Fig. 1B). However, genetic risk loci at 5p15 were observed in squamous cell lung cancer and lung adenocarcinoma, but not in small cell lung carcinoma (Fig. 1B). Moreover, angina pectoris and myocardial infarction were commonly associated with squamous cell lung cancer and lung adenocarcinoma (Fig. 7A, B). Yet, angina pectoris and myocardial infarction were not genetically associated with small cell lung

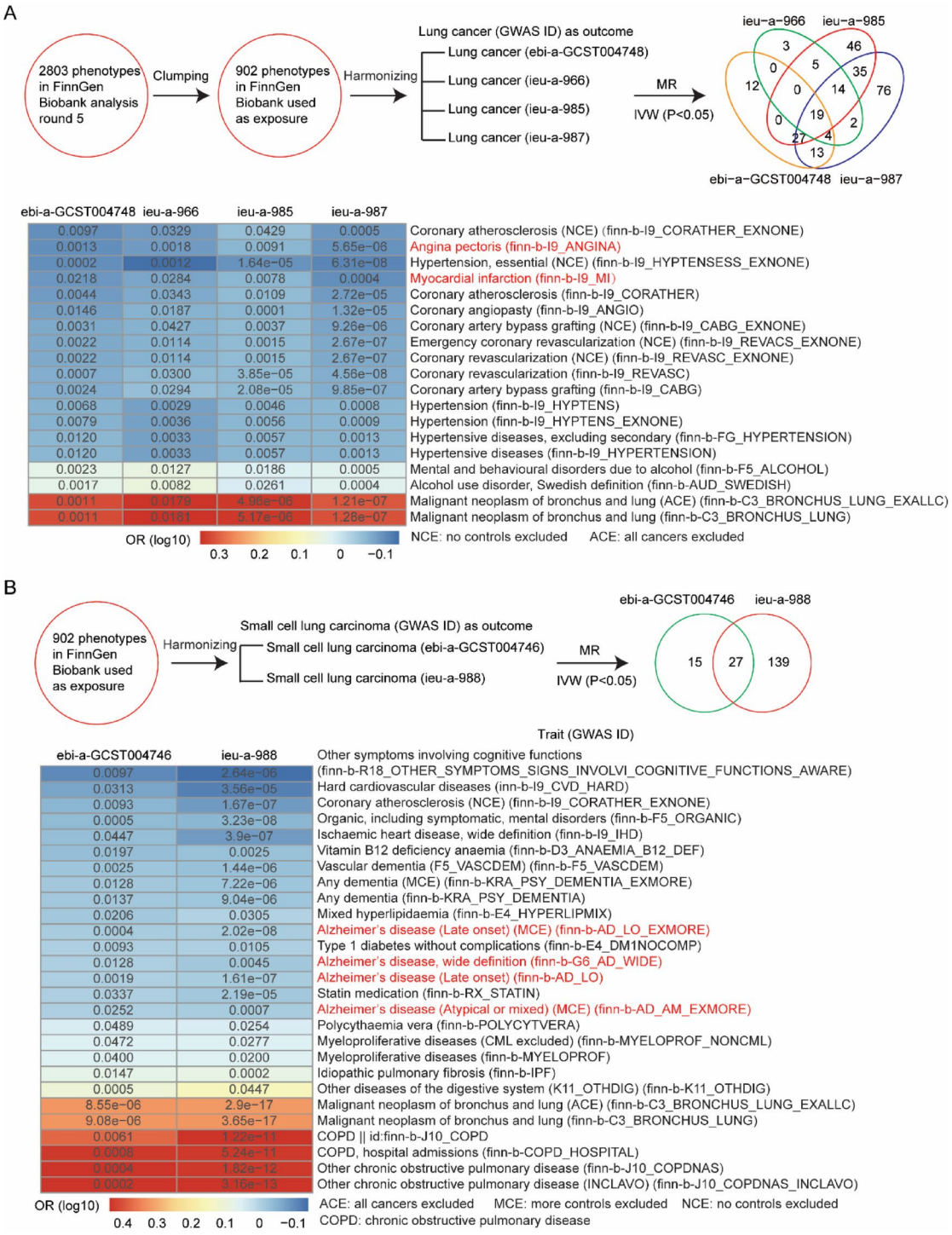

Fig. 6. Genetic risk factors in FinnGen Biobank associated with lung cancer or small cell lung carcinoma. (**A**) GWAS of 2,803 phenotypes were deposited in FinnGen Biobank. After standard clumping, 902 traits were remained as exposure. The correlations of those 902 traits with lung cancer were determined. The overlapped risk factors in FinnGen Biobank associated with lung cancer (ebi-a-GCST004748, ieu-a-966, ieu-a-985 and ieu-a-987) were illustrated. (**B**) The correlations of 902 traits in FinnGen Biobank with small cell lung carcinoma (ebi-a-GCST004746 and ieu-a-988) were determined. The OR and *P* values were determined by IVW method in two sample Mendelian randomization analysis. The number in the heatmap represented the P values and the color represented the OR (log10).

