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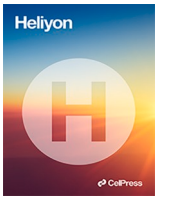

Hypothyroidism reduces the risk of lung cancer through oxidative stress response and the PI3K/Akt signaling pathway: An RNA-seq and Mendelian randomization study

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ABSTRACT

Hypothyroidism has been suggested to play a role in tumor progression. However, the causal association between hypothyroidism and lung cancer remains unknow. To elucidate the potential association between hypothyroidism and lung cancer risk, we employ a Mendelian randomization (MR) approach. MR was performed to analyze pooled data from the International Lung Cancer Consortium (11,348 cases and 15,861 controls; European ancestry) to determine the causal relationship between hypothyroidism and lung cancer. We used 36, 83, and 14 single nucleotide polymorphisms as instrumental variables for hypothyroidism/myxoedema, hypothyroidism, and exercise, respectively. We further investigated the mechanisms involved in transcriptome analysis using data from The Cancer Genome Atlas and Genotype-Tissue Expression database. We conducted an initial validation of intermediary factor using a two-step MR analysis. Genetically predicted hypothyroidism was significantly related to the risk of overall lung cancer, specifically the risk of lung squamous cell cancer (LSCC) but not with the risk of lung adenocarcinoma (LUAD) as assessed using the inverse-variance weighted (IVM) method. A similar causal association was found between hypothyroidism/myxoedema and the risk of lung cancer, LSCC, and LUAD. Transcriptome analysis showed that genes associated with hypothyroidism, lung cancer, and LSCC were enriched in the PI3K/Akt signaling pathway and oxidative stress response. However, genes related to hypothyroidism and LUAD did not exhibit enrichment in these pathways. Hypothyroidism was significantly associated with strenuous sports or other exercises. Moreover, genetically predicted exercise was significantly related to the risk of overall lung cancer, and LSCC, but not LUAD. We detected no horizontal pleiotropy using the MR-PRESSO and MR Egger regression intercept. Hypothyroidism was causally associated with a lower risk of lung cancer, and these effects might be mediated by the oxidative stress response and the PI3K/Akt signaling pathway. Therefore, our study suggests that the potential factors and viable etiologies of hypothyroidism that contributed to lung cancer risk deserve further investigation.

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1. Introduction

Lung cancer is a formidable global health challenge, representing a leading cause of cancer-related mortality [[1]]. In 2021, it ranked second in cancer incidence after breast cancer in women and prostate cancer in men [[2]]. The urgency to identify modifiable risk factors for lung cancer is evident, as this could significantly enhance prevention strategies and alleviate the substantial burden that lung cancer imposes. While smoking remains a prominent contributor to lung cancer incidence [[3–5]], the present study revolves around exploration of a distinct and novel factor concerning lung cancer risk.

Hypothyroidism is a prevalent medical condition characterized by a reduction in the body's metabolic activity due to a decrease in the synthesis and secretion of thyroid hormones or their efficacy [[6]]. The use of immunotherapeutic drugs in clinical practice for treating lung cancer can induce thyroid dysfunction [[7,8]]. In the context of cancer treatment, which includes radiotherapy and immunotherapy, hypothyroidism emerges as a relatively common immune-related adverse event [[9,10]]. The size and attenuation of the thyroid can serve as diagnostic markers to identify patients who may have hypothyroidism when undergoing lung cancer screening [[11]]. Notably, hypothyroidism was associated with the development of various types of cancers [[12,13]]. Immune checkpoint and tyrosine kinase inhibitors used in cancer therapy increase the risk of hypothyroidism. Moreover, although most individual tumors are more common in hypothyroid populations, we, in a previous study, observed a significant decrease in the frequency of prostate, lung, colorectal, and liver cancers in hypothyroid patients over 60 years old [[14]]. However, no study has investigated the direct impact of hypothyroidism on the risk of developing lung cancer.

To address this research gap and elucidate the potential association between hypothyroidism and lung cancer risk, we aimed to employ a Mendelian randomization (MR) approach. MR utilizes genetic variation as instrumental variables (IVs) to comprehensively examine the relationships between exposures and disease outcomes. Genetic variation is randomly assigned at conception and usually independent of confounding factors, reducing residual confounding [[15,16]]. In addition, these genetic variants used to represent the effects of exposure are established at conception and remain unaffected by the onset and progression of outcomes, minimizing reverse causation [[17]]. Two-sample MR studies have already shown that hypothyroidism is significantly associated with a lower risk of breast cancer, which aligns with observational cohort studies [[18]]. Therefore, in a pioneering attempt, we aimed to conduct a two-sample MR study to investigate the potential association between hypothyroidism and risk of developing lung cancer, to shed light on an aspect of lung cancer risk factors that has been fully explored before.

