Original Article

Age at first sexual intercourse, age at menarche, and age at menopause: a mendelian randomization study on lung cancer risk

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Background: There is increasing evidence that sex hormones are involved in the development of lung cancer, but the correlation between the reproductive behavior that changes sex hormone levels and lung cancer is not yet clear. Many previous studies have investigated the association between reproductive factors and lung cancer risk, but the results have been inconsistent. Therefore, we conducted a two-sample Mendelian randomization (MR) analysis to explore the potential relationship between age at first sexual intercourse (AFS), age at menarche, and age at menopause, and lung cancer.

Methods: We performed a MR analysis of the data from the genome-wide association study (GWAS) of European ancestry to evaluate the independent effects of three reproductive behaviors on lung cancer overall (LUCA), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and small cell lung cancer (SCLC). We mainly used the inverse-variance weighting method for the MR analysis. Sensitivity was determined by a MR-pleiotropy residual sum and outlier analysis, a weighted median analysis, a MR-Egger analysis, and a leave-one-out analysis.

Results: The MR analysis results revealed that older AFS had a causal relationship with LUCA [odds ratio (OR) =0.6283, 95% confidence interval (CI): 0.4959–0.7961, P=0.0001), LUAD (OR =0.7042, 95% CI: 0.4967–0.9984, P=0.049), and LUSC (OR =0.6231, 95% CI: 0.4386–0.8853, P=0.0083).

Conclusions: Our results revealed a causal relationship between older AFS and a lower risk of lung cancer. Our findings emphasize the importance of providing sex education, as early sexual intercourse may have undesirable effects. In addition, early psychological treatment is also essential.

Keywords: Reproductive behaviors; lung cancer; Mendelian randomization analysis (MR analysis); age at first sexual intercourse (AFS); lung cancer prevention

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Introduction

Globally, the incidence of lung cancer is declining (1); however, it remains the second most common cancer and the most common cause of cancer-related death (2). With the development of surgery, targeted therapy, immunotherapy, and other treatments, the 5-year survival rate of lung cancer patients has improved. However, the prognosis of most patients with lung cancer remains poor (3).

Smoking is a recognized risk factor for lung cancer (4-6), but we are seeing an increasing number of patients with lung cancer who have no history of smoking (7,8).

Consequently, the identification of potential modifiable risk factors and making adjustments are essential for lung cancer prevention.

Previous studies have reported that hormones, especially sex hormones, may be related to the occurrence, development, and prognosis of lung cancer (9-11). These findings suggest that sex hormones may play a role in the development of lung cancer. Therefore, we believe that some reproductive behaviors that can alter sex hormone levels, such as age at first sexual intercourse (AFS), age at menarche, and age at menopause, may affect the development of lung cancer.

A large number of observational studies have attempted to explore the relationship between reproductive factors and lung cancer, but their results have not been the same (12-15).

However, traditional observational study designs capture exposure through questionnaires, biochemical testing, or imaging, whereas genetic variants are present at birth and remain stable throughout life. Therefore, the associations obtained by MR are not affected by causal inversion and are less likely to be affected by confounders. Due to the inherent limitations of observational studies, the observed association between reproductive factors and lung cancer may not so reliable and requires further verification (16). Taking these factors into account, we used a new genetic epidemiological tool [i.e., a Mendelian randomization (MR) analysis] in this study. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-480/rc).

Highlight box

Key findings

- We found that older age at first sexual intercourse (AFS) was a protective factor for lung cancer.

What is known, and what is new?

- Previous studies have reported that hormones, especially sex hormones, may be related to the occurrence, development, and prognosis of lung cancer. Therefore, we believe that some reproductive behaviors, such as AFS, age at menarche, and age at menopause, can alter sex hormone levels, which may in turn affect the development of lung cancer.
- Older AFS was a protective factor for lung cancer, while age at menarche, and age at menopause were not significantly associated with lung cancer.

What is the implication, and what should change now?