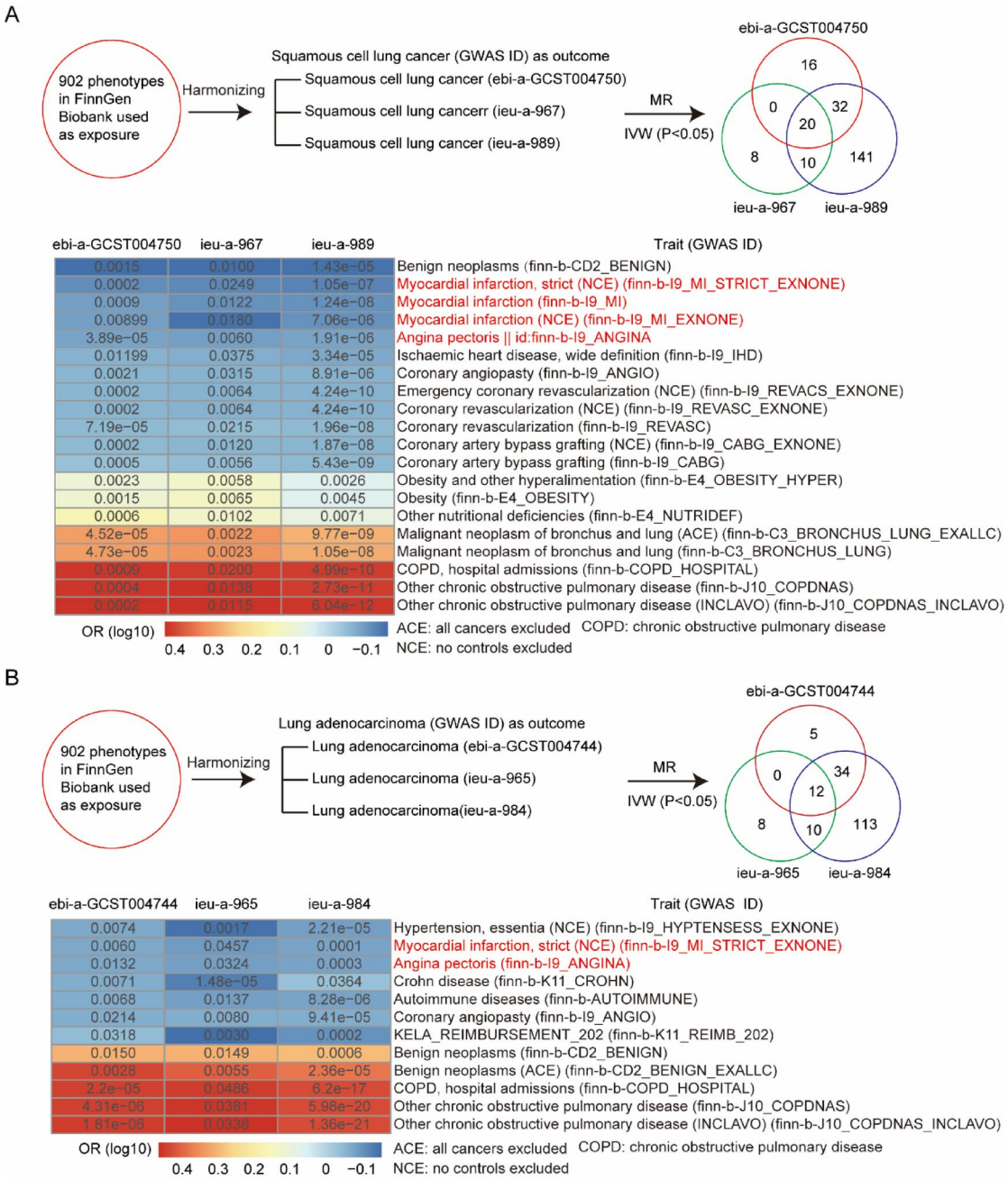

Fig. 7. Genetic risk factors in FinnGen Biobank associated with squamous cell lung cancer or lung adenocarcinoma. (**A**) The correlations of 902 traits from FinnGen Biobank with squamous cell lung cancer were determined. The overlapped risk factors in FinnGen Biobank associated with squamous cell lung cancer (ebi-a-GCST004750, ieu-a-967 and ieu-a-989) were illustrated. (**B**) The correlations of 902 traits from FinnGen Biobank with lung adenocarcinoma (ebi-a-GCST004744, ieu-a-965 and ieu-a-984) were determined. The OR and *P* values were determined by IVW method in two sample Mendelian randomization analysis. The number in the heatmap represented the *P* values and the color represented the OR (log10).

carcinoma. These results further highlight the different pathology of small cell lung carcinoma, suggesting that risk factors of small cell lung carcinoma may be different from those of squamous cell lung cancer and lung adenocarcinoma.

In the UK Biobank, our analysis showed that Illnesses of mother: Alzheimer's disease/dementia (ukb-b-14699) was negatively associated with small cell lung carcinoma (ebi-a-GCST004746 and ieu-a-988) in Mendelian randomization IVW method (Fig. 3). Similarly, in FinnGen Biobank, Alzheimer's disease late onset (finn-b-AD_LO and finn-b-AD_LO_EXMORE) and Alzheimer's disease wide definition (finn-b-G6_AD_WIDE) were negatively associated with small cell lung carcinoma in Mendelian randomization IVW method (Fig. 6B).

