Original Article

Association between systemic lupus erythematosus and lung cancer: results from a pool of cohort studies and Mendelian randomization analysis

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Background: Epidemiological evidence suggested that systemic lupus erythematosus (SLE) might be correlated with an increased risk of lung cancer. Nevertheless, few studies have comprehensively investigated their correlation and the causal effect remains unclear. With a meta-analysis and Mendelian randomization (MR) approach, we were able to systematically investigate the relationship between SLE and lung cancer risk.

Methods: A systematic search of cohort studies was conducted using network databases from the inception dates to February 1, 2020. Meta-analysis was performed to calculate standardized incidence rate (SIR) and their 95% CI. Furthermore, utilizing 33 SLE-related single nucleotide polymorphisms as instrumental variables (IVs) identified by the latest genome-wide association studies (GWASs), we investigated the correlation between genetically predisposed SLE and lung cancer risk using summary statistics from the International Lung Cancer Consortium (11,348 cases and 15,861 controls). The Inverse variance-weighted method was applied to estimate the causality and we further evaluated the pleiotropy by means of the weighted median and the MR-Egger regression method. Subgroup analysis according to different histotypes of lung cancer was also conducted.

Results: Through meta-analysis of 15 cohort studies involving 110,519 patients, we observed an increased risk of lung cancer among SLE patients (SIR =1.63, 95% CI, 1.39–1.90). Subgroup analysis suggested that female patients (SIR =1.28, 95% CI, 1.13–1.44) have a relatively higher lung cancer risk compared with male patients (SIR =1.15, 95% CI, 1.02–1.30). MR analysis indicated that genetically predisposed SLE was causally associated with an increased lung cancer risk (OR =1.045, 95% CI, 1.005–1.086, P=0.0276). When results were examined by histotypes, a causal relationship was observed between genetically predisposed SLE and squamous cell lung cancer (OR =1.065, 95% CI, 1.002–1.132, P=0.0429). Additionally, the results demonstrated the absence of the horizontal pleiotropy.

Conclusions: Both meta-analysis and MR analysis results suggested that SLE was associated with an increased lung cancer risk. Further investigations are warranted to investigate the etiology underlying the attribution of SLE to lung cancer.

Keywords: Systemic lupus erythematosus (SLE); lung cancer risk; meta-analysis; Mendelian randomization (MR) analysis

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease which manifested as ischemic and dysfunctional tissue generation by means of production of autoantibody, activation of complement and immune-complex deposition, thus chronic multiorgan inflammatory lesion is induced (1,2). In terms of ethnicity, prevalence is highest among African Americans, followed by Asians and Hispanics (3); in regard to sex, SLE is more prevalent among women with ratios 9 times higher than men and is typically diagnosed during reproductive years (4,5). Recent decades have seen remarkable improvement of survival in SLE patients on account of the progress of treatment, yet long-term complications such as secondary lung cancer have become the major issue of prognosis (6).

Considered as the major cause of cancer death, lung cancer remains the most commonly diagnosed cancer worldwide (7,8). Previous studies have reported that SLE may play a role in the formation of pulmonary lesion via tissue fibrosis and vascular inflammation causing acute or chronic complications, e.g., interstitial lung disease (ILD) (9), thus potentially promoting the occurrence of lung cancer (10).

Previous epidemiological evidence concerning the correlation between SLE and lung cancer was inconsistent. A population-level cohort studies including 30,478 SLE patients in America reported a significantly increased risk of lung cancer among SLE patients (11). Likewise, a latest meta-analysis conducted in 2018 indicated that patients with SLE had a remarkably increased lung cancer risk of 62% (12). However, more recently, a nationwide population-based study in Korea demonstrated no association between SLE and an increased risk of lung cancer (13). Previous observational studies have done a great job of selecting appropriate SLE patients since there are various classification criteria and meanwhile, the diagnosis remains challenging due to the heterogeneity of SLE (14). Some studies obtained valuable data of cigarette consumption and drug exposure like cyclophosphamide (CTX) among SLE patients (15,16), which are beneficial to our better understanding of the potential roles of environmental and drug factors contributing to the pathogenesis of SLE. Notably, due to the nature of observational studies, these studies could be biased by confounders or reverse causation, making the current conclusions less accurate or invalid. Additionally, the causal effect between SLE and lung cancer remains unknown.

As a novel epidemiological genetic method, Mendelian randomization (MR), is designed to estimate the causality between risk factors and outcome of diseases, utilizing genetic variants as instrumental variables (IVs) by finding a genetic marker that satisfies IV assumptions. Single-nucleotide polymorphisms (SNPs) are used as the IVs, as their alleles are assigned to individuals before any exposure or outcome and thus, they are non-modifiable, ensuring lifelong exposure and reducing the occurrence of reverse causation and potential confounders (17). These genetic variants can be used as unconfounded proxies for modifiable risk factors because they are randomly assigned before birth and fixed at conception, similar to randomized controlled trials (RCTs) in an observational (non-experimental) setting. Nowadays, taking the advantage of the published summary data of recent discovered large-scale genome-wide association studies (GWASs), in-depth study on the causal inferences on genetic aspects has become a feasible approach. Several chromosomes (18) had anteriorly found to reveal the hereditary relationship of the lung cancer risk. Also, in terms of SLE, genetic variants play a role in SLE occurrence, which has been confirmed since the heritability of SLE was estimated from 8.7% to 16.0% (19). Therefore, the MR analysis may offer a means to evaluate the causality between SLE and lung cancer.

Making attempt to investigate the correlation between SLE and risk of lung cancer, we first conducted a meta-analysis based on 15 population-level cohort studies (We present the following article in accordance with the PRISMA reporting checklist). Furthermore, utilizing 33 SLE-related SNPs as IVs identified by the latest GWASs, we investigated the correlation between genetically predisposed SLE and lung cancer risk using summary

statistics from the International Lung Cancer Consortium (ILCCO, 11,348 cases and 15,861 controls). We also conducted additional MR analyses to investigate whether genetically predisposed SLE would be associated with common confounders and mediators of lung cancer risk based on existing literature, including obesity, alcohol consumption and smoking status (20). As far as we know, our study provided the latest evidence for assessing the causality between SLE and lung cancer through MR for the first time. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-2462).

Methods

Meta-analysis

Academic retrieval strategies

A systemic search was conducted using online databases, including Embase, Web of Science, Cochrane Library, PubMed and Web of Science, up to February 1, 2020. We used "systemic lupus erythematosus" or "lupus" or "SLE" combined with "lung cancer", "neoplasm" and "tumor" as well as their Medical Subject Headings (MeSH) terms. The references lists originating from retrieved review articles and conference abstracts were searched manually.

Studies regarding lung cancer risk among patients with SLE were included if they met the following criteria (21): (I) study design of population-level cohort studies of SLE patients, (II) sample size of patients more than 200, (III) data on lung cancer incidence obtained from official registers, (IV) studies provided relative risks (RRs), standardized incidence ratios (SIRs), odds ratios (ORs) or hazard ratios (HRs) with corresponding 95% CIs of lung cancer among SLE patients and (V) studies with eligible follow-up time (>5 years or >1,000 person-years). Studies were excluded if any of the following criteria was met: (I) case-control studies, cross-sectional studies or case report, (II) studies from referral centers and (III) studies not published in English, duplicate publications or conference abstracts without follow-up publication.

Data extraction

Three authors (H.P., W.X., Y.W.) extracted the available data independently and any divergences came to a unanimous decision after discussion among the 3 investigators. The name of the first author, sources of SLE patients, follow-up time (mean or median person-years or years), diagnosis of SLE, number of SLE patients (gender), number of lung cancer patients, SIRs with 95% CIs, country, study period and publication year of each study were recorded.

Quality assessment

Quality assessment was carried out based on Meta-analysis of Observational Studies in Epidemiology (MOOSE) (22) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (23) criteria based on a scale of 0–6 points, with 6 reflecting the best quality. One point was assigned for each of the following: (I) reasonable criteria of selected participants, (II) accurate SLE diagnosis based on American Rheumatology Academy (ARA), American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR) classification criteria (24,25), (III) descriptive data, such as the characteristics of participants and information of follow-up period, (IV) outcome data of lung cancer which was diagnosed in accordance with acknowledged clinical criteria (26), (V) adjusting for age and gender, (VI) other relevant adjustments such as smoking, race, past medical history and immunosuppressant therapy. Notably, if the SLE diagnosis was not precise or was not mentioned in the articles, the one would score 0 point on the project "Appropriate SLE diagnosis".