2. Methods

2.1. Study design

We used two-sample MR and publicly available datasets that provide genome-wide association results for hypothyroidism, lung cancer, and exercise. First, we tested the effects of hypothyroidism on lung cancer. Transcriptome analysis was performed to analyze the underlying mechanisms associated with hypothyroidism and lung cancer. Considering the findings from our transcriptome analysis results and in line with previous studies [[19,20]], we hypothesized that exercise may be a potential mediator of the association between hypothyroidism and lung cancer. To investigate this hypothesis, we conducted a two-step MR analysis. In the first step, we assessed how hypothyroidism affects exercise. In the second step, we examined the impact of exercise on the risk of developing lung cancer.

2.2. Data collection

We obtained GWAS summary statistics for lung cancer, lung squamous cell cancer (LSCC), and lung adenocarcinoma (LUAD) from a meta-analysis of GWAS (comprising 11,348 cases and 15,861 controls of European ancestry) by the International Lung Cancer Consortium (ILCCO) [[21]]. Summary statistics of exercises were obtained from GWAS based on 225,650 controls and 124,842 cases of European ancestry [[22]]. Summary statistics for hypothyroidism were obtained from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/), including data on hypothyroidism (GWAS ID: ukb-b-4226; 9,674 cases and 453,336 controls of European ancestry) and hypothyroidism/myxoedema (GWAS ID: ukb-a-77; 16,376 cases and 320,783 controls of European ancestry). Details on the datasets used are shown in Table 1. After excluding single nucleotide polymorphisms (SNPs) with linkage disequilibrium (clump

Table 1
Details of epidemiological individual-level data included in our Mendelian randomization analyses.

Trait	First author	Consortium	Population	Number of cases	Number of controls	Proportion of cases	PubMed ID
Lung cancer	Y Wang	ILCCO	European	11,348	15,861	0.42	24880342
Lung squamous cell cancer	Y Wang	ILCCO	European	3,275	15,038	0.22	24880342
Lung adenocarcinoma	Y Wang	ILCCO	European	3,422	14,894	0.23	24880342
Hypothyroidism	Ben Elsworth	MRC-IEU	European	9,674	453,336	0.02	NA
Hypothyroidism/myxoedema	Neale	Neale Lab	European	16,376	320,783	0.05	NA
Strenuous sports or other exercises	Klimentidis YC	NA	European	124,842	225,650	0.36	29899525

ILCCO, International Lung and Cancer Consortium; MRC-IEU, MRC Integrative Epidemiology Unit.

distance <10,000 kb and r2 >0.001), 36, 83, and 14 SNPs were used as instrumental variables for hypothyroidism/myxoedema, hypothyroidism, and exercise, respectively (P < 5E-08).

We assessed the strength of the instrumental variables by calculating the SNP's contribution to explaining the variance in the occurrence of hypothyroidism or differences in exercise levels. Subsequently, we further computed the F-statistic for each SNP. Transcriptome data was obtained from 501 patients with LUAD, 501 patients with LSCC, and 100 normal lung tissues from The Cancer Genome Atlas (TCGA) database. An additional 381 normal lung tissues were sourced from the Genotype-Tissue Expression (GTEx) database. Hypothyroidism-related genes were obtained from GeneCards: The Human Gene Database (https://www.genecards.org/).

2.3. MR analysis

The two-sample MR method helps mitigate pleiotropy, which can be a concern in single-sample MR. In single-sample MR, numerous potential pleiotropic factors may confound the results. By separating datasets, we can more effectively control these potential confounders, enhancing the accuracy of our results [[23]]. Our MR approach was based on the following three underlying assumptions: (I) IVs, i.e., SNPs, are strongly associated with exposure; (II) IVs influence outcomes solely through their impact on exposure, devoid of any other pathways; and (III) IVs are independent of confounding factors present in the relationship between exposure and outcome [[24]]. MR analysis was performed using the TwoSampleMR and MRPRESSO R packages. The inverse-variance weighted (IVW) method was used for the major analysis of MR. It was supplemented with comprehensive sensitivity analyses, including weighted median, MR-Egger, simple mode, and weighted mode analyses [[25–27]]. By comparing the results of these different methods, we can improve the reliability and consistency of the results [[28]]. We used MR-Egger regression and funnel plots to assess horizontal pleiotropic effects (P < 0.05) [[27]]. MR-PRESSO analyses were used to detect outlier instruments and eliminate possible outlier SNPs, reducing the impact of horizontal pleiotropy [[29]]. We conducted leave-one-SNP-out analyses and Cochrane Q statistics to assess the heterogeneity among estimates of SNPs in each analysis.