- Premature sexual intercourse increases the risk of lung cancer, and we should pay attention to sex education for adolescents. For adolescents with a history of early sexual intercourse, lung cancer screening and psychological counseling should be carried out in a timely manner.

Methods

Data source

In this study, we used pooled data from a genome-wide association study (GWAS) to explore the relationship between three reproductive factors and lung cancer through a two-sample MR analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

For reproductive factors, we searched the IEU-Open GWAS (https://gwas.mrcieu.ac.uk/) website for aggregate GWAS data from Mills *et al.* (17) and the UK Biobank. For AFS, Melinda C Mills *et al.* included 397,338 pooled individuals (n=182,791 males; n=214,547 females) from the UK Biobank. AFS was treated as a continuous measure with individuals considered as eligible if they had given a valid answer and ages lower than 12 excluded (17). For lung cancer, we searched the IEU-Open GWAS website for GWAS pooled data from Wang *et al.* (18) and FinnGen (19). Wang *et al.* conducted imputation to the 1000 Genomes Project of four GWAS of lung cancer in populations of European ancestry (11,348 cases and 15,861 controls) and genotyped an additional 10,246 cases and 38,295 controls for follow-up. Tumors from patients were classified as adenocarcinomas, squamous carcinomas, and other non-small cell lung cancer histologies following either the International Classification of Diseases for Oncology (ICD-O) or World Health Organisation (WHO) coding (18).

We extracted the single nucleotide polymorphisms (SNPs) that were reliably associated with AFS (ebi-a-GCST90000047), age at menarche (ukb-a-315), and age at menopause (ukb-b-17422) from the data sets archived in the GWAS database. We also obtained summary-level data for the outcome events "LUCA, LUAD, LUSC, SCLC" from the "ieu-a-966, ieu-a-965, ieu-a-967, finn-b-C3_SCLC" data sets. All the SNPs were selected from European populations to meet the Hardy-Weinberg law and eliminate demographic distribution bias (20). The GWAS data are listed in *Table 1*.

Table 1 The genome-wide association study data of our study

Exposure and outcome	GWAS-ID	PMID	Population	Number of SNPs	Sample size
Exposure					
Age at first sexual intercourse	ebi-a-GCST90000047	34211149	European	16,359,424	397,338
Age at menarche	ukb-a-315	NA	European	10,894,596	176,008
Age at menopause	ukb-b-17422	NA	European	9,851,867	143,819
Outcome					
Lung cancer	ieu-a-966	24880342	European	8,945,893	Case: 11,348; control: 15,861
Lung adenocarcinoma	ieu-a-965	24880342	European	8,881,354	Case: 3,442; control: 14,894
Lung squamous cell carcinoma	ieu-a-967	24880342	European	8,893,750	Control: 15,038; sample size: 18,313
Small cell lung cancer	finn-b-C3_SCLC	NA	European	16,380,466	Case: 179; control: 218,613

SNP, single nucleotide polymorphism; NA, not available.