Statistical analysis

Given that the lung cancer risk is relatively low among SLE patients, we anticipated similar estimate in SIRs with HRs/ORs/RRs in accordance with Lin *et al.* described (27). Hence, study-specific SIRs with 95%CIs for lung cancer were gathered to combine the data. Utilizing the I^2 statistic and the Cochran's Q test, heterogeneity was evaluated. If an I^2 statistic ≥50% then, the statistical heterogeneity was considered significant. A random-effects model was conducted if significant heterogeneity ($P<0.5$, $I^2>50\%$) was observed, otherwise a fixed-effects model was employed. Stratified analysis based on gender was carried out. Funnel plot tests, Egger's test and Begg's test were used to evaluate the publication bias. Sensitivity analysis was employed by omitting the studies singly. All the statistical manipulation was carried out using Stata software (version 15, StataCorp, TX, USA). Statistical significance was considered as $P<0.05$. The PRISMA checklist for reporting systematic reviews and meta-analyses was used. Review protocol of this meta-analysis was registered in PROSPERO (ID CRD42020159082).

Table 1 Details of International Lung and Cancer Consortium (ILCCO) included in Mendelian randomization analyses

Trait	First author	Consortium	Number of cases	Number of controls	Sample size	Year
Lung cancer	Wang Y	ILCCO	11,348	15,861	27,209	2014
Squamous cell lung cancer	Wang Y	ILCCO	3,275	15,038	18,313	2014
Lung adenocarcinoma	Wang Y	ILCCO	3,422	14,894	18,336	2014

ILCCO, the International Lung Cancer Consortium.

Mendelian randomization

Data sources

One hundred and six loci from 82 SNPs associated with SLE from 9 Genome-wide association studies (GWASs) published between 2008 and 2016 (19,28-35) (*Table S1*) were extracted from European ethnicity at the genome-wide significance threshold of $P<5\times10^{-8}$. An exclusion was performed utilizing linkage disequilibrium (LD) analysis once mutual LD surpassed the limited value ($R^2<0.001$). Eventually, 33 SNPs (*Table S1*) remained as the final genetic variants, explaining over 16% (19) of the heritability totally. Given the 27,209 individual sample size and 33 instrumental variants included in our study, the F-statistic was 5,183.67 (F>100) as estimated using the formulae from Burgess *et al.* (36), suggesting the instruments used strongly predicted SLE.

Our study included 11,348 lung cancer cases and 15,861 controls from ILCCO as epidemiological individual data (*Table 1*). In order to explore the possible association between SLE and specific cancer types, subgroup analysis was further conducted, including lung adenocarcinoma and squamous cell lung cancer.

Power calculation

Supposing the SNPs explain a total of 16% variance of SLE in accordance with previous estimates, our sample size of 11,348 cases of lung cancer and 15,861 controls had an approxiamted 100.0% power to detect the estimated causal effect size of SLE (SIR =1.66) previously (11) at a significance level of 0.05, based on the methods illustrated by Burgess (37). Alternatively, given our sample size, we also had 100% power to detect a minimal SIR of 1.30 (38) at a statistical significance level of 0.05.

Statistical analysis

Several MR approaches were used to investigate MR estimates of SLE for lung cancer. We performed a random effects inverse variance-weighted (IVW) Wald-type estimator to derive a MR estimate of multiple IVs. Given that the SNP effects on SLE cumulatively, the IVW estimate of the causal effect can be combined with the ratio estimate and standard error of a single SNP using the method of Burgess *et al.* (39). All previous hypotheses are assumed to be consistent with the previously described genetic variant P (P=1 ... P); which is correlated with the mean change in SLE (Xp) of the risk factor observed with each other variant allele with standard error (σXp) as well as observed (Yp) logarithmic change in the outcome of each allele with standard error (σYp). The calculation is as follows:

$$\hat{\beta}_{IVW}=\frac{\sum_{i=1}^{P}X_pY_p\sigma_{Yp}^{-2}}{\sum_{i=1}^{P}X_p{}^2\sigma_{Yp}^{-2}};se\left(\hat{\beta}_{IVW}\right)=\sqrt{\frac{1}{\sum_{i=1}^{P}X_p{}^2\sigma_{Yp}^{-2}}}$$

Using $\hat{\beta}_{IVW}$ and se $\left(\hat{\beta}_{IVW}\right)$, we calculated corresponding ORs and 95% CIs.

Sensitivity and pleiotropy analysis

Three suppositions (40) establish the foundation for MR analysis: (I) the IVs are closely relevant to SLE; (II) the IVs of SLE affect lung cancer only in a straight-forward pathway omitting any other alternative pathways in causality; and (III) the genetic markers are independent with any other confounders. The first assumption was met since the SNPs in our final IV set were all below the genome-wide significance threshold ($P=5\times10^{-8}$). Leave-one-out analysis was performed, during which we omitted one SNP at a time sequentially and examined variation in causality and overall IVW estimation, to assess whether the estimation of MR analysis was biased or driven by a single SNP.

To verify the second hypothesis, weighted median method and MR-Egger regression were introduced as pleiotropy test by assessing the global pleiotropic effects. To assess whether the causal effect estimation of SLE on lung cancer was consistent across each individual SNP (41), Cochran's Q test was performed as heterogeneity test. The third assumption was examined to investigate the

Table 2 Details of studies included in confounders and mediators of systemic lupus erythematosus

Trait	First author	Consortium	Study participants	Year	Website
Obesity class 1 (BMI: 30–34.9 kg/m^2)	Berndt SI	GIANT	98,697	2013	http://giant.princeton.edu/
Obesity class 2 (BMI: 35–39.9 kg/m^2)	Berndt SI	GIANT	72,546	2013	http://giant.princeton.edu/
Obesity class 3 (BMI: ≥40 kg/m^2)	Berndt SI	GIANT	50,364	2013	http://giant.princeton.edu/
Previous smoker	Neale	Neale Lab	336,024	2017	http://www.nealelab.is/uk-biobank
Current smoker	Neale	Neale Lab	336,024	2017	http://www.nealelab.is/uk-biobank
Alcohol consumption	Clarke	UK Biobank	112,117	2017	http://www.ukbiobank.ac.uk/

GIANT, the Genetic Investigation of Anthropometric Traits.

potential confounding factors between the progress of SLE and lung cancer. Due to the fact that cigarette smoking, alcohol consumption as well as obesity are common factors affecting lung cancer incidence among SLE patients, we further performed additional MR analyses between confounders and the genetic variants of SLE (20). In detail, genetic effects on alcohol consumption status and smoking status were retrieved from Neale Lab, obesity levels were retrieved from The Genetic Investigation of Anthropometric Traits (GIANT) consortium (*Table 2*). Furthermore, we attempted to investigate whether the chosen SNPs for our study were also related to any confounders of both SLE and lung cancer indirectly by retrieving the previously published GWASs.

MR analysis was performed using the package TwoSampleMR (version 0.5.0) (42) in R (version 3.6.2).

Results

Meta-analysis results

Search results and study characteristics

Figure 1 demonstrated the flow diagram for searching and inclusion of studies with the ones excluded for reasons. At last, 15 population-based cohort studies were enrolled in our meta-analysis (*Table 3*). A total of 110,519 patients with SLE (89,963 females and 20,556 males) were represented. The follow-up period ranged from 1,000 person-years to 157,969 person-years or from 4.8 years to 32 years. In total, 1,615 lung cancer cases were reported (*Table 3*).

Quality assessment

The quality scores ranged from 4 to 6 points with 11 of the 15 studies (73%) scored more than 5 points, highlighting the high quality. In terms of SLE diagnosis, 3 studies (20%) utilized the ARA criteria (53), 8 studies (53%) used ACR criteria (54) and the 4 remaining studies (25%) did not mention which diagnostic criteria were used. 7 studies (44%) had adjusted for other factors. Only 1 study met all criteria of the quality assessment tool (*Table S2*).

Overall lung cancer risk in SLE

A total of 15 population-level cohort studies concerning the analysis of SLE and lung cancer were carried out utilizing random-effects model on the basis of the low heterogeneity among studies (I^2=45.0%, P=0.031, Cochran's Q test =25.56). The findings demonstrated that SLE was correlated with an increased risk of lung cancer (SIR =1.63, 95% CI, 1.39–1.90). A forest plot of the SIRs is displayed in *Figure 2*.

