Original Article

Association between strenuous sports or other exercises and lung cancer risk: a mendelian randomization study

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Background: Studying the relationship between strenuous sports or other exercises (SSOE) and lung cancer risk remains underexplored. Traditional observational studies face challenges like confounders and inverse causation. However, Mendelian randomization (MR) provides a promising approach in epidemiology and genetics, using genetic variants as instrumental variables to investigate causal relationships. By leveraging MR, we have scrutinized the causal link between SSOE and lung cancer development.

Methods: Twelve single-nucleotide polymorphisms (SNPs) associated with SSOE, as identified in previously published genome-wide association studies, were utilized as instrumental variables in our investigation. Summary genetic data at the individual level were obtained from relevant studies and cancer consortia. The study encompassed a total of 11,348 cases and 15,861 controls. The statistical technique of inverse variance-weighting (IVW), commonly employed in meta-analyses and MR studies, was employed to assess the causal relationship between SSOE and lung cancer risk.

Results: The MR risk analysis indicated a causal relationship between SSOE and the incidence of lung cancer, with evidence of a reduced risk for overall lung cancer [odds ratio (OR) =0.129; 95% confidence interval (CI): 0.021–0.779; P=0.03], lung adenocarcinoma (OR =0.161; 95% CI: 0.012–2.102; P=0.16) and squamous cell lung cancer (OR =0.045; 95% CI: 0.003–0.677; P=0.03). The combined OR for lung cancer from SSOE (controlling for waist circumference and smoking status) was 0.054 (95% CI: 0.010–0.302, P<0.001).

Conclusions: Our MR analysis findings indicate a potential correlation between SSOE and a protective effect against lung cancer development. Further investigation is imperative to uncover the precise mechanistic link between them.

Keywords: Lung cancer; exercise; Mendelian randomization (MR); multivariable MR

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Introduction

Lung cancer is a global and common aggressive disease that affects people all over the world. Although morbidity and mortality rates vary greatly between men and women in different parts of the world, lung cancer is the cancer that causes the most deaths in men and the second most deaths in women. Men are about twice as likely as women to develop and die from lung cancer (1). Despite recent therapeutic advancements, lung cancer remains a major public health issue in the United States and globally (2). With a 5-year survival rate of only 19% (3), the identification of preventable and modifiable factors that effectively mitigate the risk of lung cancer is of paramount importance.

Consumption of fruit and vegetables, breakfast cereals, and dietary fiber have been inversely associated with the risk of lung cancer (4). In contrast, there are numerous factors that are positively associated with the risk of lung cancer, including occupational exposures, smoking, and radiation exposure, to mention a few. Smoking is a widely recognized catalyst for lung cancer, profoundly impacting individual susceptibility. Extensive studies since the 1950s have unequivocally demonstrated the carcinogenic effects of tobacco smoke on lung health (5). Persistent smokers face a 20- to 50-fold greater risk of developing lung cancer compared to nonsmokers. The duration of smoking plays a pivotal role in determining this risk (6-9). Furthermore, exercise has been suggested as a potential preventive factor against lung cancer (5). Potential biological factors may underlie the effectiveness of exercise in the prevention and treatment of lung cancer. These mechanisms include promoting p53-mediated apoptosis, supporting immune cell infiltration, suppressing lung cancer cell growth and survival, improving the tumor microenvironment, reducing chronic inflammation, turning on DNA repair enzymes, and reducing oxidative stress (7-16).

Recent studies have demonstrated that voluntary exercise can increase immune cells in tumors and significantly reduce tumor incidence and development across multiple rodent models (13). It is hypothesized that this relationship between exercise and the immune system could be leveraged in cancer treatment, particularly in conjunction with immunotherapy, given the similarity in immune cell activation processes during exercise in both rodents and humans (17). In addition, exercise is often employed as a therapy for lung cancer (18).

However, the associations between these factors remain uncertain due to inconsistent findings and potential biases such as residual confounding, misclassification, and reverse causality.

Mendelian randomization (MR) (*Figure 1*) design can enhance causal inference by utilizing genetic variants as instrumental variables or proxies for exposures (19), such as exercise (20). As genetic variants are randomly distributed at conception, confounding is minimized, and one trait is typically unrelated to other traits. Moreover, genetic variants are not influenced by the onset or progression of the disease, thereby reducing the risk of reverse causation bias (21). Herein, we employed MR design to explore whether strenuous sports or other exercises (SSOE) are associated with a protective effect against lung cancer (22). To increase accuracy and lower potential bias and confounders, our study concentrated more on intense exercise, used a larger dataset, and employed the most recent genetic methods for physical activity features. We also removed a number of factors. What sets us apart from other studies (23) is the unique methodology we employ to enhance the validity and trustworthiness of our results. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-810/rc) (24).