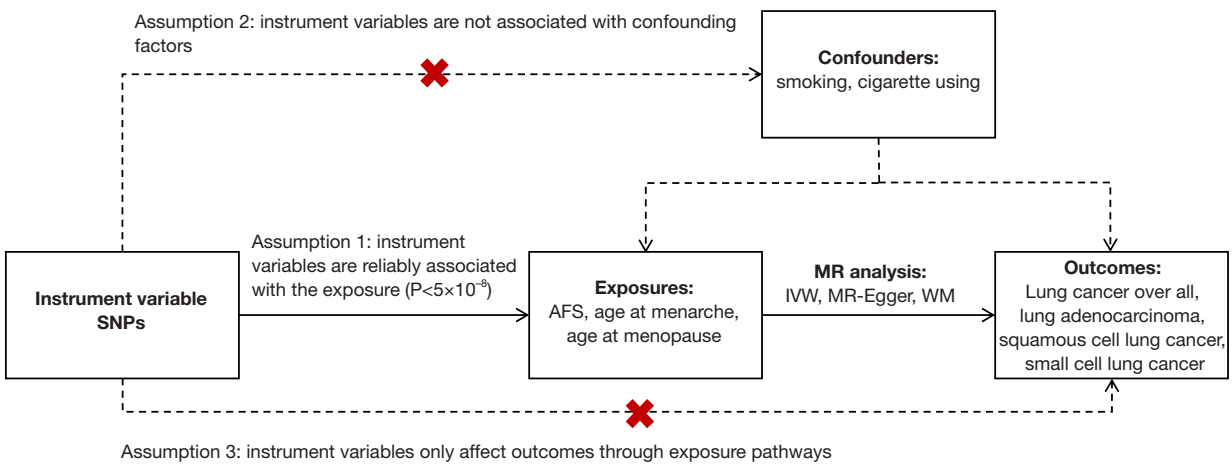

Figure 1 MR study flow diagram to determine the causal effect of three exposures on lung cancer, The dashed lines indicate potential pleiotropic or direct causal effects between the variables that may violate MR assumptions. MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; AFS, age at first sexual intercourse; IVW, inverse-variance weighted; WM, weighted median.

Statistical approach

A MR analysis is a novel approach for solving problems in human biology and epidemiology that uses genetic variation as instrumental variables (IVs) (21). Genetic information refers to the information that organisms transmit from their parents to their offspring, or from cells to cells during each cell division, to replicate the same information as themselves (22), and it is difficult for genetic information to be influenced by confounding factors and reverse causality. A MR analysis can be used to identify genetic variations related to target exposure through large-scale GWAS and these genetic variations can then be applied to independent data sets to generate unbiased estimates of exposure and outcome (23).

Selection of IVs

To be reliable, an IV needs to meet the following conditions: (I) be reliably associated with the exposure ($P<5\times10^{-8}$); (II) not be associated with confounding factors; and (III) only affect outcomes through exposure pathways (24,25). *Figure 1* provides an overview of the basic principles, design, and process of our MR analysis.

First, we extracted the SNPs that were strongly associated with three reproductive factors ($P<5\times10^{-8}$) from the GWAS data sets as the respective IVs. Second, we selected the SNPs with a distance of 10,000 kb from each other to exclude the SNPs with linkage disequilibrium (LD) ($R^2<0.001$). As smoking is a common risk factor for lung cancer, the SNPs associated with "smoking" and "cigarette use" were also removed. Third, to avoid the bias caused by weak IVs, we calculated the F-statistic for each SNP using the following formula (26):

$$\boldsymbol{F}=\frac{\boldsymbol{N}-\boldsymbol{k}-1}{\boldsymbol{k}}\times\frac{\boldsymbol{R}^2}{1-\boldsymbol{R}^2} \quad [1]$$

to estimate the strength of the genetic instruments, where N is the sample size, and k is the total number of the SNPs selected for the MR analysis. The following formula was used to calculate the R^2 for each significant SNP (26):

$$\boldsymbol{R}^2=\frac{2\times\mathbf{BETA}^2\times\mathbf{EAF}\times(1-\mathbf{EAF})}{2\times\mathbf{BETA}^2\times\mathbf{EAF}\times(1-\mathbf{EAF})+2\times\mathbf{EAF}\times(1-\mathbf{EAF})\times\mathbf{N}\times\mathbf{SE}^2} \quad [2]$$

where BETA is the estimated effect on exposures, EAF is the effect allele frequency, N is the sample size, and SE is the standard error for each SNP. A F-statistic >10 suggests that the SNP is a sufficiently strong instrument to explain phenotypic variation, while a F-statistic <10 suggests that the SNP is a weak instrument (27). The F-statistic results for the three reproductive factors are shown in online table (available at https://cdn.amegroups.cn/static/public/tlcr-24-480-1.xls). Fourth, we extracted the SNPs that were strongly associated with four outcomes from the three reproductive factor associated SNPs based on a correlation criterion of $R^2<0.01$. Further, the fuzzy SNPs with alleles of different origin and palindromic SNPs with fuzzy chains were directly excluded from the MR analysis. We also excluded the SNPs with a LD distance >10,000 kb and minor allele frequency (MAF) <0.01, as well as palindrome and multidirectional outlier SNPs. The number of SNPs for the three reproductive factors in cancer is shown in online tables (available at https://cdn.amegroups.cn/static/public/tlcr-24-480-1.xls; https://cdn.amegroups.cn/static/public/tlcr-24-480-2.xls; https://cdn.amegroups.cn/static/public/tlcr-24-480-3.xlsx, respectively).