Subgroup analysis concerning gender was employed with 6 studies which provided accessible data. Stratified analysis indicated that female patients (SIR =1.28, 95% CI, 1.13–1.44, I^2=63.9%, P=0.017, Cochran's Q test =14.70) were related with the higher risk of lung cancer than male patients (SIR =1.15, 95% CI, 1.02–1.30, I^2 =0.0%, P=0.691, Cochran's Q test =3.23) (*Figure 2*).

Sensitivity analysis

For sensitivity analysis, several studies were excluded which possessed the lowest score of qualification to assess the stability of our overall study. The results conclusively indicated a stabilization of the cohort studies we applied for the meta-analysis (*Figure S1*).

Heterogeneity and publication bias

The funnel-plot was not symmetric in appearance (*Figure S2*), indicating the existence of publication bias. Thus, meta regression was performed, which indicated that the divergence of sample size in different cohorts led to the original heterogeneity. Both Egger's test (P=0.379), Begg's

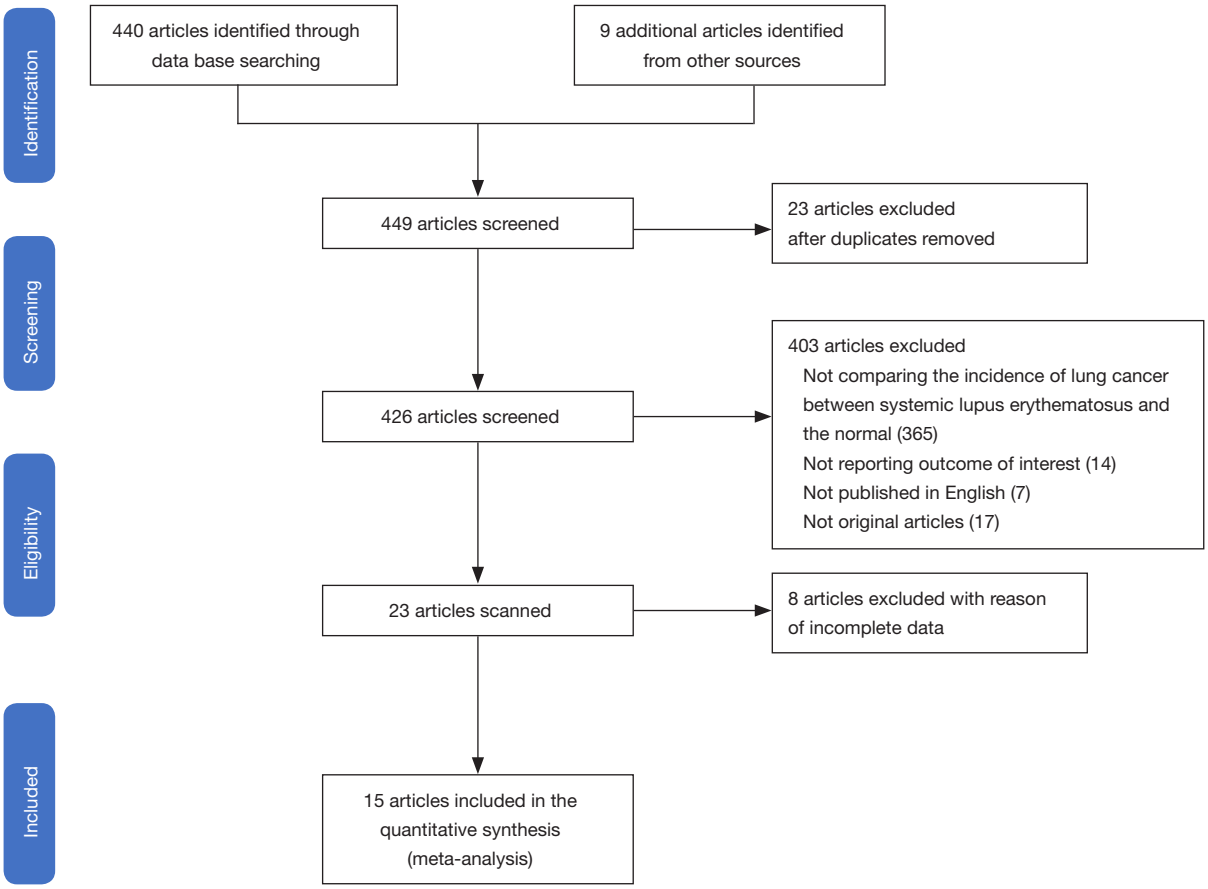

Figure 1 Flow diagram detailing the search strategy and identification of studies used in meta-analysis.

test (P=0.163) and Funnel plot test indicated no publication bias (*Figures S3*,*S4*).

Mendelian randomization results

Individual SNP data

Accessible summary statistics from the GWAS were adopted. 82 genetic variants from 106 loci were recognized as reaching genome-wide significance ($P<5\times10^{-8}$) in the consortium study, explaining 16% (19,28) of phenotypic variation in SLE. Eventually, 33 mutually uncorrelated variants were selected to carry out the IVs in the MR analysis. The details of the 82 SNPs enrolled in our study were represented in *Table S1* and the Supplementary Data (available online: https://cdn.amegroups.cn/static/application/9a5e7d9ae8bd7b0db69e57a4f55a4eec/JTD-20-2462-1.pdf).

MR estimates for multi-polymorphism scores

Being consistent with the findings in the meta-analysis, the conventional IVW method indicated a causal association between genetically predisposed SLE and overall lung cancer (OR =1.045, 95% CI, 1.005–1.086, P=0.0276). Subgroup analysis demonstrated the existence of causality between genetically predisposed SLE and squamous cell lung cancer (OR =1.065, 95% CI, 1.002–1.132, P=0.0429 for IVW) as well (*Table 4*). Likewise, the MR-Egger and weighted median methods produced similar effect estimation, firmly indicating the result of the causation in our study (*Table 4*).

Sensitivity analysis

Leave-one-out analysis suggested that no single instrument was strongly driving the overall effect of SLE on lung cancer and squamous cell lung cancer, indicating that these results were not sensitive to SNP selection. (*Figures S5*,*S6*). No evidence was found for unbalanced pleiotropy among the IVs since MR-Egger regression had suggested (intercept =−0.0120, P=0.16 for lung

Table 3 Characteristics of the included studies in the meta-analysis

Author	Sources of SLE patients	Follow-up (mean or median person-years)	SLE diagnosis	Number of SLE patients (gender)	Number of lung cancer	SIR (95% CI)
Bae *et al.* (13)	Korean National Health Insurance Service database	1,000 person-years	NA	21,016 (2,056 males and 18,960 females)	763	1.34 (0.95, 1.98)
Tallbacka *et al.* (43)	Finnish Cancer Registry	25.7 years	ARA criteria	205 (23 males and 182 females)	3	2.20 (0.58, 8.31)
Yu *et al.* (44)	Taiwan National Health Insurance Research Database (NHIRD)	35.3 years	NA	15,623 (1,930 males and 13,693 females)	395	1.38 (1.00, 1.91)
Rees *et al.* (16)	UK Clinical Practice Research Datalink	8.4 years	NA	7,732 (1,098 males and 6,634 females)	81	3.84 (2.48, 5.95)
Bernatsky *et al.* (45)	Multi-center cohort	121,283 person-years	ACR criteria	16,409 (1,641 males and 14,768 females)	12	1.30 (1.05, 1.61)
Liang *et al.* (46)	National Health Insurance system of Taiwan	8 years	NA	2,150 (486 males and 1,664 females)	18	1.41 (0.70, 2.84)
Grönhagen *et al.* (47)	Swedish National Patient Register	NA	NA	3,663 (852 males and 2,811 females)	32	1.60 (0.80, 3.20)
Dreyer *et al.* (48)	Danish Cancer Registry	13.2 years	ACR criteria	576 (68 males and 508 females)	5	1.40 (0.59, 3.33)
Parikh-Patel *et al.* (11)	Statewide patient discharge data	157,969 person-years	ACR criteria	30,478 (3,345 males and 27,133 females)	218	1.66 (1.45, 1.90)
Bernatsky *et al.* (38)	Canadian Institutes of Health Research (CIHR)	76,948 patient-years	ACR criteria	9,547 (8,592 males and 955 females)	62	1.37 (1.06, 1.77)
Ragnarsson *et al.* (49)	Icelandic SLE database	12.8 years	ARA criteria	238 (25 males and 213 females)	3	1.72 (0.46, 6.38)
Sultan *et al.* (50)	University College London Lupus Clinic Database	4.8 years	ARA criteria	297 (48 males and 249 females)	3	3.10 (1.26, 7.64)
Cibere *et al.* (15)	University of Saskatchewan Rheumatic Disease Unit	12 years	ACR criteria	276 (18 males and 258 females)	1	2.09 (0.55, 7.97)
Mellemkjaer *et al.* (51)	Danish Hospital Discharge Register	15 years	ACR criteria	1,585 (277 males and 1,308 females)	15	1.90 (1.13, 3.19)
Abu-Shakra *et al.* (52)	University of Toronto Lupus Clinic	7,233 patient-years	ACR criteria	724 (97 males and 627 females)	4	1.54 (0.50, 4.72)

SLE, systemic lupus erythematosus; SIR, standardized incidence rate.