Highlight box

Key findings

- The study findings indicate that the total odds ratio (OR) for lung cancer from strenuous sports or other exercises (SSOE) was estimated at 0.129 [95% confidence interval (CI): 0.021–00.779], suggesting a significant protective effect. Furthermore, the combined OR for lung cancer from SSOE was estimated at 0.054 (95% CI: 0.01–0.302), indicating a significant inverse relationship.

What is known and what is new?

- Voluntary exercise has been shown in various rodent models to boost immune cells in tumors and significantly reduce tumorigenesis and progression.
- Studying the relationship between SSOE and lung cancer risk remains underexplored.

What is the implication, and what should change now?

- SSOE is beneficial in reducing the risk of lung cancer and helping to develop individualized exercise treatment plans for cancer patients to optimize their quality of life and treatment outcomes.

Methods

Study design

MR refers to a methodological approach in epidemiology

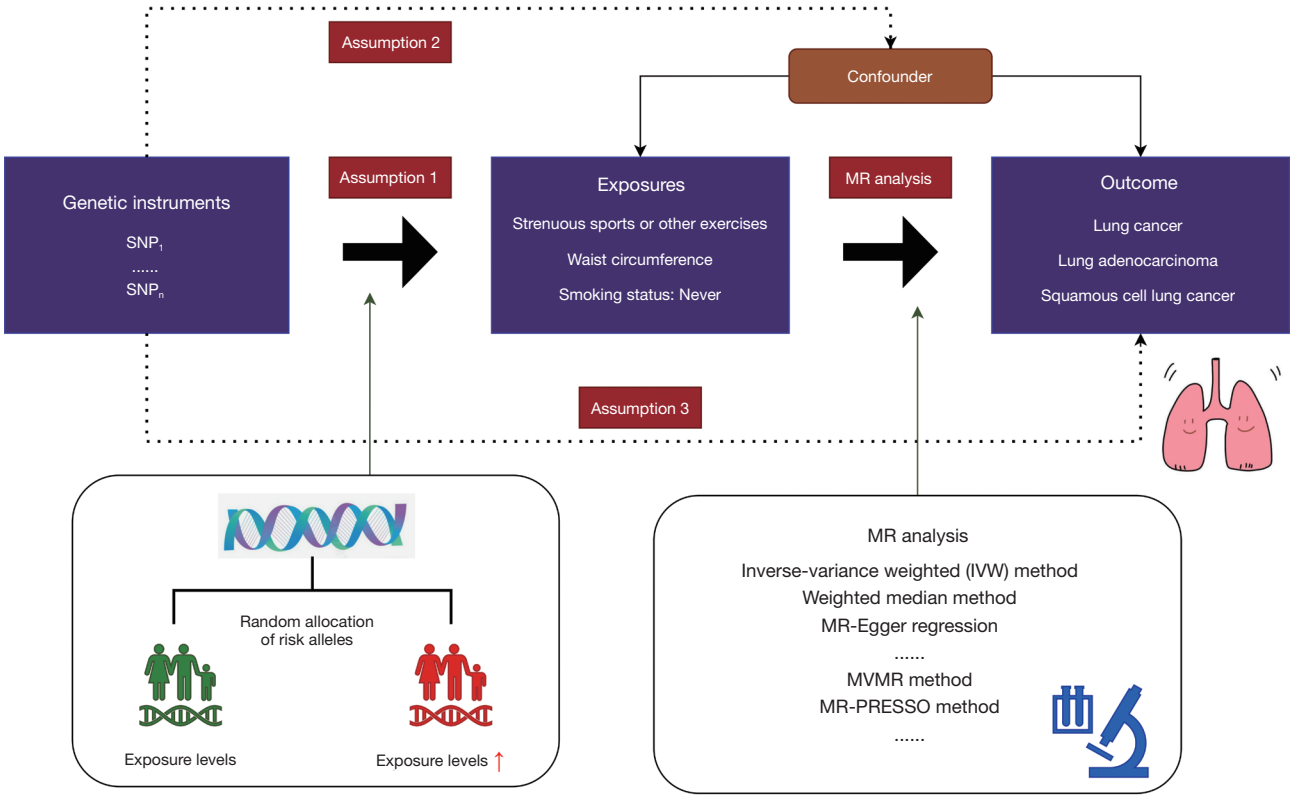

Figure 1 Mendelian randomization. SNP, single nucleotide polymorphism; MR, Mendelian randomization; MVMR, multivariable MR; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