Statistical analysis

Our study applied a MR analysis to explore the genetic associations of three reproductive factors (AFS, age at menarche, and age at menopause) and four outcomes [lung cancer overall (LUCA), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and small cell lung cancer (SCLC)].

To evaluate the causal impact of each reproductive factor on the risk of lung cancer and to test the sensitivity of the results to different patterns that violate IV assumptions, we mainly used the following three statistical methods: the inverse variance weighted (IVW) method, the MR-Egger method, and the weighted median (WM) method (28). The IVW method requires each genetic variation to satisfy the assumption of the IVs, when this condition is met, its statistical efficiency is significantly higher than that of the other two methods (29). Thus, it was used as the main statistical method. The MR-Egger method provides a sensitivity analysis for the robustness of the MR analysis results (30). The WM method generates consistent estimates even if more than 50% of the information comes from invalid IVs (31). The estimated effects of the three reproductive factors are reported as the odds ratio (OR) with the corresponding 95% confidence interval (CI).

The MR-pleiotropy residual sum and outlier (MR-PRESSO) method was used to check whether there were any outliers in the SNPs and remove them (32). After removed outliers in the SNPs, we mainly used the three methods to test the sensitivity of the results of our MR analysis. We tested the heterogeneity of the SNPs using the IVW and MR-Egger methods, and we used funnel plots as the validation method (33,34). We applied the MR-Egger method to evaluate whether there was horizontal pleiotropy in the SNPs (35). In addition, we employed the leave-one-out method to detect whether there was an individual single SNP that had a significant impact on the outcomes (36).

All the MR analyses, including the two-sample MR analysis, MR-Egger, and MR-PRESSO, were conducted using R software (version 4.2.3) with R packages.

Results

We found that older AFS was a protective factor for LUCA (OR =0.6283, 95% CI: 0.4959–0.7961, P=0.0001), LUSC (OR =0.6231, 95% CI, 0.4386–0.8853, P=0.008), and LUAD (OR =0.7042, 95% CI: 0.4967–0.9984, P=0.049), but was not related to SCLC (OR =0.3916, 95% CI: 0.0982–1.5608, P=0.18). Age at menopause and age at menarche were not associated with lung cancer. The effects of genetic causality between the three reproductive factors and lung cancer were analyzed using the three MR methods (i.e., the IVW, MR-Egger, and WM methods) as shown in *Figure 2*.