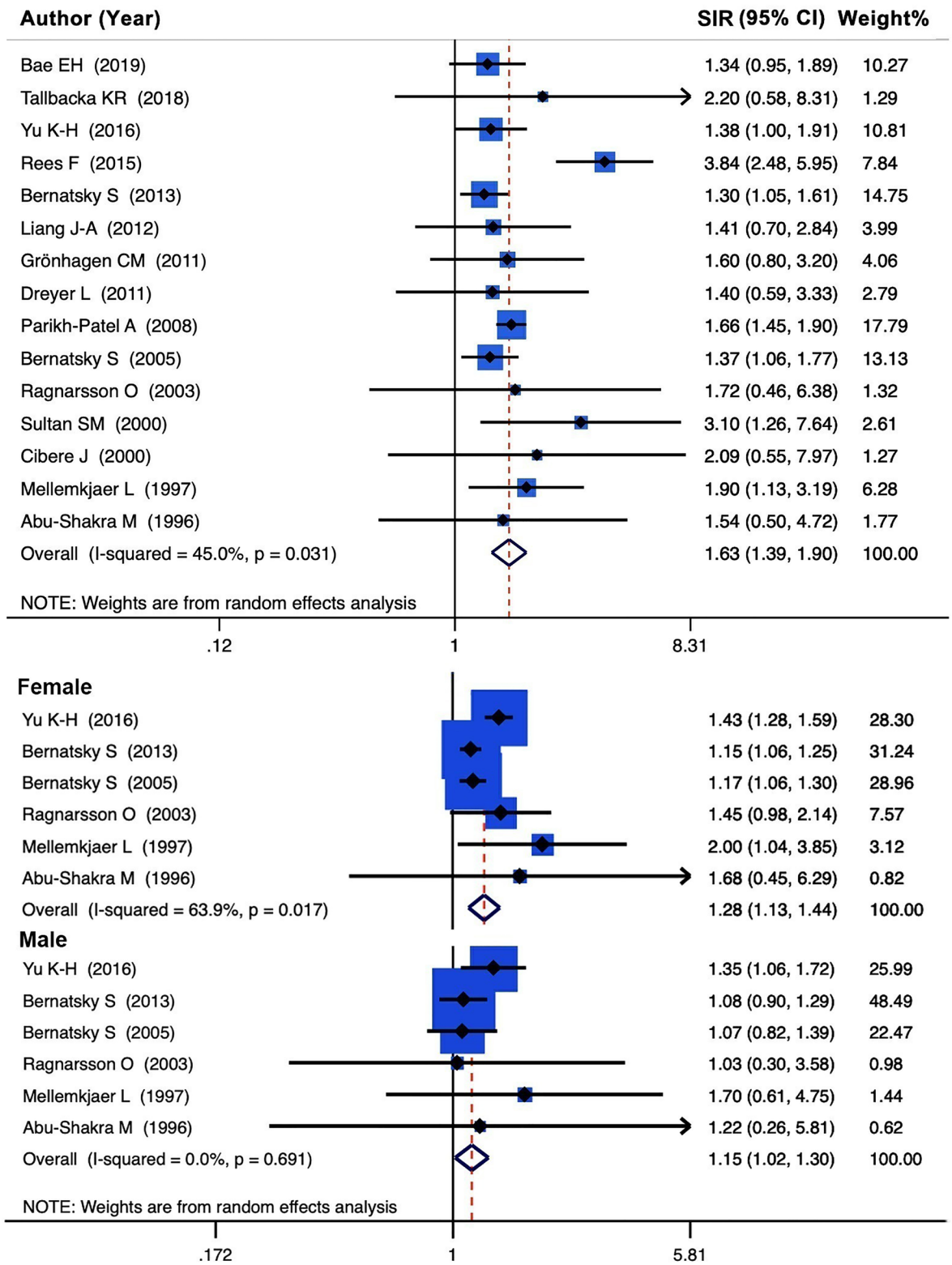

Figure 2 Comparing of lung cancer incidence in patients with or without systemic lupus erythematosus based on meta-analysis of populational-level cohort studies.

Table 4 MR estimates of the causality between genetically predisposed systemic lupus erythematosus and lung cancer.

Outcome	IVW method		MR-Egger		Weighted median method	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Lung cancer overall	1.045 (1.005, 1.086)	0.0276	1.086 (1.016, 1.162)	0.0236	1.039 (0.993, 1.088)	0.0090
Squamous Cell Lung Cancer	1.065 (1.002, 1.132)	0.0429	1.128 (1.015, 1.254)	0.0349	1.060 (0.990, 1.134)	0.0939
Lung adenocarcinoma	1.000 (0.965, 1.066)	0.5825	1.055 (0.966, 1.151)	0.2440	1.030 (0.965, 1.099)	0.3735

IVW, inverse variance-weighted; OR, odds ratio.

Table 5 Causal effects between genetically predisposed SLE and potential confounders and mediators.

Outcomes	Causal effect (95% CI)	P value
Obesity class 1 (BMI: 30–34.9 kg/m^2)	1.005 (0.982, 1.029)	0.6864
Obesity class 2 (BMI: 35–39.9 kg/m^2)	1.015 (0.980, 1.051)	0.4046
Obesity class 3 (BMI: ≥40 kg/m^2)	1.078 (1.005, 1.155)	0.0352
Previous smoker	0.999 (0.996, 1.002)	0.5838
Current smoker	0.999 (0.998, 1.000)	0.1314
Alcohol consumption	1.001 (1.000, 1.001)	0.4594

cancer; intercept =−0.0210, P=0.11 for squamous cell lung cancer) (*Table S3*). Further, The IVW results we evaluated whether the correlation between SLE and lung cancer was influenced by obesity, smoking and alcohol consumption status demonstrated that genetically predisposed SLE were not causally associated with these potential confounders and mediators except obesity class 3 (BMI: ≥40 kg/m^2), the risk of which increased by 7.8% (OR =1.078, 95% CI, 1.005–1.155, P=0.0352). Given that the results of epidemiological studies concerning the effects of obesity on lung cancer risk were conflicting (55,56), the confounder (obesity) was unlikely to influence the SLE-lung cancer relation from our study (*Table 5*, *Table S4*). However, evidence in the published GWAS stated that a few SNPs associated with SLE in our study were associated with other systemic autoimmune diseases. Hence, caution is required in interpreting the outcomes.

The MR analysis therefore supported a causality between genetically predisposed SLE and lung cancer.

Discussion

As far as we know, our analysis comprehensively evaluated the relationship between SLE and lung cancer risk for the first time. Fifteen published population-level cohort studies, including 89,963 females and 20,556 males with SLE, were enrolled in the meta-analysis, the results of which suggested that SLE was correlated with an increased risk of lung cancer (SIR =1.63, 95% CI, 1.39–1.90). Simultaneously, given that we only chose the population-based cohort studies to conduct meta-analysis, it was reasonable to state that our study held a relatively stronger statistical power than previous meta-analyses combined both case-control studies and cross-sectional studies (12,57). Moreover, stratified analysis suggested that female patients (SIR =1.28, 95% CI, 1.13–1.44) appeared to be more susceptible to lung cancer than male patients (SIR =1.15, 95% CI, 1.02–1.30).

Considering the shortcoming of observational studies that the causality cannot be inferred from the association between an exposure and an outcome, the association might be affected by reverse causality or confounders. Simultaneously, in view of the relatively long incubation period between SLE and the occurrence of lung cancer, it might be infeasible to investigate the causality through RCTs, which are widely accepted to answer questions of causality. From the point, our study can provide evidence by means of a novel type of study design, the two-sample MR, which also supported a positive association between SLE and risk of lung cancer. Several strengths of our study are as follow. First, to the very best of our knowledge, it is the largest study to investigate the causality between SLE and lung cancer risk using genetic variants. With large sample sizes (n=27,209) and robustly associated IVs (F-statistics

=5,183.67), our MR study with adequate statistical power could offer a relatively precise estimation of causal effect. Second, since once SLE-associated SNPs included in our study were also correlated with confounding factors, an accurate estimation of the causality between SLE and lung cancer would not be provided. Thus, we conducted additional MR analyses which indicated that genetically predisposed SLE was not causally associated with the potential confounders, including obesity, smoking and alcohol consumption, suggesting a relatively independent association between SLE and lung cancer. In addition, we stratified our outcomes according to histotypes, which was usually ignored by previous observational studies, further revealing a positive association between genetically predisposed SLE and squamous cell lung cancer.