and genetics that utilizes genetic variants as instrumental variables to investigate causal relationships between an exposure and an outcome. This approach leverages the random assortment of genetic alleles during meiosis, similar to Mendel's laws of inheritance, to provide unbiased estimates of causal effects in observational studies. Essentially, it mimics the random assignment of individuals to different levels of exposure in a randomized controlled trial, thereby reducing the risk of confounding and reverse causation biases commonly encountered in observational studies. The research design of the MR study investigating the relationship between smoke exposure (SSOE) and lung cancer is illustrated in *Figure 1*. The study sought to ascertain the correlation between SSOE and lung cancer, encompassing distinct subtypes such as lung adenocarcinoma and squamous cell lung cancer. It accounted for etiological heterogeneity stemming from cancer pathologic subtypes or clinical characteristics. To enhance analytical capability, we merged estimates from various data sources and introduced two additional variables, waist circumference (25) and smoking status, to adjust for the impact of SSOE. The study employed both mediation analysis and the multivariable MR approach. We utilized summary-level data from published genome-wide association studies (GWASs) for our analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) (26).

Genetic instrument selection

Two-sample MR

We identified single-nucleotide polymorphisms (SNPs) linked to SSOE (22) at the genome-wide significance level ($P \leq 5 \times 10^{-8}$) from corresponding GWASs. Linkage disequilibrium among these SNPs was assessed using the 1000 genomes linkage disequilibrium European panel as reference (27). In this MR investigation, 12 independent SNPs with the most significant P values for SSOE were chosen as genetic instruments, while excluding SNPs in moderate linkage disequilibrium ($r^2 > 0.01$ and clump window <10,000 kb).

Multivariable MR

SNPs associated with SSOE, waist circumference, and smoking status: never at the genome-wide significance level ($P \leq 5 \times 10^{-8}$) were obtained from corresponding GWASs. Linkage disequilibrium among these SNPs for each exposure was estimated utilizing the PLINK clumping method, within the context of the European population as defined by the 1000 Genomes reference panel (27). We excluded SNPs with linkage disequilibrium ($r^2 > 0.01$ and clump window <10,000 kb) and retained the SNP with the lowest P value. In this MR study, we applied 8, 17, and 57 SNPs associated with SSOE, waist circumference, and smoking status: never, respectively, as genetic instruments.

Data sources for lung cancer, squamous cell lung cancer, and lung adenocarcinoma

We extracted summary-level data for lung cancer, squamous cell lung cancer, and lung adenocarcinoma from GWASs for the associations of exposure-associated SNPs, including 11,348 lung cancer cases and 15,861 non-cases (controls) in lung cancer, 3,275 squamous cell lung cancer cases, and 15,038 non-cases (controls) in squamous cell lung cancer, and 3,442 lung adenocarcinoma cases and 14,894 non-cases (controls) in squamous cell lung cancer (28). Age, sex, and major genetic principal components were adjusted for association tests.

Physical activity data selection

Information on physical activity for the experimental component was collected through self-report questionnaires and objective assessments. Self-report surveys measure the frequency, duration, and intensity of various types of exercise through interviews or self-administered questionnaires. In addition, subjects are assessed objectively over several days or weeks using an accelerometer or wearable activity monitor, a machine that monitors daily activity patterns and provides objective measurements such as step counts, moderate-to-vigorous physical activity (MVPA) duration, and sedentary behavior. We classified intense exercise using recognized intensity and duration criteria. Strenuous activities involved a considerable increase in heart rate and respiratory rate. Running, swimming, cycling, and other strenuous activities were given as examples. We also assessed the duration of activities, with a minimum of 30 minutes of continuous high-intensity activity. This ensured that only continuous vigorous activity was classified as demanding exercise. Furthermore, we recognized that different types of physical activity contribute to total activity levels but may not match the requirements for high intensity. This category included moderate-intensity activities such as brisk strolling, recreational sports, and moderate aerobic exercise.