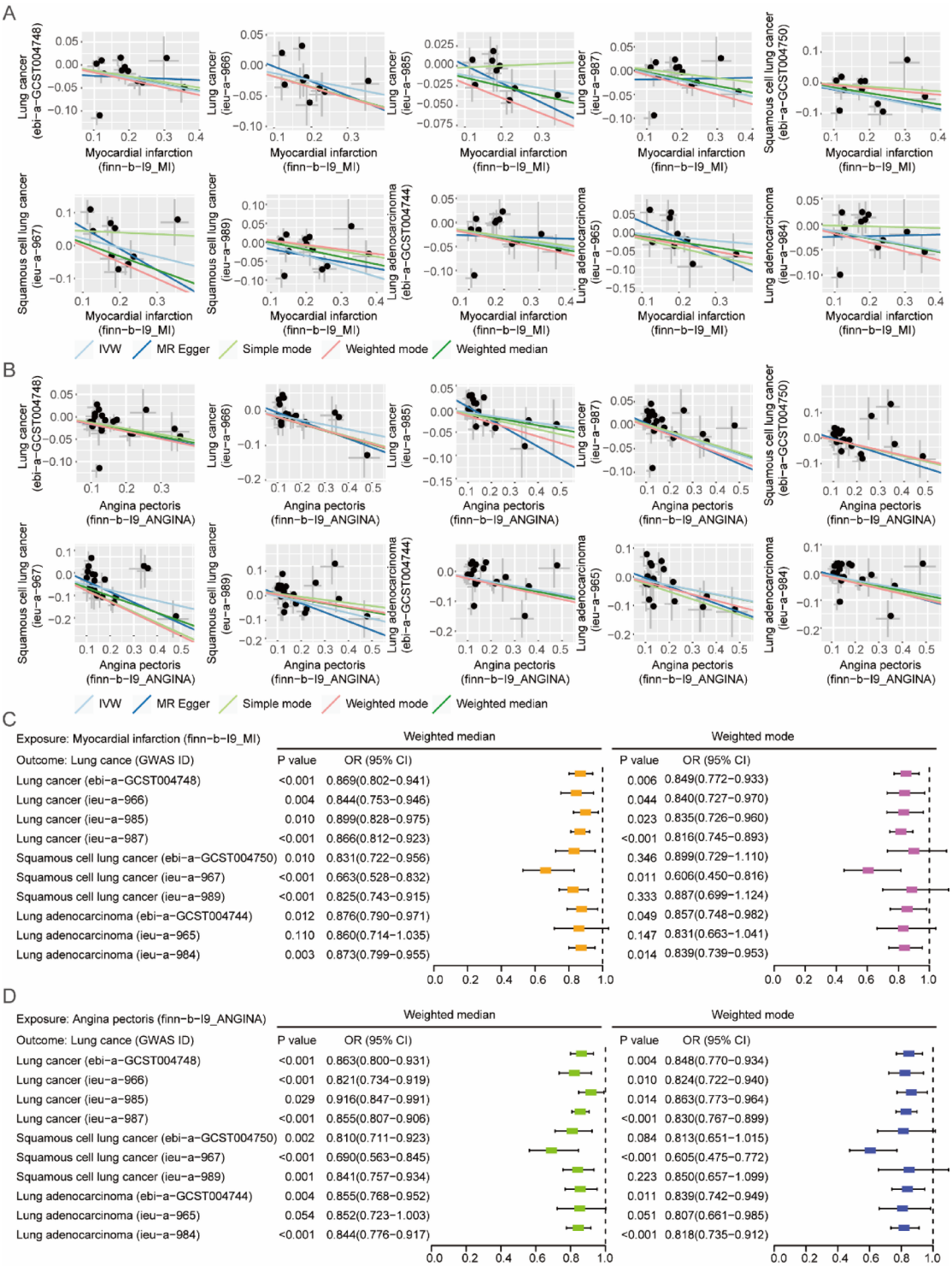

Fig. 8. The associations of myocardial infarction and angina pectoris with lung cancer and squamous cell lung cancer and lung adenocarcinoma subtypes. (**A**) Scatter plots of the associations of myocardial infarction with lung cancer, squamous cell lung cancer and lung adenocarcinoma by IVW, MR-Egger, weighted median, weighted mode and simple mode methods. (**B**) Scatter plots of the associations of angina pectoris with lung cancer, squamous cell lung cancer and lung adenocarcinoma by IVW, MR-Egger, weighted median, weighted mode and simple mode methods. (**C**) Forest plots showed the associations of myocardial infarction with lung cancer, squamous cell lung cancer and lung adenocarcinoma by weighted median and weighted mode methods. (**D**) Forest plots showed the associations of angina pectoris with lung cancer, squamous cell lung cancer and lung adenocarcinoma by weighted median and weighted mode methods. OR: odd ratio; CI: confidence interval;