Possible mechanisms have been proposed to explain the positive association between SLE and lung cancer risk. The Toll-like receptors (TLRs) are pattern-recognition receptors which play an important role in innate immunity, but inappropriate TLR responses could contribute to the pathogenesis of autoimmune diseases, including SLE, rheumatoid arthritis, systemic sclerosis and so on (58). Previous study has demonstrated that the type I interferon pathway mediated by TLRs is important in the pathogenesis of SLE, with high IFN-α levels and increased expression of interferon-inducible genes (59). Consequently, inappropriate TLR responses in SLE may be the key inducers of the whole inflammatory cascade (60). The activated inflammation ultimately results in a release of inflammatory mediators into the extracellular environment, with subsequent activation of innate immune cells (61). Furthermore, the chronic inflammation has been reported to be one of the most important pathogeneses of ILD among SLE patients (62). And the chronic inflammation in ILD could lead to extensive DNA damage, which is believed to be the underlying mechanism of the increased incidence of lung cancer (63,64). The chronic inflammation may also promote the carcinogenesis of lung by the production of nitrogen species and reactive oxygen, the proliferation of cells and increase in angiogenesis during tissue repair, and the up-regulation of antiapoptotic genes through the nuclear factor kappa B (NF-κB) pathway (65). Despite that parenchymal involvement in SLE is commonly considered to be relatively infrequent, some SLE patients, especially those with longstanding disease, may be more susceptible to developing chronic fibrotic lupus pneumonitis and the incidence of lung cancer might increase consequently (66). In addition, regarded as the independent risk factor for lung cancer, cigarette smoking has also been verified for the association with active SLE (67). Also, known as the main treatment for SLE patients, immunosuppressive drugs such as CTX and glucocorticoid which suppress immune surveillance by facilitating the survival and proliferation of abnormal cells have been reported to be related with its carcinogenic potential (68). Regarded as the first-line treatment for ILD and progressive skin-related diseases through inhibiting the progression of fibrosis, CTX makes a significant difference in the progression of malignancy because of the cellular injury during the process. Meanwhile, CTX has been reported to potentially increase the risk of bladder cancer (69). Use of mycophenolate is also an important facilitation of the cancerization (70). Nevertheless, related studies regarding carcinogenic effect of immunosuppressive drugs on lung cancer are rare and its mechanism remains unclear. Overall, the exact etiology underlying the attribution of SLE to risk of lung cancer remains unclear and more studies are warranted to further investigate their interaction.

Both meta-analysis and MR analysis results revealed an association between SLE and increased lung cancer risk. Further investigations with larger sample sizes and better designs are needed to verify our findings. Secondly, from the prospective of public health, discovering the etiology underlying the attribution of SLE to lung cancer is essential, which contributes to the long-term improvement of prognosis. Thirdly, early diagnosis of lung cancer among SLE patients is of vital importance, effective approaches including Low-dose CT (LDCT) screening (71), aspiration biopsy, targeted DNA methylation sequencing of circulating tumor DNA (ctDNA) (72) are accessible. It is also worth noting that the absolute numbers of SLE patients who died from lung cancer are relatively small even though a positive association between the two diseases was presented in our study. In conclusion, further studies will allow patients with SLE to be advised and monitored accordingly.

There are several limitations to our study. First, the inconsistency or lack of SLE diagnosis in some of the included studies could be the source of heterogeneity. Secondly, due to the finite original data from population-level cohort studies, we were only able to employ subgroup analysis stratified by gender, thus the effects of other confounders like age, smoking status, career exposure and treatments could not be evaluated or clarified. Third, articles written in languages other than English were not

included in this study, which might impede generalization of the conclusions.

Limitations of MR analysis exist. First, though we've used the most comprehensive set of genetic variants so far, it merely explained a part of variance of SLE across individuals. It is possible that some unknown SLE-related SNPs could also play an important role in the development of lung cancer. Second, all three MR assumptions could not be absolutely tested in our study and potential violations may occur. Due to the fact that the second assumption cannot be evaluated directly, additional sensitivity analyses were implemented in our study. No horizontal pleiotropic effects existed in our study, suggesting no violation of the second MR assumption. It is possible that some of the genetic variants were also associated with confounders of SLE and lung cancer in our study and caution is needed in considering the gross effect. Further, despite that 82 SLE-related SNPs were obtained from the published GWASs, a score including more SNPs up to date from other network database would have stronger power to detect a causal effect.

In summary, there is no doubt that the cancer prevention is the key to lowering the morbidity and mortality of cancers. Consequently, we ought to attach great importance to identifying more modifiable risk factors correlated with cancers. Afterwards, we are able to employ effective interventions to reduce the disease burden worldwide, especially in developing countries. Population-level cohort studies with more samples, appropriate and explicit SLE diagnostic criteria, better epidemiological design and suitable follow-up period are necessary. MR estimate constructed using genetic variants associated with different mechanisms, such as chronic inflammation and extensive DNA damage, may be beneficial in understanding the etiology of the occurrence and development of lung cancer among patients with SLE (73).

Conclusions

Consistent with the findings of the meta-analysis, MR results pointed to the existence of the causality. Both IVW, weighted median, and MR-Egger regression were employed to verify the reliability and accuracy of our findings, resulting in the authentic conclusions. Our results identified a causal risk factor for lung cancer which might contribute to long-term improvement of prognosis, including early-stage diagnosis of lung cancer and to take precautions against complications among SLE patients. From the prospective of public health, the etiology underlying the attribution of SLE to lung cancer warrants further investigation. Better designed population-level cohort studies and MR analysis using more genetic variants and individual-level samples are necessary to examine our findings and deeper our understanding of the two diseases.

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Supplementary

Table S1 Information of the SNPs enrolled in MR study

SNP	Chr	Region	Gene	EA	OA	LDd exclusion	PubMed ID
rs6762714	3	3q28	LPP	T	C	No	27399966
rs597325	6	6q15	BACH2	G	A	No	
rs17603856	6	6p22.3	ATXN1	T	G	No	
rs17321999	2	2p23.1	LBH	C	A	No	
rs1170426	16	16q22.1	ZFP90	C	T	No	
rs9782955	1	1q42.3	LYST	C	T	No	26502338
rs9652601	16	16p13.13	CIITA	G	A	No	
rs9311676	3	3p14.3	ABHD6	C	T	No	
rs849142	7	7p15.1	JAZF1	A	G	No	
rs7726414	5	5q31.1	TCF7	T	C	No	
rs704840	1	1q25.1	TNFSF4	G	T	No	
rs6932056	6	6q23.3	TNFAIP3	C	T	No	
rs4948496	10	10q21.2	ARID5B	C	T	No	
rs4917014	7	7p12.2	IKZF1	T	G	No	
rs3794060	11	11q13.4	DHCR7	C	T	No	
rs3768792	2	2q34	IKZF2	C	T	No	
rs34572943	16	16p11.2	ITGAM	A	G	No	
rs3024505	1	1q32.1	IL10	T	C	No	
rs2736340	8	8p23.1	BLK	T	C	No	
rs2289583	15	15q24.2	CSK	A	C	No	
rs2286672	17	17p13.2	PLD2	T	C	No	
rs2111485	2	2q24.2	IFIH1	G	A	No	
rs12802200	11	11p15.5	IRF7	C	A	No	
rs1270942	6	6p21.33	MHC class III	C	T	No	
rs11644034	16	16q24.1	IRF8	G	A	No	
rs10774625	12	12q24.12	SH2B3	A	G	No	
rs10028805	4	4q24	BANK1	G	A	No	
rs8023715	15	15q26.2	SPATA8	A	-	No	24871463
rs11697848	20	20q13.13	RNF114	T	C	No	
rs11073328	15	15q14	FAM98B	T	C	No	
rs10911628	1	1q25.3	EDEM3	A	C	No	
rs849142	7	7p15.1	JAZF1	T	C	No	19838195
rs3024505	1	1q32.1	IL10	A	G	No	
rs2070197	7	7q32.1	IRF5	C	T	No	

SNP, single-nucleotide polymorphism.