Statistical analysis

Two-sample MR

Inverse variance-weighting (IVW) is a statistical method commonly used in meta-analysis and MR studies. In the context of MR, IVW is used to combine individual genetic variant-exposure and genetic variant-outcome associations into a single estimate of the causal effect. For the two-sample MR analysis, we employed the IVW method with random effects as our main analysis, as it has been widely used and has good performance (29). We also conducted supplementary analyses using other methods, including the weighted median method (30), MR-Egger regression (31), the simple mode, and the weighted mode. Furthermore, we conducted a leave-one-out analysis by omitting a single SNP at a time to examine whether the MR outcome was influenced or biased by any single SNP. Additionally, we performed pleiotropy and heterogeneity tests to assess the validity of our results.

Multivariable MR

Regarding the multivariable MR analysis, we employed the IVW method with random effects, MR-Egger regression, the multivariable median method, and the MR pleiotropy residual sum and outlier (MR-PRESSO) model. The weighted median method was also utilized to provide consistent estimates, assuming that more than 50% of the weight comes from valid SNPs (30). In instances where the intercept test identified significant horizontal pleiotropy (P for intercept <0.05), the MR-Egger analysis was conducted to produce pleiotropy-corrected estimates, although this model is often characterized by limited statistical power (31). The multivariable median method, on the other hand, was similar to the univariable weighted median method but was implemented using quantile regression. The regression model was multivariable and weighted by the inverse of the variances of the variant-specific estimates. Finally, the MR-PRESSO approach was employed to detect any possible outliers and to generate estimates after their removal, and its embedded distortion test could distinguish the differences between estimates before and after outlier removal (32). Horizontal pleiotropy was evaluated using a modified

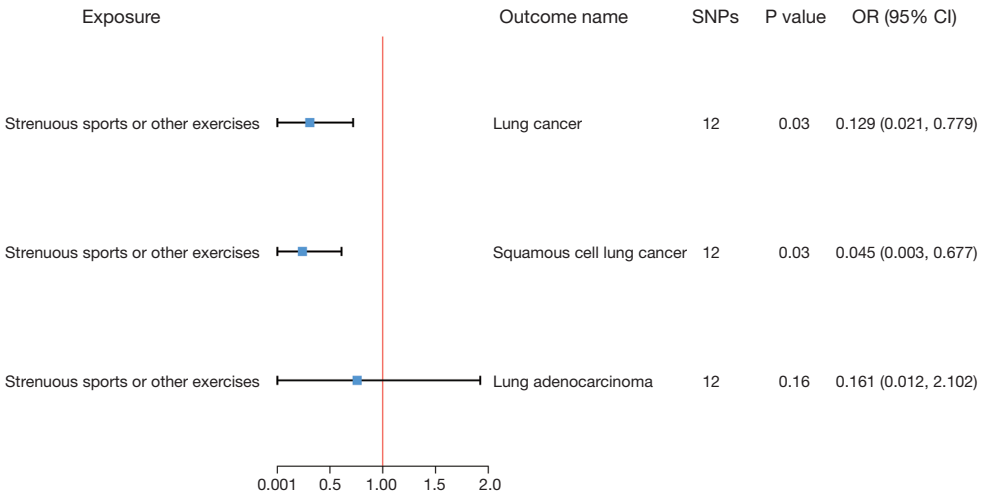

Figure 2 OR and P value of two-sample MR. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

form of Cochran's Q statistic, which assessed differences in MR estimates across the set of instruments. All analyses were conducted using the TwoSampleMR (33) and MR-PRESSO (32) packages in R software (version 4.2.2).

Results

Two-sample MR

Our two-sample MR analysis revealed that genetic predisposition to SSOE is inversely associated with lung cancer risk. The total OR for lung cancer from SSOE was estimated at 0.129 [95% confidence interval (CI): 0.021–0.779, P=0.03], indicating a significant protective effect. To further validate the robustness of our findings, we conducted several supplementary analyses, including the weighted median method and MR-Egger regression. The weighted median analysis generated an OR estimate of 0.281 (95% CI: 0.033–2.377; P=0.24), which was consistent with the IVW method. MR-Egger regression analysis detected a non-significant causal estimate with an OR of 3.471 (95% CI: 0.001–1.24×10^4; P=0.77), which suggests the absence of pleiotropy bias. When we compared the association of SSOE with different lung cancer subtypes, we observed a stronger inverse relationship with squamous cell lung cancer (OR =0.045; 95% CI: 0.003–0.677; P=0.03) than with lung adenocarcinoma (OR =0.161; 95% CI: 0.012–2.102; P=0.16) (*Figures 2*,*3*, *Tables 1*,*2*). Sensitivity analysis by omitting individual SNPs reveal that no influence on the causal effect of SSOE on lung cancer, squamous cell lung cancer, or lung adenocarcinoma (*Figure 3*). Additionally, the heterogeneity and pleiotropy tests did not indicate any significant impact of horizontal pleiotropy or heterogeneity (P=0.44 and P=0.11, respectively), suggesting that the effect of SSOE on lung cancer was mainly through a single pathway (*Table 3*).