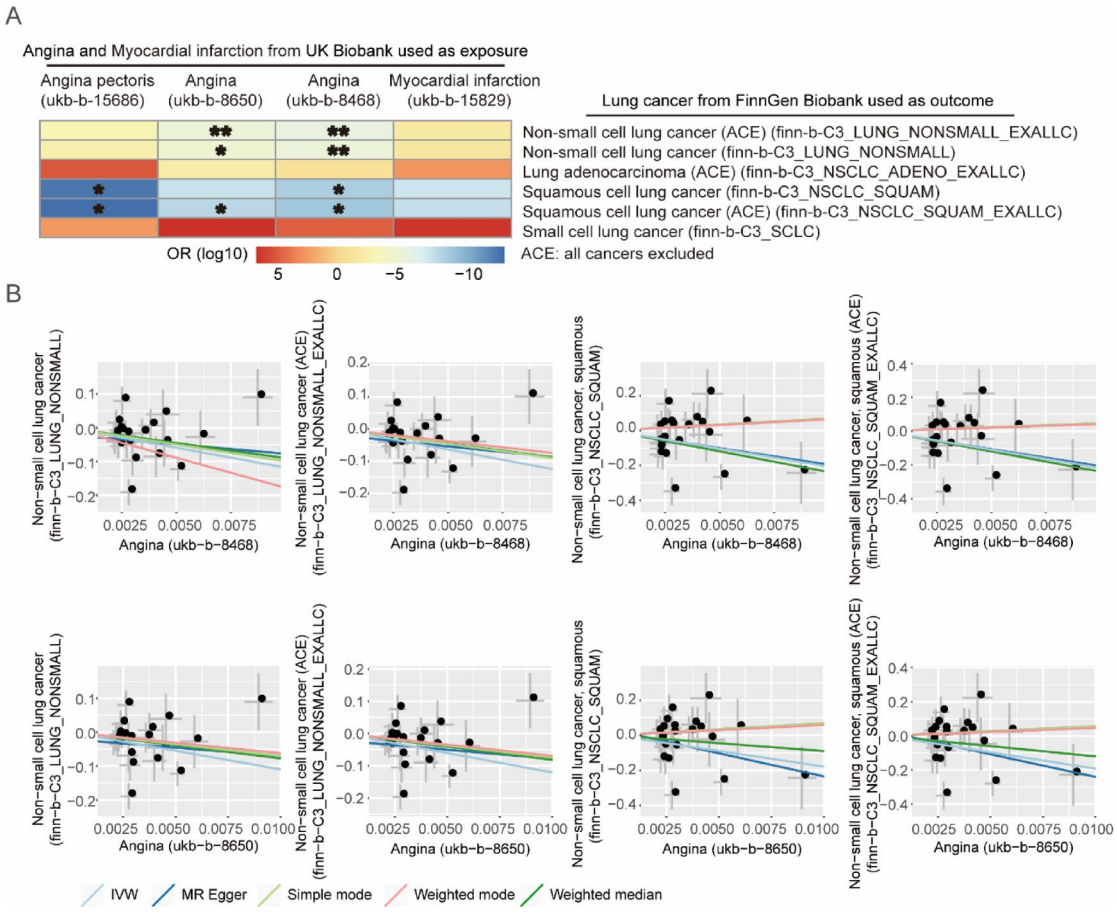

Fig. 9. The associations of angina pectoris with non-small cell lung cancer and squamous cell lung cancer. (**A**) Using angina and myocardial infarction from UK Biobank as exposure, and lung cancer from FinnGen Biobank as outcome, associations of angina and myocardial infarction with non-small cell lung cancer, squamous cell lung cancer, small cell lung carcinoma and lung adenocarcinoma were determined. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ were shown. (**B**) Scatter plots of the associations of angina pectoris with non-small cell lung cancer and squamous cell lung cancer by IVW, MR-Egger, weighted median, weighted mode and simple mode methods.

However, Alzheimer's disease was not commonly correlated with lung cancer, squamous cell lung cancer and lung adenocarcinoma in both the UK Biobank and FinnGen Biobank.

Apart from the IVW method, the ME Egger, simple mode, weighted median, and weighted mode methods also showed similar negative correlations of Alzheimer's disease (ukb-b-14699, finn-b-AD_LO, finn-b-AD_LO_EXMORE, and finn-b-G6_AD_WIDE) with small cell lung carcinoma (ebi-a-GCST004746 and ieu-a-988) (Fig. 10A). The detailed results of the weighted median and weighted mode methods in relation to the associations of Alzheimer's disease with small cell lung carcinoma were further illustrated in scatter plots. In the Mendelian randomization weighted median method, Alzheimer's disease (ukb-b-14699, finn-b-AD_LO, finn-b-AD_LO_EXMORE, and finn-b-G6_AD_WIDE) was negatively associated with small cell lung carcinoma (ebi-a-GCST004746 and ieu-a-988) (Fig. 10B).

Genetical associations of Alzheimer's disease with lung cancer and squamous cell lung cancer subtype

Although Alzheimer's disease was not commonly associated with lung cancer, squamous cell lung cancer, and lung adenocarcinoma in the UK Biobank and FinnGen Biobank, we observed negative correlations between Alzheimer's disease and lung cancer in certain GWAS datasets. Specifically, Alzheimer's disease (ukb-b-14699, finn-b-AD_AM_EXMORE, finn-b-AD_LO_EXMORE, finn-b-AD_LO) from the UK Biobank or FinnGen Biobank showed negative associations with lung cancer (ebi-a-GCST004748, ieu-a-985, ieu-a-987) but not with lung cancer ieu-a-966 in the Mendelian randomization IVW method (Fig. 11A). Additionally, Alzheimer's disease from the UK Biobank or FinnGen Biobank exhibited negative associations with squamous cell lung cancer (ebi-a-GCST004750, ieu-a-989) but not with squamous cell lung cancer ieu-a-967 in Mendelian randomization IVW method (Fig. 11A). Scatter plots further illustrated these negative correlations between Alzheimer's disease (ukb-b-14699, finn-b-AD_AM_EXMORE, finn-b-AD_LO) and lung cancer (ieu-a-985, ieu-a-987) as well as squamous cell lung cancer (ieu-a-989) (Fig. 11B).