Table S2 Quality score of the enrolled studies in the meta-analysis

Author	Country	Study Type	Study Period	Eligibility criteria of selecting participants	Appropriate SLE diagnosis	Described participants' characteristics	Ascertainment of lung cancer	Adjustments for age and sex	Other relevant adjustments	Quality Score (0–6)
Bae *et al.* (13)	Korea	Cohort	2008–2014	Yes	No	Yes	Yes	Yes	Yes	5
Tallbacka *et al.* (43)	Finland	Cohort	1967–1987	Yes	Yes	Yes	Yes	No	Yes	5
Yu *et al.* (44)	China	Cohort	1997–2010	Yes	No	Yes	Yes	Yes	No	4
Rees *et al.* (16)	England	Cohort	1999–2012	Yes	No	Yes	Yes	Yes	Yes	5
Bernatsky *et al.* (45)	America	Cohort	1980–1988	Yes	Yes	Yes	Yes	No	No	4
Liang *et al.* (46)	America	Cohort	1996–2008	Yes	No	Yes	Yes	Yes	Yes	5
Grönhagen *et al.* (47)	Sweden	Cohort	1997–2007	Yes	No	Yes	Yes	Yes	No	4
Dreyer *et al.* (48)	Denmark	Cohort	1991–2005	Yes	Yes	Yes	Yes	No	No	4
Parikh-Patel *et al.* (11)	America	Cohort	1991–2002	Yes	Yes	Yes	Yes	Yes	No	5
Bernatsky *et al.* (38)	Canada	Cohort	2005	Yes	Yes	Yes	Yes	Yes	No	5
Ragnarsson *et al.* (49)	Iceland	Cohort	1957–2001	Yes	Yes	Yes	Yes	Yes	No	5
Sultan *et al.* (50)	England	Cohort	1975–1985	Yes	Yes	Yes	Yes	Yes	No	5
Cibere *et al.* (15)	Canada	Cohort	1978–1999	Yes	Yes	Yes	Yes	No	Yes	5
Mellemkjaer *et al.* (51)	Denmark	Cohort	1977–1989	Yes	Yes	Yes	Yes	Yes	Yes	6
Abu-Shakra *et al.* (52)	Canada	Cohort	1978–2002	Yes	Yes	Yes	Yes	Yes	No	5

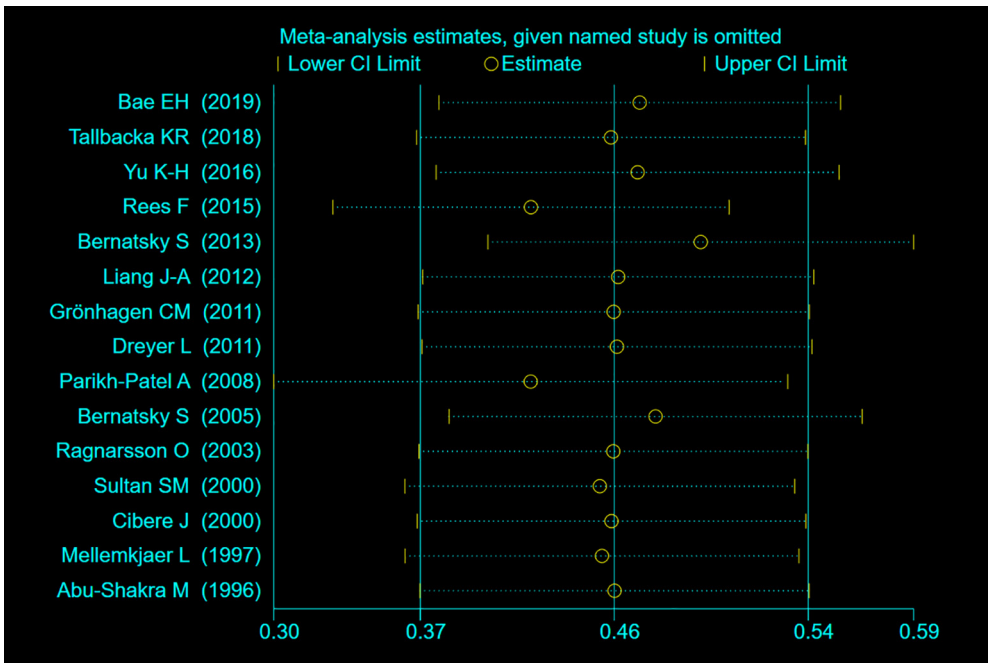

Figure S1 Sensitivity analysis of Meta-analysis.

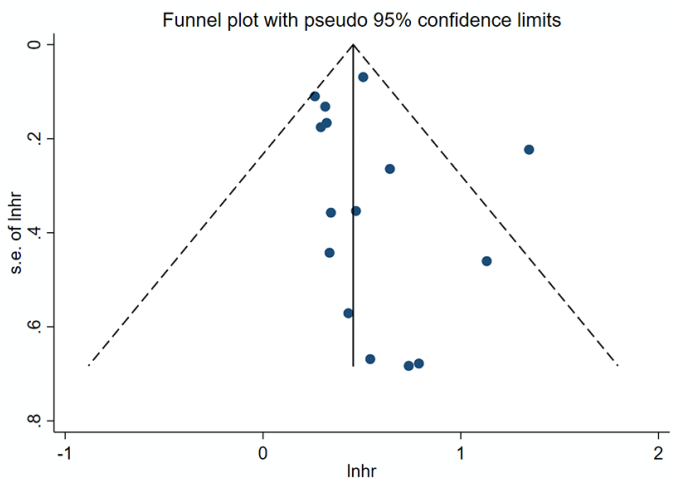

Figure S2 Funnel plot of meta-analysis.

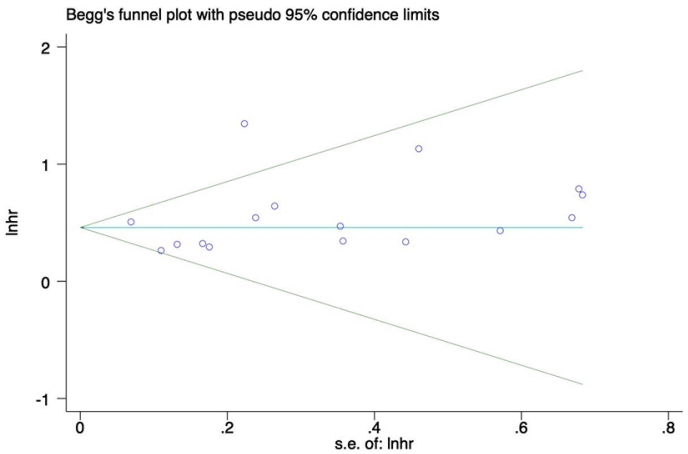

Figure S3 Begg's test of meta-analysis.

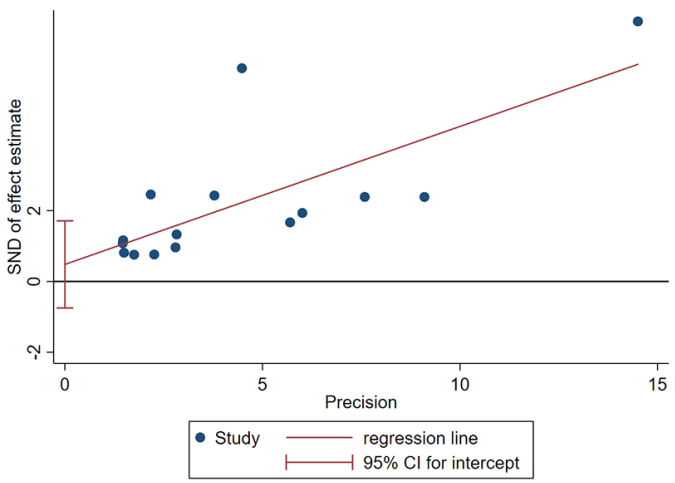

Figure S4 Egger's test of meta-analysis.