Multivariable MR

We conducted a multivariable MR analysis to investigate the effect of SSOE on lung cancer after adjusting for waist circumference and smoking status (never). The combined OR for lung cancer from SSOE was estimated at 0.054 (95% CI: 0.010–0.302, P<0.001), which indicates a significant inverse relationship (*Figure 4*). We also conducted an MR-Egger regression analysis (P=0.44), which showed a non-significant pleiotropic effect. To further test the robustness of our findings, we performed Cochran's Q statistic and MR-PRESSO model to detect possible outliers. The P value of the Q statistic was 0.055, indicating no significant heterogeneity. Moreover, no outliers were detected in the MR-PRESSO model (P=0.07), suggesting the absence of bias in the multivariable MR analysis (*Table 4*). Overall, our multivariable MR analysis confirms that genetic predisposition to SSOE is inversely associated with lung cancer risk, even after adjusting for waist circumference and smoking status.

Discussion

The current MR analysis has revealed a favorable association

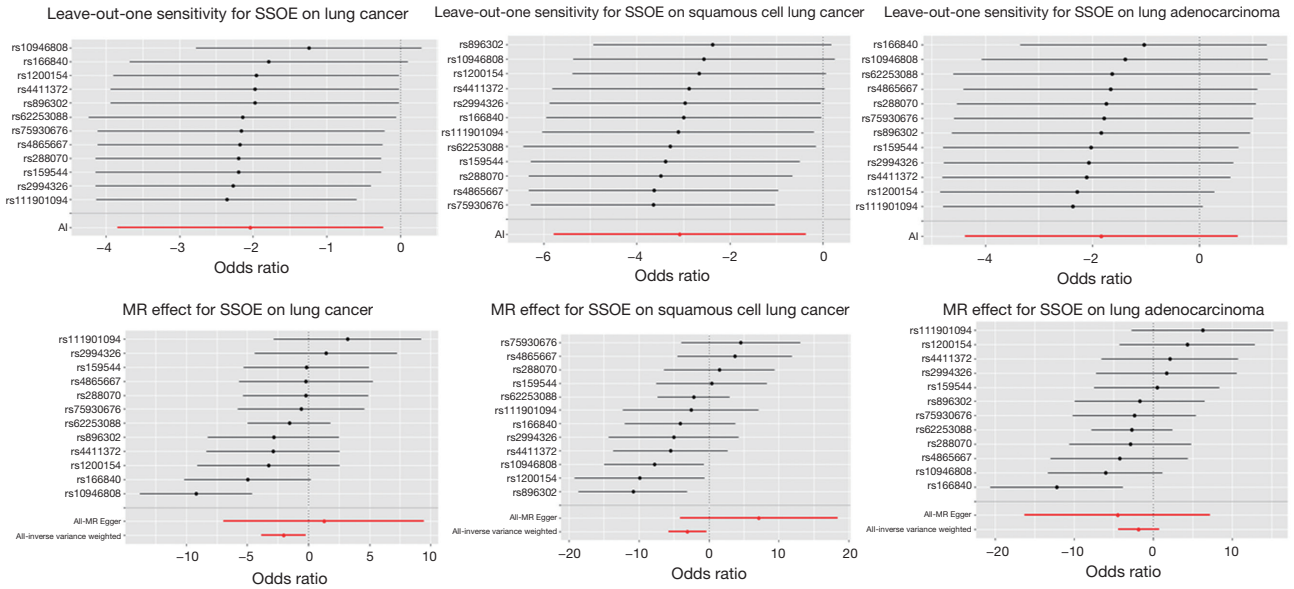

Figure 3 Leave-out-one sensitivity and MR effect for SSOE. SSOE, strenuous sports or other exercises; MR, Mendelian randomization.