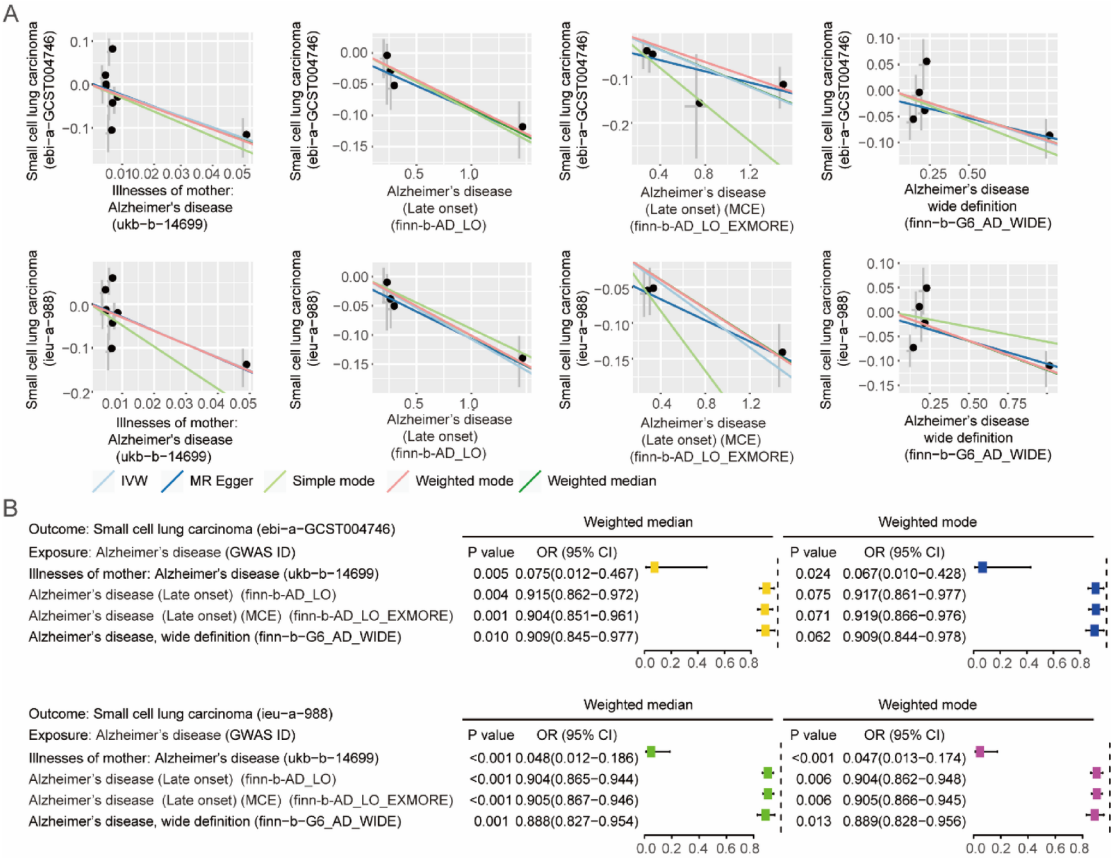

Fig. 10. The associations of Alzheimer's disease and small cell lung carcinoma. (**A**) Scatter plots of the associations of Alzheimer's disease and small cell lung carcinoma by IVW, MR-Egger, weighted median, weighted mode and simple mode methods. (**B**) Forest plots showed the associations of Alzheimer's disease and small cell lung carcinoma by weighted median and weighted mode methods. OR: odd ratio; CI: confidence interval;

Horizontal pleiotropy in the correlations of myocardial infarction, angina pectoris and Alzheimer's disease with lung cancer in sensitivity analysis

Sensitivity analyses were conducted to identify heterogeneity and horizontal pleiotropy in the correlations between myocardial infarction, angina pectoris, and Alzheimer's disease with lung cancer. No horizontal pleiotropy was found in the genetic associations of myocardial infarction (finn-b-I9_MI) with lung cancer (ebi-a-GCST004748, ieu-a-966, ieu-a-985, and ieu-a-987), squamous cell lung cancer (ebi-a-GCST004750, ieu-a-967, and ieu-a-989), and lung adenocarcinoma (ebi-a-GCST004744, ieu-a-965, and ieu-a-984) as shown in Table 2. Similarly, no horizontal pleiotropy was observed in the genetic associations of angina pectoris (finn-b-I9_ANGINA) with lung cancer, squamous cell lung cancer, and lung adenocarcinoma also presented in Table 2. Additionally, there was no horizontal pleiotropy in the genetic associations of Alzheimer's disease (ukb-b-14699, finn-b-AD_LO, finn-b-AD_LO_EXMORE, and finn-b-G6_AD_WIDE) with small cell lung carcinoma (ebi-a-GCST004746 and ieu-a-988) as indicated in Table 3. The existence of some heterogeneity did not influence our analysis.

The associations of myocardial infarction, angina pectoris and Alzheimer's disease with lung cancer given other risk factors in multivariable Mendelian randomization analysis

In previous research, we used phenome-wide Mendelian randomization analysis to identify that pack years adult smoking as proportion of life span exposed to smoking (ukb-b-7460), beef intake (ukb-b-2862), time spent watching television (ukb-b-5192), alcohol usually taken with meals (ukb-b-16878) and number of cigarettes currently smoked daily (ukb-b-469) were all commonly risk factors for lung cancer, small cell lung carcinoma, squamous cell lung cancer, and lung adenocarcinoma in UK Biobank. Also, we identified the associations of myocardial infarction (ukb-b-15829), angina pectoris (ukb-b-8468) and Alzheimer's disease (ukb-b-14699) with lung cancer or its subtypes. In a multivariable Mendelian randomization analysis that included myocardial infarction, beef intake, pack years of adult smoking, and time spent watching television, only myocardial infarction and pack years of adult smoking as a proportion of lifespan exposed to smoking retained potentially associations with lung cancer and squamous cell lung cancer (Fig. 12A).

Furthermore, in multivariable Mendelian randomization analysis, it was found that angina (ukb-b-8650 and ukb-b-8468) and pack years of adult smoking, as a proportion of life span exposed to smoking, had potentially