2.4. Testing transcriptome data reliability

We downloaded the original "CEL" files for the microarray data from Affymetrix. To ensure the quality and reliability of transcriptome data, we conducted rigorous data preprocessing which involved removal of low-quality samples, normalization of gene expression values, and batch effect correction to minimize potential confounding effects. All data were quantile-normalized using a log2-scale transformation to ensure standardization. Any gene symbols detected using more than one probe were evaluated using their mean expression levels. Quality control checks were performed to identify and address any anomalies in the data.

2.5. Identification of differentially expressed genes (DEGs)

We merged normal lung tissue samples from the GTEx database, lung tissue samples, and lung cancer tissues from the TCGA dataset using normalization via R package "limma". DEGs were identified by comparing LUAD samples (501 patients) with 481 lung normal samples, LSCC samples (501 patients) with 481 lung normal samples, and lung cancer samples (501 patients with LUAD and 501 patients with LSCC) with 481 lung normal samples from the TCGA and GTEx dataset. DEGs were defined using a threshold of | log2 fold-change | > 2 and a false discovery rate threshold <0.05, employing the R package "limma."

Table 2
Mendelian randomization estimated the effects of hypothyroidism with or without myxoedema on lung cancer risk including histological subtypes.

Exposure	Outcome	Method	OR (95%CI)	P value
Hypothyroidism	Lung cancer overall	IVW	0.0078 (0.00021–0.29)	0.0083
		MR-Egger	0.0029 (1.56E-07-53.02)	0.25
		Weighted median	0.0043 (4.29E-05-0.42)	0.020
	Lung squamous cell cancer	IVW	0.00055 (4.4E-06-0.069)	0.0023
		MR-Egger	0.14 (3.36E-07-58666.22)	0.77
		Weighted median	0.0004442 (8.93E-07-0.22)	0.015
	Lung adenocarcinoma	IVW	0.040 (0.00034–4.55)	0.18
		MR-Egger	2.73E-06 (1.04E-11-0.71)	0.05
		Weighted median	0.00037 (7.50E-07-0.18)	0.012
Hypothyroidism/myxoedema	Lung cancer overall	IVW	0.0078 (0.00021–0.29)	0.0083
		MR-Egger	0.16 (0.011–2.39)	0.19
		Weighted median	0.10 (0.019–0.56)	0.56
	Lung squamous cell cancer	IVW	0.10 (0.018–0.58)	0.0099
		MR-Egger	0.090 (0.0016–5.22)	0.25
		Weighted median	0.053 (0.0045–0.61)	0.018
	Lung adenocarcinoma	IVW	0.36 (0.082–1.57)	0.17
		MR-Egger	0.047 (0.0015–1.47)	0.086
		Weighted median	0.19 (0.019–1.88)	0.16

IVW, inverse-variance weighted.

2.6. Identification of double disease-associated genes and enrichment analysis

To identify genes associated with both hypothyroidism and lung cancer, we intersected hypothyroidism-related genes with DEGs from LUAD, LSCC, and lung cancer. For enrichment analysis, we used Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses on the genes associated with both diseases. These analyses were performed using the clusterProfiler, org. Hs.eg.db, and enrichplot R packages to identify relevant biological processes.

3. Results and discussion

3.1. Impact of hypothyroidism on lung cancer

Using the IVM method, we demonstrated that genetically predicted hypothyroidism was significantly related to an overall lung cancer risk (odds ratio (OR), 0.0078; 95 % confidence interval (CI), 0.00021–0.29; P = 0.0083), and specifically with LSCC risk (OR, 0.00055; 95 % CI, 0.0000044–0.069; P = 0.0023), but not with LUAD risk (OR, 0.040; 95 % CI, 0.00034–4.55; P = 0.18) (Table 2). The IVW method indicated that genetically predicted hypothyroidism/myxoedema was also related to lower lung cancer risk (OR, 0.20; 95 % CI, 0.063–0.62; P = 0.0055) (Table 2). Similar trends were observed in the LSCC subgroup (OR, 0.10; 95 % CI, 0.018–0.58; P = 0.0099) but not in the LUAD subgroup (OR, 0.36; 95 % CI, 0.082–1.57; P = 0.17) (Table 2). Various degrees of symptomatic hypothyroidism were significantly associated with a decreased risk of lung cancer. Although we detected slight heterogeneity in the MR-Egger regression, no evidence of horizontal pleiotropy was observed according to the MR-PRESSO and MR-Egger regression intercept (Fig. S1, Table 3). Our leave-one-out sensitivity analysis did not identify an individual SNP that strongly influenced the overall impact of hypothyroidism on lung cancer (Fig. S2).