Table 1 Details of exposure and outcome

Exposure or outcome	Unit	Author	Sample size	Year	PMID	Population
Strenuous sports or other exercises	NA	Klimentidis YC	350,492	2018	29899525	European
Lung cancer	Log-odds	Wang Y	27,209	2014	24880342	European
Squamous cell lung cancer	Log-odds	Wang Y	18,313	2014	24880342	European
Lung adenocarcinoma	Log-odds	Wang Y	18,336	2014	24880342	European

NA, not available.

between engagement in SSOE and a reduced risk of lung cancer. Even after adjusting for waist circumference and excluding never-smokers, the MR analysis still identified an inverse relationship between SSOE and lung cancer risk. Waist circumference has been previously linked to lung cancer, even in individuals who have never smoked (34). Therefore, the exclusion of never-smokers and the impact of waist circumference was necessary to enhance the accuracy of the study.

Individuals who engaged in SSOE for 2–3 days or more each week, for a duration of 15–30 minutes or greater, were included in the study, while those who had not participated in SSOE in the previous four weeks were used as controls. Extreme values were chosen due to the highly skewed and zero-inflated distribution of these variables (22).

While the precise biological pathways linking SSOE to tumorigenesis remain incompletely elucidated, it is widely acknowledged that SSOE plays a role in maintaining a healthy body weight, thereby reducing the risk of metabolic disorders, chronic low-grade inflammation, and excessive endogenous sex hormone activity. There is accumulating evidence indicating that promoting physical activity and reducing sedentary behaviors confer significant preventive health advantages against cancer. Moreover, the accumulation of ectopic fat tissue, characterized by the storage of triglycerides outside of adipose tissue in areas such as the liver, skeletal muscle, heart, and pancreas, poses a notable concern due to its potential disruption of normal cellular and organ functions, thereby heightening the risk of various chronic diseases, including cancer (35).

Exercise has been shown to be beneficial for cancer patients, as it can reduce the risk of developing cancer and inhibit tumor progression. Numerous studies have found that exercise can reduce the incidence of lung cancer

Table 2 Details of all methods of two-sample MR

Exposure	Outcome	Method	SNPs	P value	OR	95% CI	
						Lower limit	Upper limit
Strenuous sports or other exercises	Lung adenocarcinoma	MR Egger	12	0.47	0.011	0.000	1.370×10^{3}
		Weighted median	12	0.11	0.086	0.004	1.700
		Inverse variance-weighted	12	0.16	0.161	0.012	2.102
		Simple mode	12	0.49	0.142	0.001	29.791
		Weighted mode	12	0.28	0.096	0.002	5.612
Strenuous sports or other exercises	Lung cancer	MR Egger	12	0.77	3.471	0.001	1.240×10^{4}
		Weighted median	12	0.24	0.281	0.033	2.377
		Inverse variance-weighted	12	0.03	0.129	0.021	0.779
		Simple mode	12	0.58	0.422	0.022	8.142
		Weighted mode	12	0.46	0.330	0.020	5.481
Strenuous sports or other exercises	Squamous cell lung cancer	MR Egger	12	0.24	1.220×10^{3}	0.016	9.295×10^{7}
		Weighted median	12	0.11	0.066	0.002	1.769
		Inverse variance weighted	12	0.03	0.045	0.003	0.677
		Simple mode	12	0.24	0.018	0.000	9.736
		Weighted mode	12	0.27	0.051	0.000	7.617

MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

Table 3 Heterogeneity and pleiotropy test

Exposure	Outcome	Heterogeneity P value	Pleiotropy P value
Strenuous sports or other exercises	Lung cancer	0.11	0.44
Strenuous sports or other exercises	Squamous cell lung cancer	0.14	0.10
Strenuous sports or other exercises	Lung adenocarcinoma	0.20	0.66

by generating changes in tumor microenvironmental categories (36,37). There are several mechanisms for this, including the possibility that exercise improves systemic immunity by increasing the number of circulating immune cells, or that exercise influences immune cell activity within the tumor by modulating local environmental conditions (e.g., oxygen and nutrient supply), as well as the degree of inflammation and stress response (37,38). Furthermore, exercise can reduce the levels of inflammatory factors (e.g., TNF-a, IL-6, IL-1b) and reactive oxygen species in tumor tissues, reducing tumor growth (39-41). Exercise has an epigenetic influence on telomeres, and preventing telomere dysregulation by protecting telomeres from noncoding RNA transcription mistakes that occur during cell division is another mechanism being studied (42). The recent focus in the scientific community has been on investigating the interactions between SSOE and metabolic genes, particularly mitochondrial markers such as ACOT11 and PDHB, in relation to lung cancer. These studies have garnered significant attention in the field (43-45). Other mechanisms that may be talked about include p53-mediated apoptosis, inhibition of lung cancer cell proliferation and survival, enhancement of host immunity, promotion of immune cell infiltration, improvement of the tumor microenvironment, attenuation of chronic inflammation, activation of DNA repair enzymes, and enhancement of anti-oxidative stress (7-16). Preclinical studies have demonstrated that exercise can directly slow malignant