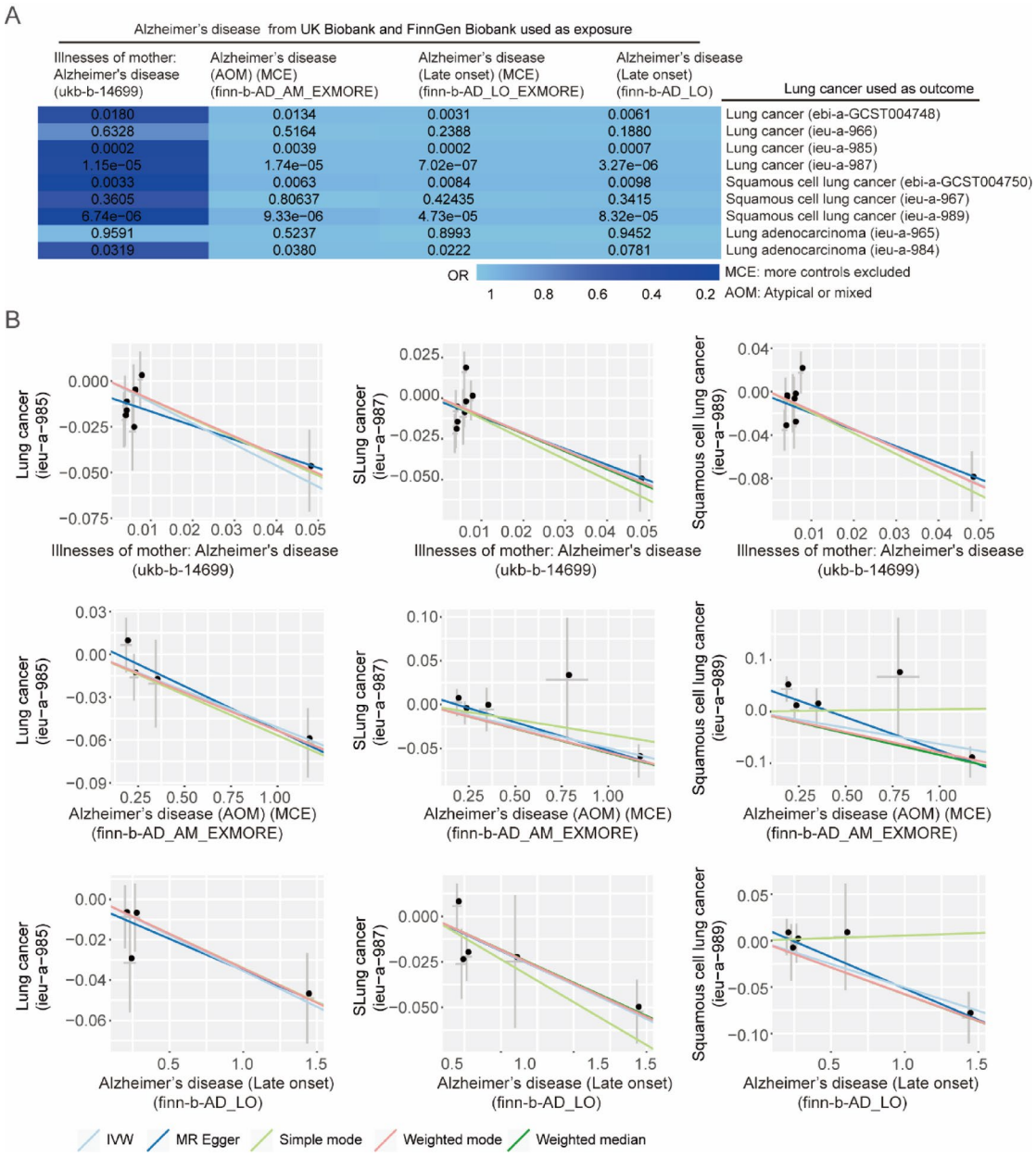

Fig. 11. The associations of Alzheimer's disease with lung cancer and squamous cell lung cancer and lung adenocarcinoma subtypes. (**A**) Associations of Alzheimer's disease with lung cancer, squamous cell lung cancer and lung adenocarcinoma were determined by IVW. The number in the heatmap represented the P values and the color represented the OR. (**B**) Scatter plots of the associations of Alzheimer's disease with lung cancer and squamous cell lung cancer by IVW, MR-Egger, weighted median, weighted mode and simple mode methods.

associations with squamous cell lung cancer (Fig. 12A). Similarly, Alzheimer's disease (ukb-b-14699) and pack years of adult smoking as a proportion of life span exposed to smoking showed potentially relationships with small cell lung carcinoma when assessed together with factors such as beef intake and time spent watching television.

In the FinnGen Biobank, COPD (finn-b-COPD_HOSPITAL) was found to have a positive association with small cell lung carcinoma (Fig. 6B), squamous cell lung cancer (Fig. 7A), and lung adenocarcinoma (Fig. 7B). Obesity (finn-b-E4_OBESITY) was also positively associated with squamous cell lung cancer (Fig. 7A). When myocardial infarction, COPD, and obesity were assessed together, myocardial infarction and COPD maintained strong associations with squamous cell lung cancer (Fig. 12B). Additionally, angina pectoris and COPD showed strong associations with squamous cell lung cancer when analyzed together with obesity (Fig. 12B). Furthermore, Alzheimer's disease and COPD appeared to have potential associations with small cell lung carcinoma when analyzed together with obesity in multivariable Mendelian randomization analysis (Fig. 12B).