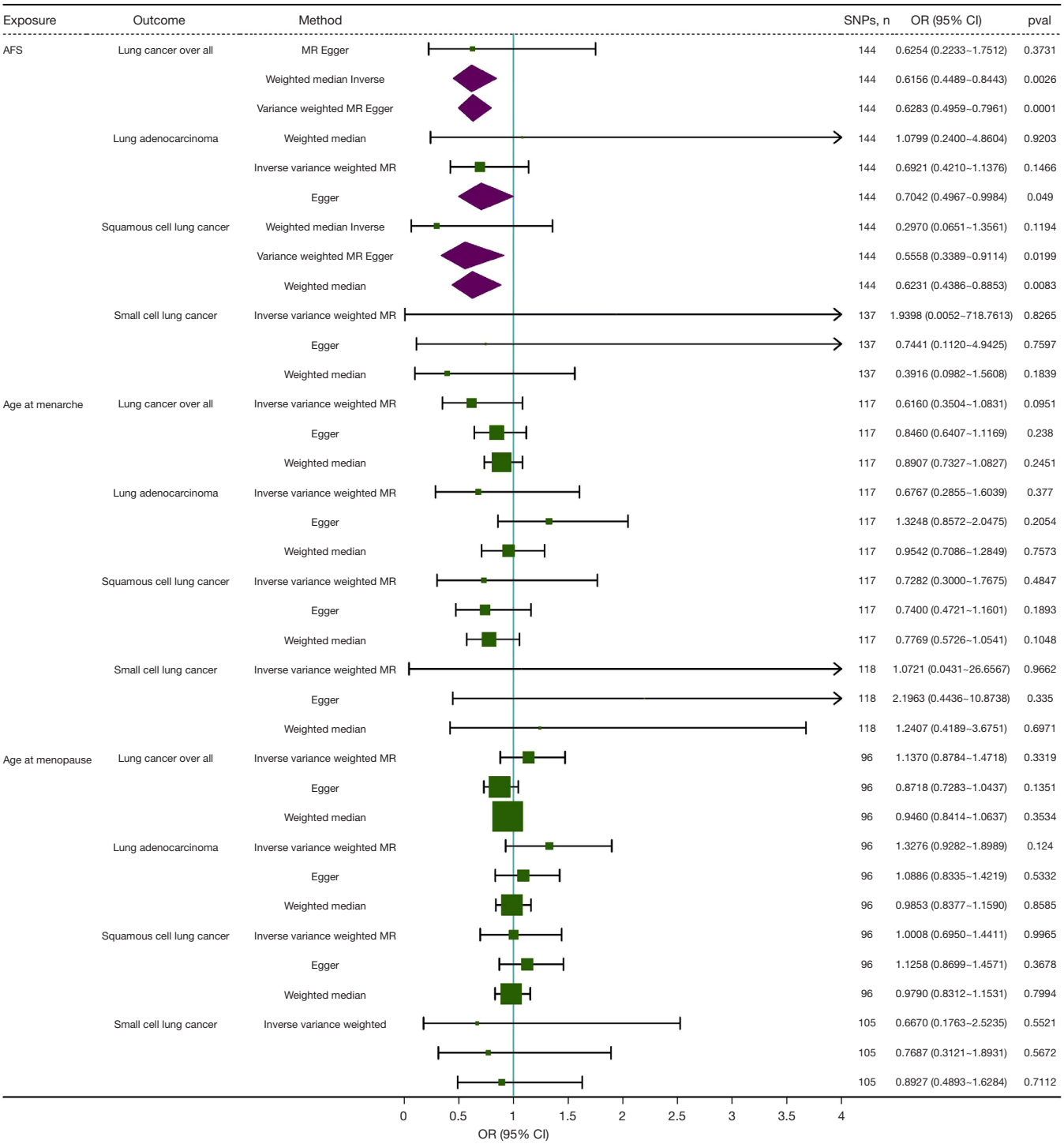

Figure 2 Relationship of three exposures with lung cancer by a MR analysis. Sensitivity was determined by the listed methods. MR, mendelian randomization; OR, odds ratio; CI, confidence interval; AFS, age at first sexual intercourse; SNPs, single nucleotide polymorphisms.

In addition, the effects of the three reproductive factors on the risk of lung cancer are shown in the scatter plots (Figure S1). The results of our MR analysis for the effect size of the three reproductive factors on the four outcomes are shown in the forest maps (Figure S2). To assist in verifying the heterogeneity, the results are all presented in the funnel plots (Figure S3). A funnel plot that was symmetrical on both sides indicated that there was no heterogeneity in the results (37,38).

The three reproductive factors showed significant heterogeneity in some outcomes; however, most results remained consistent after the MR-PRESSO analysis (Table S1). No significant difference in pleiotropy was observed in the effect estimates of the three exposures (Table S1). This indicates that after the data correction, the results showed that older AFS may reduce the risk of lung cancer, especially LUSC and LUAD. When any SNP was removed, the sensitivity analysis of the leave-one-out method did not reveal any significant changes that affected the estimation (Figure S4), indicating that our MR analysis results were robust.