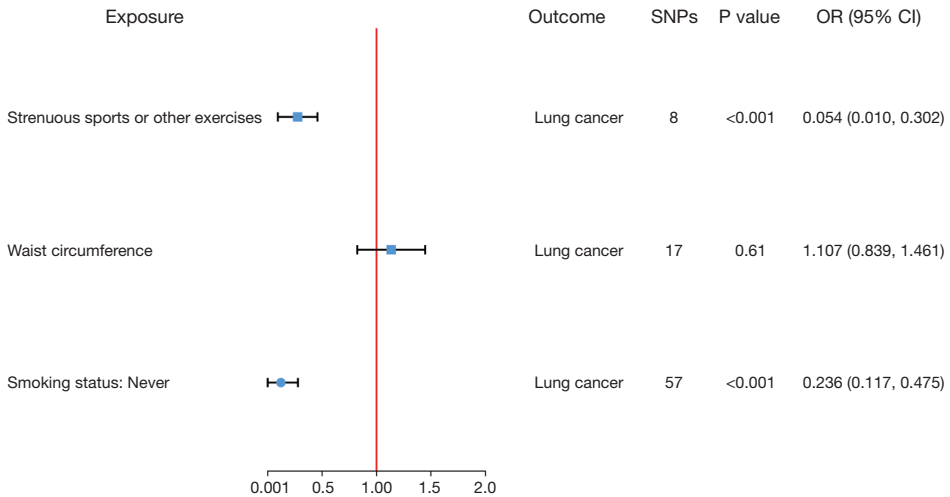

Figure 4 Details of MVMR. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; MVMR, multivariable Mendelian randomization.

Table 4 Details of MVMR

Exposure	Outcome	Egger-intercept	P value	Q-statistic P value	95% CI of MV medium	P value of MV medium	MR-PRESSO results in P value
Strenuous sports or other exercises	Lung cancer	−0.027	0.44	0.055	−5.455, −1.120	0.003	0.07
Waist circumference	Lung cancer	0.009	0.61		−0.360, 0.305	0.87	
Smoking status: never	Lung cancer	−0.005	0.71		−2.146, −0.306	0.009	

MVMR, multivariable Mendelian randomization; CI, confidence interval; MV, multivariable; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

progression in mouse models of lung cancer. A pooled analysis of prospective studies has found a direct association between exercise frequency and a reduced risk of seven different cancers, further supporting the notion that regular exercise and healthy lifestyle choices can lower the risk of cancer (46).

A review of 25 studies found no significant difference in the risk of lung cancer between nonsmokers who exercised and those who did not (47), while smokers who exercised had a lower risk of lung cancer. These findings are consistent with the results of our MR study. Exercise is often used as a complementary therapy for lung cancer patients (48), with pre- and post-surgery exercise interventions demonstrating beneficial effects for patients undergoing surgery (49). In a preliminary randomized clinical trial, it was observed that a combination of aerobic exercise and high-intensity respiratory muscle training enhanced exercise capacity, respiratory muscle strength, and blood IGFBP-3 levels among non-small cell lung cancer patients after undergoing lung resection (50). The current MR analysis has revealed a favorable association between engagement in SSOE and a reduced risk of lung cancer. Even after adjusting for waist circumference and excluding never-smokers, the MR analysis still identified an inverse relationship between SSOE and lung cancer risk. Waist circumference has been previously linked to lung cancer, even in individuals who have never smoked (34). Therefore, the exclusion of never-smokers and the impact of waist circumference was necessary to enhance the accuracy of the study. Additionally, increasing physical activity among smokers can lower their risk of developing lung cancer. One possible explanation for this could be that exercise lowers the risk of lung cancer by reducing the level of chronic inflammation, particularly C-reactive protein (51), since chronic inflammation is known to accelerate the development of cancer in a number of cancers, including lung cancer, by interfering with processes

like cell migration, survival, and proliferation (52-54). Even though exercise has demonstrated encouraging results in the treatment of lung cancer, more research is necessary to examine any potential synergistic anticancer effects of exercise in addition to immunotherapy (7,11).