Exposure	Outcome	egger_intercept	SE	*P* value
Myocardial infarction (finn-b-I9_MI)	Lung cancer (ebi-a-GCST004748)	−0.0202	0.0338	0.5638
	Lung cancer (ieu-a-966)	0.0227	0.0379	0.5677
	Lung cancer (ieu-a-985)	0.0270	0.0216	0.2318
	Lung cancer (ieu-a-987)	−0.0309	0.0253	0.2365
	Squamous cell lung cancer (ebi-a-GCST004750)	−0.0045	0.0380	0.9086
	Squamous cell lung cancer (ieu-a-967)	0.0696	0.0791	0.4082
	Squamous cell lung cancer (ieu-a-989)	−0.0194	0.0277	0.4939
	Lung adenocarcinoma (ebi-a-GCST004744)	−0.0173	0.0340	0.6231
	Lung adenocarcinoma (ieu-a-965)	0.0685	0.0495	0.2092
	Lung adenocarcinoma (ieu-a-984)	−0.0254	0.0271	0.3610
Angina pectoris (finn-b-I9_ANGINA)	Lung cancer (ebi-a-GCST004748)	−0.0014	0.0208	0.9481
	Lung cancer (ieu-a-966)	0.0192	0.0157	0.2395
	Lung cancer (ieu-a-985)	0.0329	0.0093	0.0012
	Lung cancer (ieu-a-987)	0.0088	0.0132	0.5101
	Squamous cell lung cancer (ebi-a-GCST004750)	0.0133	0.0191	0.4955
	Squamous cell lung cancer (ieu-a-967)	0.0390	0.0310	0.2261
	Squamous cell lung cancer (ieu-a-989)	0.0217	0.0176	0.2258
	Lung adenocarcinoma (ebi-a-GCST004744)	0.0003	0.0220	0.9895
	Lung adenocarcinoma (ieu-a-965)	0.0233	0.0267	0.3951
	Lung adenocarcinoma (ieu-a-984)	0.0117	0.0159	0.4656

Table 2. Horizontal pleiotropy in the correlations of other coagulation defects and spontaneous miscarriage in the sensitivity analyses. *SE* standard error.

Exposure: Alzheimer's disease	Outcome: Small cell lung carcinoma	egger_intercept	se	*P* value
finn-b-AD_LO	ebi-a-GCST004746	−0.0133	0.0261	0.6605
	ieu-a-988	−0.0133	0.0189	0.5123
finn-b-AD_LO_EXMORE	ebi-a-GCST004746	−0.0387	0.0307	0.3343
	ieu-a-988	−0.0375	0.0213	0.1532
finn-b-G6_AD_WIDE	ebi-a-GCST004746	−0.0171	0.0283	0.5878
	ieu-a-988	−0.0122	0.0224	0.6011
ukb-b-14699	ebi-a-GCST004746	0.0031	0.0240	0.9000
	ieu-a-988	0.0021	0.0139	0.8847

Table 3. Horizontal pleiotropy in the correlations of other coagulation defects and spontaneous miscarriage in the sensitivity analyses. *SE* standard error.

Discussion

Lung cancer is a complex and heterogeneous disease, which includes small cell lung cancer, lung adenocarcinoma, and lung squamous cell carcinoma. These subtypes have distinct differences in genetic characteristics. A meta-analysis of 14,900 cases and 29,485 controls suggested specific effects for 5p15, 6p21, and 12p13 loci, but not for the 15q25 region[7]. Our study also showed that lung cancer, small cell lung carcinoma, squamous cell lung cancer, and lung adenocarcinoma share similar genetic architectures, such as the 15q25 locus. Genetic risk loci at 5p15 were observed in squamous cell lung cancer and lung adenocarcinoma, but not in small cell lung carcinoma. Similarly, genetic risk loci at 6p21 were only observed in squamous cell lung cancer, not in lung adenocarcinoma. Further research is needed to investigate the specific functions of SNPs associated with lung cancer subtypes.

Consistent with previous results, our analysis also revealed that smoking[10] consumption of alcohol[11], age at first birth[13], obesity[14] and time spent watching television[15] were all genetically associated with lung cancer, small cell lung carcinoma, squamous cell lung cancer and lung adenocarcinoma. However, we identified the new roles of myocardial infarction and angina pectoris in relation to lung cancer, squamous cell lung cancer and lung adenocarcinoma. Myocardial infarction and angina pectoris are both coronary heart-associated diseases. Myocardial infarction is characterized by sudden cardiac death[35], while, angina pectoris refers to the chest pain or discomfort because of coronary heart disease[36,37]. Several cohort studies have demonstrated an increased risk of cancer in myocardial infarction patients[38–41]. However, in genetic aspect, we showed the associations of myocardial infarction and angina pectoris with lung cancer, squamous cell lung cancer and lung adenocarcinoma, even considered with beef intake, pack years adult smoking as proportion of life span exposed to smoking and time spent watching television, COPD and obesity together. However, the inverse correlations of myocardial