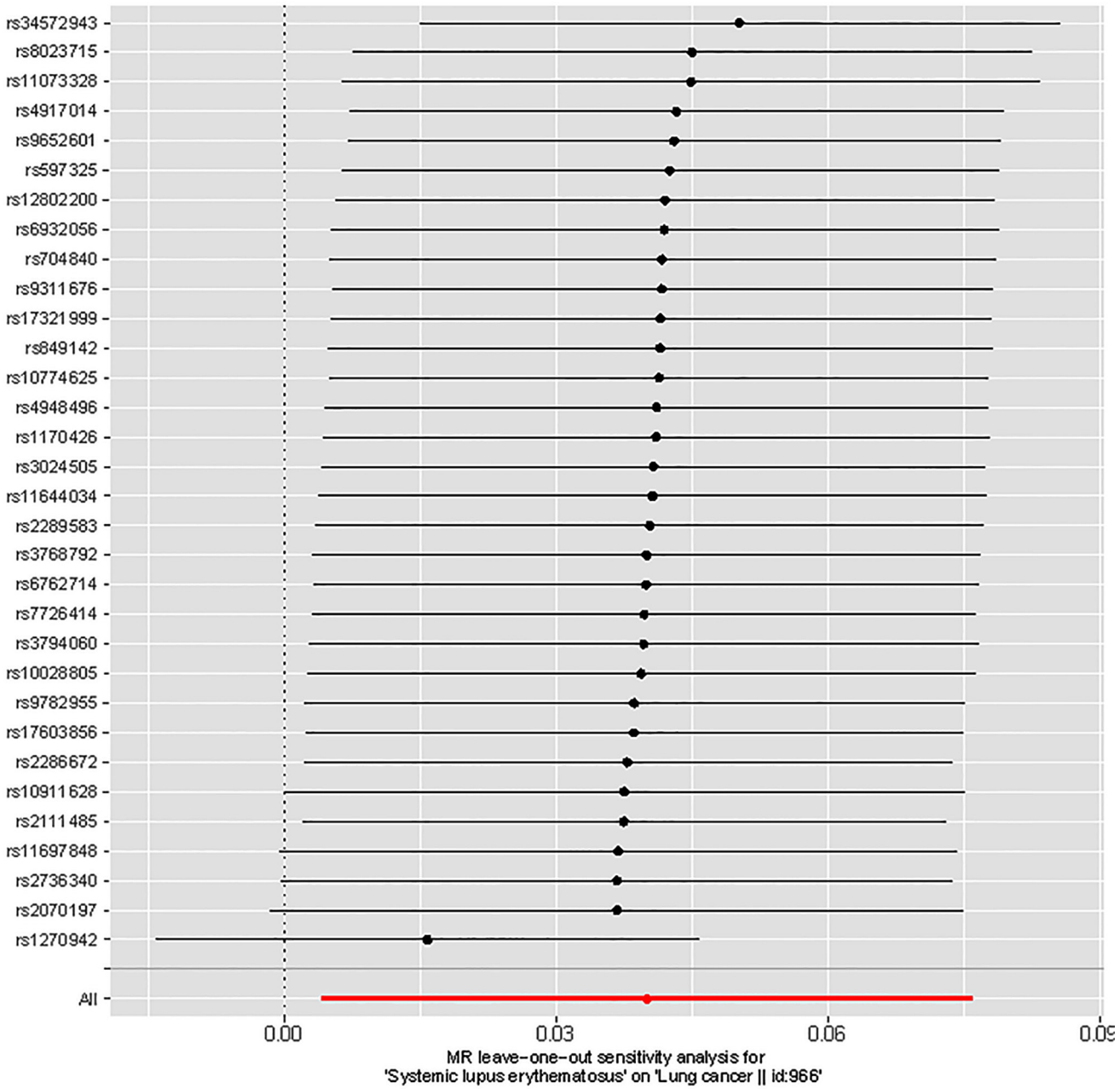

Figure S5 Leave-one-out analysis suggested that no single instrument was strongly driving the overall effect of SLE on lung cancer. SLE, systemic lupus erythematosus.

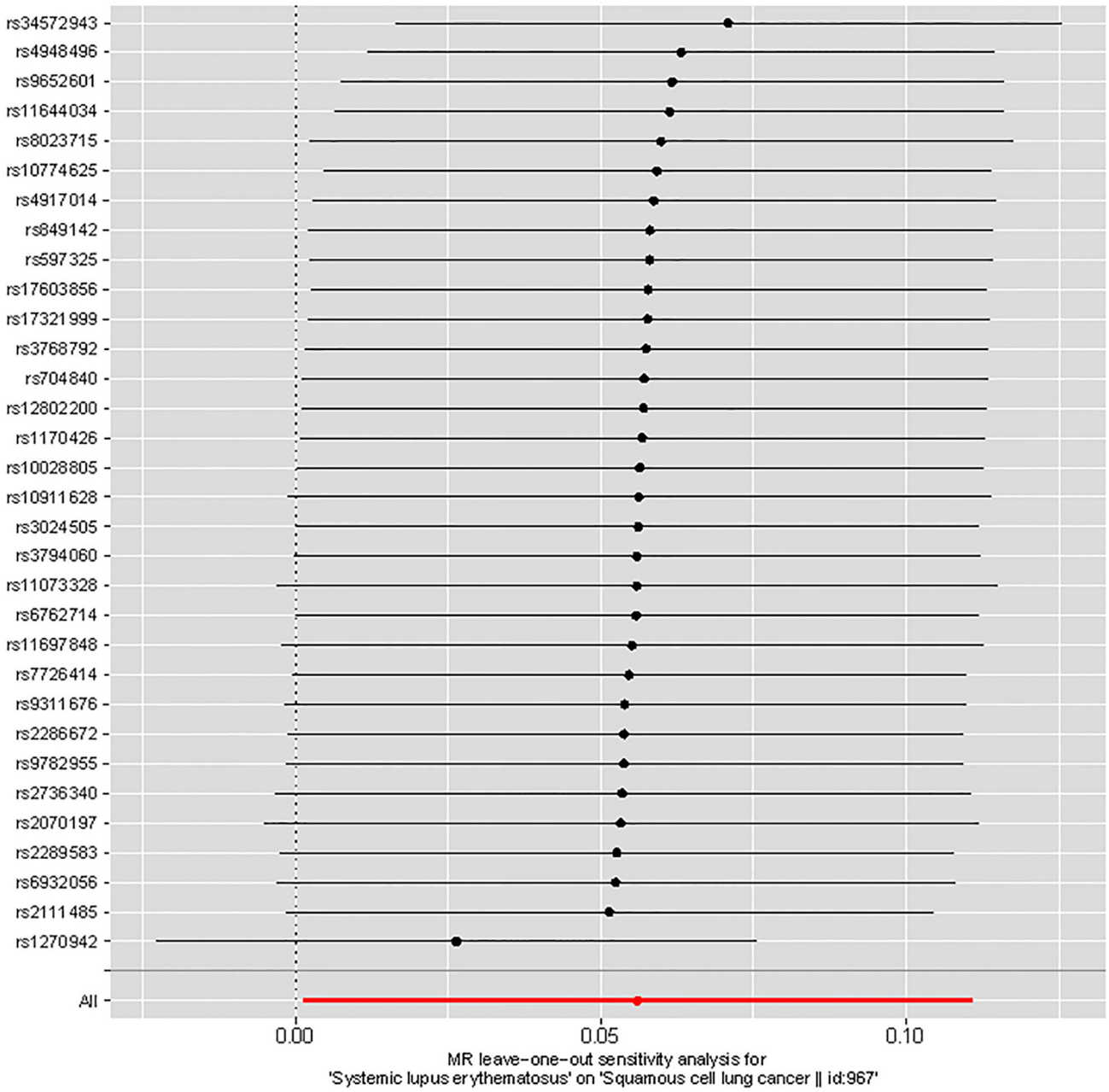

Figure S6 Leave-one-out analysis suggested that no single instrument was strongly driving the overall effect of SLE on squamous cell lung cancer. SLE, systemic lupus erythematosus.

Table S3 MR-Egger pleiotropy test of the associations between SLE and risk of lung cancer with types and sites

Outcome	MR-Egger method	
	Intercept	P value
Lung cancer overall	–0.0120	0.16
Type		
Lung adenocarcinoma	–0.0092	0.45
Squamous cell lung cancer	–0.0210	0.11

SLE, systemic lupus erythematosus.