The utilization of the MR design in this study represents a significant strength, as it minimizes residual confounding and reverse causality, thereby enhancing causal inference regarding the association between SSOE and lung cancer. Furthermore, the multivariable MR analysis method was applied to account for pleiotropic effects stemming from waist circumference and never-smokers, both of which are genetically linked to SSOE. The primary hurdle encountered in this study is the issue of horizontal pleiotropy, whereby certain genetic instrument characteristics may impact the risk of the outcome not through exposure but via alternative pathways. However, it is unlikely that this pleiotropic effect has biased our findings. The majority of associations in the current MR analysis did not reveal any evidence of pleiotropy as indicated by the MR-Egger intercept test. Although a few outliers were identified by the MR-PRESSO analysis for some associations with significant hints of horizontal pleiotropy, the relationship persisted or strengthened after the removal of outlying SNPs. Moreover, the consistency of the results was maintained even after adjustment for factors with high phenotypic and genetic correlations using the multivariable MR method.

It is worth noting that Xian *et al.* (23) used a MR approach and did not find a causally protective relationship between physical activity and lung cancer risk, in contrast to our study, which performed a more detailed analysis. Our research extracted summary-level data from GWASs. We meticulously adjusted for age, sex, and major genetic principal components in our association tests. In our statistical research, we used the two-sample MR approach, principally the IVW method with random effects, which has proven to be robust and widely accepted. Supplementary analyses included weighted median, MR-Egger regression, simple mode, and weighted mode. To ensure the trustworthiness of our findings, we performed leave-one-out analyses and examined pleiotropy and heterogeneity. Furthermore, we investigated multivariable MR analysis using a variety of methods, including the IVW method with random effects, MR-Egger regression, the multivariable median method, and the MR-PRESSO model. We addressed potential pleiotropy issues using the weighted median approach and MR-Egger analysis, as well as outlier detection and adjustment analyses. Our comprehensive approach enabled a complete analysis of the relationship between physical activity and lung cancer risk, offering a deeper and more precise knowledge than earlier studies with a broader scope, such as those of Xian *et al.*

It is worth noting that our studies were conducted solely on European populations to minimize population structure bias, but this limits the generalizability of our findings to other populations. While we accounted for waist circumference and smoking status, important lifestyle factors such as diet, alcohol consumption, and occupational exposures, which are recognized influencers of lung cancer risk, were not encompassed in our analysis. For example, different dietary habits in different populations may have different effects on the development of lung cancer. High intake of meat, especially fried or fully cooked red meat, may increase the risk of lung cancer (55). This omission may introduce residual confounding and undermine the strength of our causal inferences with the STROBE-MR reporting checklist. Furthermore, the intricacies of cancer development demand a more profound exploration of gene-environment interactions and their potential to modulate the association between exercise and lung cancer risk. In forthcoming investigations, we intend to rectify these limitations by incorporating a comprehensive array of confounding factors and delving into gene-environment interactions. As such, our results must be considered in light of their limitations. In our future research endeavors, we aim to broaden our scope by incorporating a diverse range of populations. This will enhance the robustness and applicability of our findings, ensuring they are more representative and generalizable. While pursuing direct validation is critical for increasing the trustworthiness of our results, it is critical to appreciate the intricacies and practical limitations associated with reaching this goal. In future research, we will make a greater effort to confirm the effects of other confounding factors on lung cancer in various populations with varied characteristics of the disease. This is also a problem in our article, and by highlighting these limits, we hope to pique others' interest in future research areas. We will continue to develop new and efficient data collection approaches that offer possible solutions to these problems in future investigations. Ultimately, the underlying objective of our research endeavors lies in gaining a profound comprehension of lung cancer, enabling us to enhance our preventive measures and therapeutic interventions.

Conclusions

In summary, our MR analysis suggests that SSOE may be a protective factor against lung cancer, highlighting the importance of exercise in cancer prevention and treatment. Further research is needed to fully understand the molecular processes of exercise, including its impact on redox state and the interplay between metabolism and immune modulation in cancer. Nonetheless, exercise remains an essential component of treatment for various illnesses, including cancer. Personalized exercise treatment plans should be developed for patients with cancer to optimize their quality of life and treatment outcomes.

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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-23-810/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-810/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-810/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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