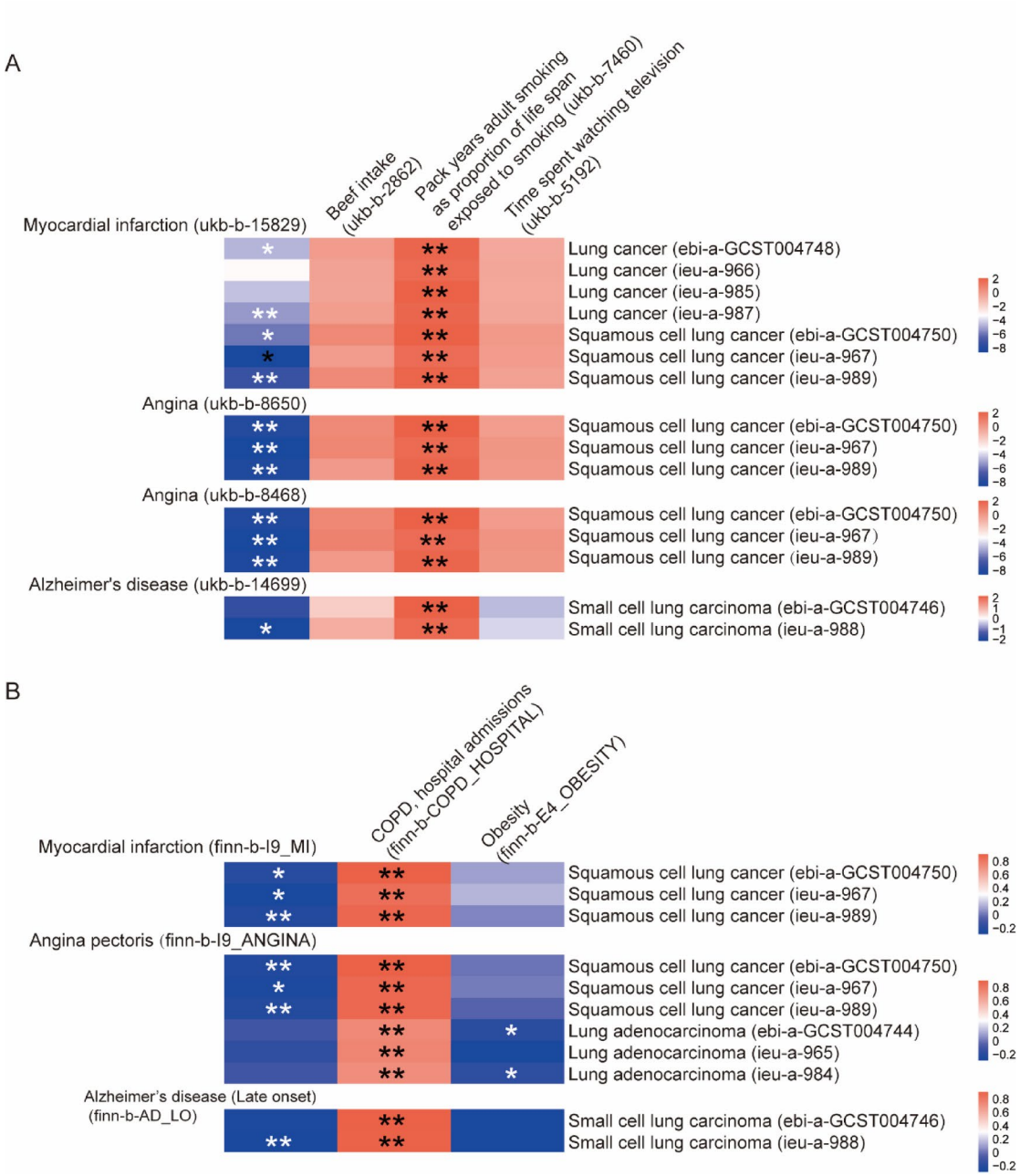

Fig. 12. The associations of myocardial infarction, angina pectoris and Alzheimer's disease with lung cancer given other risk factors in multivariable Mendelian randomization analysis. (**A**) Beef intake, pack years adult smoking as proportion of life span exposed to smoking and time spent watching television were assessed together with myocardial infarction, angina pectoris or Alzheimer's disease in UK Biobank in multivariable Mendelian randomization analysis. (**B**) COPD and obesity were assessed together with myocardial infarction, angina pectoris or Alzheimer's disease in FinnGen Biobank in multivariable Mendelian randomization analysis. $^{*}P<0.05$, $^{**}P<0.01$ and $^{***}P<0.001$ were shown.

infarction and angina pectoris with lung cancer, squamous cell lung cancer and lung adenocarcinoma should be further illustrated in observational studies.

Alzheimer's disease is a degenerative neurological condition and a common type of dementia[42]. Several observational studies have revealed the inverse associations between Alzheimer's disease and lung cancer. These studies have shown a reduced risk of developing Alzheimer's disease after a lung cancer diagnosis[43–46]. Lung cancer survivors also had a lower risk of Alzheimer's disease[45,47,48]. Conversely, retrospective cohort studies from China and South Korea suggest that individuals with Alzheimer's disease have a lower likelihood of developing lung cancer[49,50]. The mechanisms behind these associations involve opposite signaling pathways between Alzheimer's disease and lung cancer[51]. At a transcriptomic level, genes that are upregulated in Alzheimer's disease are downregulated in lung cancer, and vice versa[52,53]. Also, Alzheimer's disease and lung cancer have

potential genetic correlations[54]. In our study, we demonstrated the genetic effects of Alzheimer's disease on the small cell lung carcinoma subtype, even when considering factors such as beef intake, pack years adult smoking as proportion of life span exposed to smoking, time spent watching television, COPD, and obesity. Additionally, Alzheimer's disease showed a reverse association with lung cancer and squamous cell lung cancer. However, the correlations between Alzheimer's disease and lung adenocarcinoma were not found to be significant.

In conclusion, our phenome-wide Mendelian randomization analysis revealed both similar and distinct genetic risk factors among various subtypes of lung cancer. Additionally, we identified genetic associations between myocardial infarction, angina pectoris, and Alzheimer's disease with specific types of lung cancer, small cell lung carcinoma, squamous cell lung cancer, and lung adenocarcinoma. It is important to note that our study was limited to individuals of European ancestry, thus further research is needed in diverse populations to validate these findings. Also, our results were mainly derived from Mendelian randomization analysis, further observational studies should be carried out to validate the associations of myocardial infarction, angina pectoris, and Alzheimer's disease with lung cancer. Moreover, future studies should explore the underlying mechanisms of how myocardial infarction, angina pectoris, and Alzheimer's disease may affect lung cancer and its subtypes.

Conclusions

In a phenome-wide Mendelian randomization analysis, our results highlighted the similar and distinct genetic risk factors among different subtypes of lung cancer. Additionally, our findings revealed genetic associations between myocardial infarction, angina pectoris, and Alzheimer's disease with lung cancer.

Data availability

The datasets generated and/or analyzed during the current study are available in the IEU Open GWAS Project repository (https://gwas.mrcieu.ac.uk).

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Author contributions

Haiwei Wang designed the study, performed the data analysis and wrote the manuscript. Xinrui Wang and Na Lin revised the manuscript. Liangpu Xu and Yingying Lin supervised the work.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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