Table S4 Association between genetically predisposed systemic lupus erythematosus and potential confounders and mediators

	ID.exposure	ID.outcome	Outcome	Exposure	Method	nsnp	B	SE	P	Lo CI	Up CI	OR	OR-low 95% CI	OR-up 95% CI
1	TG1F34	ieu-a-90	Obesity class 1 || ID: ieu-a-90	Systemic lupus erythematosus	MR Egger	33	1.64E-02	2.16E-02	4.53E-01	-2.59E-02	5.87E-02	1.02E+00	9.74E-01	1.06E+00
2	TG1F34	ieu-a-90	Obesity class 1 || ID: ieu-a-90	Systemic lupus erythematosus	Weighted median	33	4.11E-03	1.37E-02	7.64E-01	-2.28E-02	3.10E-02	1.00E+00	9.77E-01	1.03E+00
3	TG1F34	ieu-a-90	Obesity class 1 || ID: ieu-a-90	Systemic lupus erythematosus	Inverse variance weighted	33	4.84E-03	1.20E-02	6.86E-01	-1.87E-02	2.84E-02	1.00E+00	9.82E-01	1.03E+00
4	TG1F34	ieu-a-90	Obesity class 1 || ID: ieu-a-90	Systemic lupus erythematosus	Simple mode	33	7.26E-03	2.24E-02	7.48E-01	-3.67E-02	5.12E-02	1.01E+00	9.64E-01	1.05E+00
5	TG1F34	ieu-a-90	Obesity class 1 || ID: ieu-a-90	Systemic lupus erythematosus	Weighted mode	33	5.91E-03	1.62E-02	7.17E-01	-2.58E-02	3.77E-02	1.01E+00	9.74E-01	1.04E+00
6	TG1F34	ieu-a-91	Obesity class 2 || ID: ieu-a-91	Systemic lupus erythematosus	MR Egger	33	5.17E-02	3.19E-02	1.15E-01	-1.09E-02	1.14E-01	1.05E+00	9.89E-01	1.12E+00
7	TG1F34	ieu-a-91	Obesity class 2 || ID: ieu-a-91	Systemic lupus erythematosus	Weighted median	33	8.58E-03	2.49E-02	7.30E-01	-4.02E-02	5.74E-02	1.01E+00	9.61E-01	1.06E+00
8	TG1F34	ieu-a-91	Obesity class 2 || ID: ieu-a-91	Systemic lupus erythematosus	Inverse variance weighted	33	1.50E-02	1.79E-02	4.05E-01	-2.02E-02	5.01E-02	1.02E+00	9.80E-01	1.05E+00
9	TG1F34	ieu-a-91	Obesity class 2 || ID: ieu-a-91	Systemic lupus erythematosus	Simple mode	33	7.66E-03	4.39E-02	8.62E-01	-7.84E-02	9.37E-02	1.01E+00	9.25E-01	1.10E+00
10	TG1F34	ieu-a-91	Obesity class 2 || ID: ieu-a-91	Systemic lupus erythematosus	Weighted mode	33	9.50E-03	3.46E-02	7.86E-01	-5.84E-02	7.74E-02	1.01E+00	9.43E-01	1.08E+00
11	TG1F34	ieu-a-92	Obesity class 3 || ID: ieu-a-92	Systemic lupus erythematosus	MR Egger	32	1.62E-01	6.24E-02	1.44E-02	3.97E-02	2.84E-01	1.18E+00	1.04E+00	1.33E+00
12	TG1F34	ieu-a-92	Obesity class 3 || ID: ieu-a-92	Systemic lupus erythematosus	Weighted median	32	1.10E-01	4.65E-02	1.81E-02	1.88E-02	2.01E-01	1.12E+00	1.02E+00	1.22E+00
13	TG1F34	ieu-a-92	Obesity class 3 || ID: ieu-a-92	Systemic lupus erythematosus	Inverse variance weighted	32	7.48E-02	3.55E-02	3.52E-02	5.18E-03	1.44E-01	1.08E+00	1.01E+00	1.16E+00
14	TG1F34	ieu-a-92	Obesity class 3 || ID: ieu-a-92	Systemic lupus erythematosus	Simple mode	32	1.03E-01	7.97E-02	2.06E-01	-5.34E-02	2.59E-01	1.11E+00	9.48E-01	1.30E+00
15	TG1F34	ieu-a-92	Obesity class 3 || ID: ieu-a-92	Systemic lupus erythematosus	Weighted mode	32	1.52E-01	6.15E-02	1.87E-02	3.20E-02	2.73E-01	1.16E+00	1.03E+00	1.31E+00
16	TG1F34	ukb-a-224	Smoking status: Previous || ID: ukb-a-224	Systemic lupus erythematosus	MR Egger	34	-2.78E-03	2.45E-03	2.65E-01	-7.59E-03	2.03E-03	9.97E-01	9.92E-01	1.00E+00
17	TG1F34	ukb-a-224	Smoking status: Previous || ID: ukb-a-224	Systemic lupus erythematosus	Weighted median	34	2.95E-04	1.51E-03	8.45E-01	-2.67E-03	3.26E-03	1.00E+00	9.97E-01	1.00E+00
18	TG1F34	ukb-a-224	Smoking status: Previous || ID: ukb-a-224	Systemic lupus erythematosus	Inverse variance weighted	34	-7.76E-04	1.42E-03	5.84E-01	-3.55E-03	2.00E-03	9.99E-01	9.96E-01	1.00E+00
19	TG1F34	ukb-a-224	Smoking status: Previous || ID: ukb-a-224	Systemic lupus erythematosus	Simple mode	34	1.67E-03	2.80E-03	5.56E-01	-3.82E-03	7.15E-03	1.00E+00	9.96E-01	1.01E+00
20	TG1F34	ukb-a-224	Smoking status: Previous || ID: ukb-a-224	Systemic lupus erythematosus	Weighted mode	34	1.46E-03	2.11E-03	4.95E-01	-2.68E-03	5.59E-03	1.00E+00	9.97E-01	1.01E+00
21	TG1F34	ukb-a-225	Smoking status: Current || ID: ukb-a-225	Systemic lupus erythematosus	MR Egger	34	-1.80E-03	1.20E-03	1.44E-01	-4.16E-03	5.57E-04	9.98E-01	9.96E-01	1.00E+00
22	TG1F34	ukb-a-225	Smoking status: Current || ID: ukb-a-225	Systemic lupus erythematosus	Weighted median	34	-9.66E-04	8.38E-04	2.49E-01	-2.61E-03	6.77E-04	9.99E-01	9.97E-01	1.00E+00
23	TG1F34	ukb-a-225	Smoking status: Current || ID: ukb-a-225	Systemic lupus erythematosus	Inverse variance weighted	34	-1.04E-03	6.90E-04	1.31E-01	-2.39E-03	3.11E-04	9.99E-01	9.98E-01	1.00E+00
24	TG1F34	ukb-a-225	Smoking status: Current || ID: ukb-a-225	Systemic lupus erythematosus	Simple mode	34	4.25E-06	1.55E-03	9.98E-01	-3.03E-03	3.04E-03	1.00E+00	9.97E-01	1.00E+00
25	TG1F34	ukb-a-225	Smoking status: Current || ID: ukb-a-225	Systemic lupus erythematosus	Weighted mode	34	-1.11E-03	9.51E-04	2.50E-01	-2.98E-03	7.51E-04	9.99E-01	9.97E-01	1.00E+00
26	TG1F34	ukb-a-227	Alcohol drinker status: Previous || ID: ukb-a-227	Systemic lupus erythematosus	MR Egger	34	2.36E-04	5.79E-04	6.87E-01	-8.99E-04	1.37E-03	1.00E+00	9.99E-01	1.00E+00
27	TG1F34	ukb-a-227	Alcohol drinker status: Previous || ID: ukb-a-227	Systemic lupus erythematosus	Weighted median	34	4.84E-04	4.64E-04	2.97E-01	-4.26E-04	1.39E-03	1.00E+00	1.00E+00	1.00E+00
28	TG1F34	ukb-a-227	Alcohol drinker status: Previous || ID: ukb-a-227	Systemic lupus erythematosus	Inverse variance weighted	34	2.47E-04	3.34E-04	4.59E-01	-4.08E-04	9.02E-04	1.00E+00	1.00E+00	1.00E+00
29	TG1F34	ukb-a-227	Alcohol drinker status: Previous || ID: ukb-a-227	Systemic lupus erythematosus	Simple mode	34	2.28E-04	7.53E-04	7.64E-01	-1.25E-03	1.70E-03	1.00E+00	9.99E-01	1.00E+00
30	TG1F34	ukb-a-227	Alcohol drinker status: Previous || ID: ukb-a-227	Systemic lupus erythematosus	Weighted mode	34	4.41E-04	4.93E-04	3.78E-01	-5.26E-04	1.41E-03	1.00E+00	9.99E-01	1.00E+00

SNP, single nucleotide polymorphism; b, beta; SE, standard error; OR, odds ratio; P, P value, ID, identification. Data citation: Wang Y. 2014; International Lung Cancer Consortium; http://ilcco.iarc.fr/; doi: 10.1038/ng.3002