3.2. Transcriptome analysis of hypothyroidism and lung cancer

We identified 1,520 DEGs related to hypothyroidism-related lung cancer, 1,568 DEGs in hypothyroidism-related LSCC, and 1,404 DEGs in hypothyroidism-related LUAD. GO analysis of the 1,520 DEGs in hypothyroidism-related lung cancer (Fig. 1A) and 1,568 DEGs in hypothyroidism-related LSCC (Fig. 1B) revealed significant enrichment of biological processes, including oxidative stress response (P < 0.05). However, this enrichment was not observed in the GO analysis of the 1,404 DEGs in hypothyroidism-related LUAD (Fig. 1C). KEGGs analysis of the 1,520 DEGs in hypothyroidism-related lung cancer (Fig. 1D) and the 1,568 DEGs in hypothyroidism-related LSCC (Fig. 1E) demonstrated that the PI3K/Akt signaling pathway was significantly enriched (P < 0.05). However, this enrichment was not observed in the KEGGs analysis of the 1,404 DEGs in hypothyroidism-related LUAD (Fig. 1F). Considering that exercise can influence oxidative stress and the PI3K/Akt signaling pathway [[19,20]], we further analyzed whether exercise serves as a mediator in the association between hypothyroidism and lung cancer.

3.3. Effect of hypothyroidism on exercise

The results of the IVM method demonstrated that genetically predicted hypothyroidism was significantly associated with participation in strenuous sports or other exercises (OR, 0.76; 95 % CI, 0.62–0.94; P = 0.0094) (Table S1). This trend was also observed with hypothyroidism/myxoedema and strenuous sports or other exercises (OR, 0.91; 95 % CI, 0.84–0.98; P = 0.013) (Table S1). Additionally, the weighted median method (OR, 0.90; 95 % CI, 0.83–0.98; P = 0.017) yielded similar results (Table S1). Various degrees of symptomatic hypothyroidism were negatively correlated with exercise. We detected slight heterogeneity, but no horizontal pleiotropy, in the MR-Egger regression, as indicated by the MR-PRESSO and MR-Egger regression intercept (Fig. S3 A-B, Table S2). Using the leave-one-out sensitivity analysis, we did not identify any individual SNP that significantly influences the overall impact of hypothyroidism on exercise, as illustrated in Figs. S3C–D.

Table 3
MR-Egger regression and heterogeneity analysis of the associations between hypothyroidism with or without myxoedema and lung cancer including histological subtypes.

Exposure	Outcome	Heterogeneity P		MR-Egger regression	
		MR-Egger	IVW	Intercept	P
Hypothyroidism	Lung cancer overall	0.0011	0.0015	0.0029	0.83
	Lung squamous cell cancer	0.042	0.042	−0.016	0.37
	Lung adenocarcinoma	0.096	0.061	0.028	0.12
Hypothyroidism/myxoedema	Lung cancer overall	0.0079	0.0097	0.0011	0.87
	Lung squamous cell cancer	0.012	0.015	0.00074	0.94
	Lung adenocarcinoma	0.46	0.44	0.011	0.20

IVW, inverse-variance weighted.