In summary, of the three reproductive factors examined in this study, only AFS was genetically associated with lung cancer using the IVW method. Thus, older AFS significantly lowered the risk of lung cancer, especially LUSC and LUAD.

Discussion

In this two-sample MR analysis, we found that older AFS was a protective factor for lung cancer. More specifically, we found that an increase in the number of units of AFS (1 year) predicted a nearly one-third reduction in lung cancer risk. After a further subgroup analysis, we found that older AFS reduced the incidence rate of LUSC and LUAD, but had no effect on the incidence rate of SCLC. In addition, the other two reproductive factors were not found to be associated with the risk of lung cancer.

To the best of our knowledge, our study is the first MR study to use large-scale GWAS data to examine the genetic causality between AFS and the risk of lung cancer. Due to the relatively long incubation period between AFS and lung cancer, randomized controlled trials, which are considered the gold standard for investigating causal relationships, cannot be conducted. We could find no published studies that explored a causal relationship between AFS and lung cancer. Based on the results of this study, we suggest that the association between AFS and the risk of lung cancer lies in physical and psychological changes after sexual intercourse.

It is well known that sex hormones play a crucial role in sexual activity (39-42). Changes in hormone levels in adolescents after first sexual intercourse may be a physiological factor in the increased incidence of lung cancer. Stabile *et al.* suggest that estrogen signaling plays a biological role in both the epithelium and the mesenchyme in the lung, and that estrogens could potentially promote lung cancer, either through direct actions on preneoplastic or neoplastic cells or through indirect actions on lung fibroblasts (43). Apart from Stabile *et al.*, numerous studies have shown that estrogen plays an important role in the development and progression of lung cancer (44-48). For example, elevated estrogen in women has been linked to a reduced ability to repair DNA, making women more susceptible to the carcinogenic effects of tobacco (46). Estrogen can act as a direct or indirect carcinogen by altering cell proliferation or regulating cell growth factors (49,50). In addition, there are also a large number of studies showing that the use of hormone replacement therapy in women at different times has different effects on lung cancer outcomes, and these studies support the impact of estrogen levels on lung cancer outcomes (51-55).

In addition to estrogen, the role of androgens also cannot be ignored (56-60). Becerra-Díaz *et al.* suggest that androgens promote the polarization of M2 macrophages, thereby enhancing tumor growth and inhibiting anti-tumor immune responses (59). We suspect that younger AFS may increase the risk of lung cancer by exposing adolescents to hormone-related risk factors earlier.

At the same time, younger AFS may also play a role in the development of lung cancer through psychological factors. Numerous studies have reported that younger AFS is associated with depression in adolescents (61-63). The findings of a large prospective cohort study over 24 years suggested that depressive symptoms may contribute to the incidence of lung cancer (64). All these studies verify the reliability of the results of our MR analysis.

In addition to indirectly increasing the risk of lung cancer by affecting the level of sex hormones or psychological factors, reproductive factors themselves can also directly affect the incidence of lung cancer. A recent prospective cohort study used a Cox proportional hazards model to assess the association between multiple reproductive factors and the risk of lung cancer development, and showed that early age at menopause, shortened reproductive life span, and early age at first birth were associated with a higher

risk of lung cancer, particularly LUAD (14). The study confirmed that multiple reproductive factors were associated with the risk of developing lung cancer, but unfortunately it did not include AFS in the study. Our findings complement those of this study.

Interestingly, our study found that menarche and age at menopause were not associated with the development of lung cancer. This may be different from most people's stereotypes, but there are some previous studies that support our conclusions (65,66).

Conclusions

As far as we know, our study is the first to describe the association between AFS and the risk of lung cancer by MR analysis. We found that older AFS was a protective factor for lung cancer. This finding may have important implications for public health policy and practice. We recommend that adolescents refrain from sexual intercourse at a young age, especially if there is a family history of lung cancer. For adolescents who already have younger AFS, early psychotherapy and earlier screening by chest computed tomography are recommended.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-480/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-480/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-480/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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