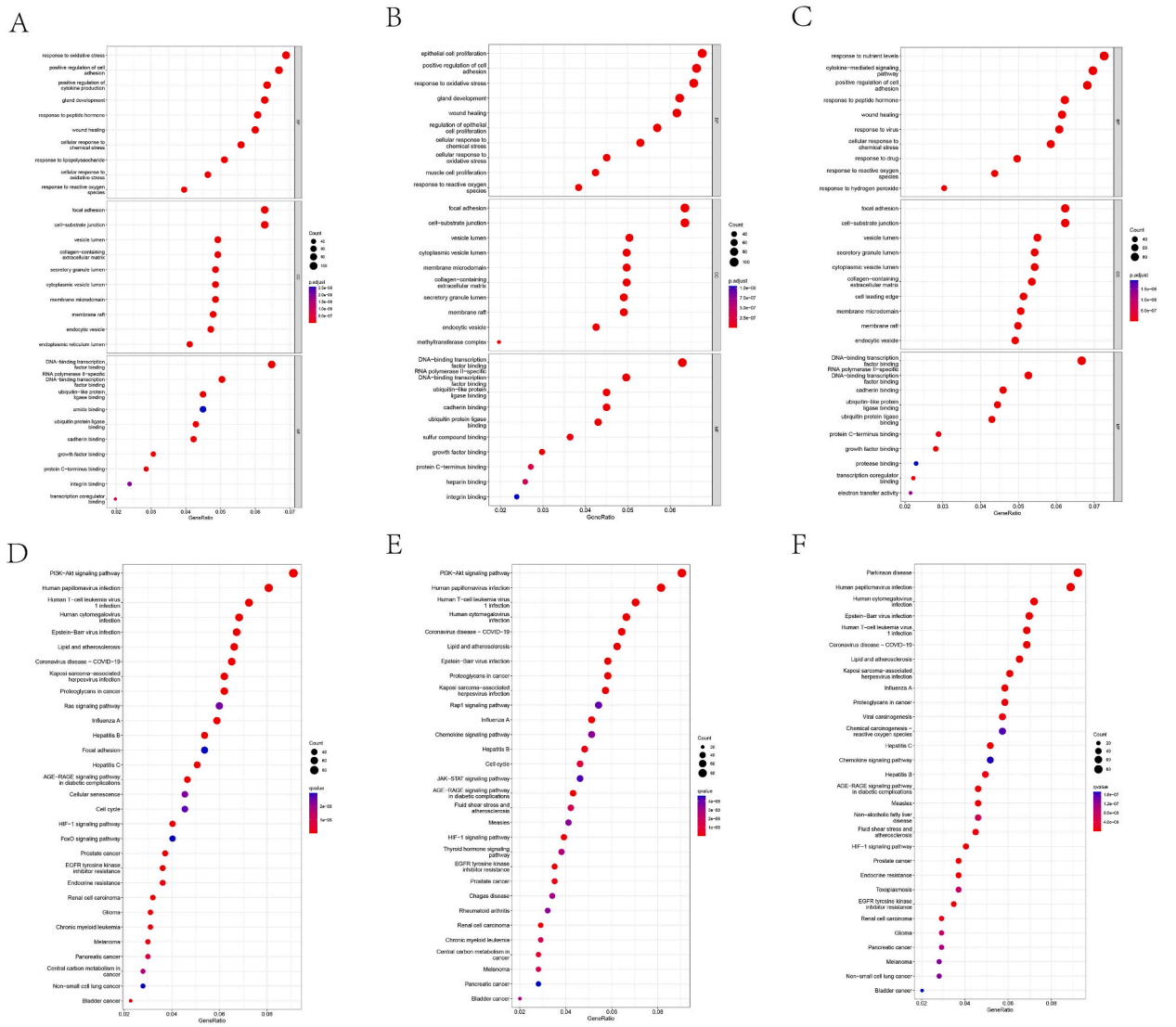

Fig. 1. GO and KEGG analysis of hypothyroidism and lung cancer. (A–C) Bar plots of GO analyses of 1520 hypothyroidism related lung cancer (A), 1568 hypothyroidism related LSCC DEGs (B), and 1404 hypothyroidism related LUAD DEGs (C). (D–F) Bar plots of KEGGs analyses of 1520 hypothyroidism related lung cancer (D), 1568 hypothyroidism related LSCC DEGs (E), and 1404 hypothyroidism related LUAD DEGs (F).

3.4. Effect of exercise on lung cancer

The results of the IVM method demonstrated that genetically predicted exercise was significantly related to the overall lung cancer risk (OR, 0.13; 95 % CI, 0.021–0.79; P = 0.027), specifically for LSCC risk (OR, 0.046; 95 % CI, 0.0031–0.69; P = 0.026), but not for LUAD risk (OR, 0.16; 95 % CI, 0.012–2.10; P = 0.16) (Table S3). We detected no evidence of heterogeneity or pleiotropy in the MR-Egger regression and MR-PRESSO (Figs. S4A–C, Table S4). Using the leave-one-out sensitivity analysis, we did not identify an individual SNP that significantly influenced the overall impact of hypothyroidism on exercise, as illustrated in Figs. S4D–F.

3.5. Discussion

To the best of our knowledge, this is the first MR study wherein the relationship between hypothyroidism and the risk of lung cancer has been systematically assessed. Our findings revealed that genetically predicted hypothyroidism was related to a lower risk of lung cancer in individuals of European ancestry, specifically for the LSCC subgroup but not for the LUAD subgroup. We analyzed underlying mechanism using transcriptome analysis and found that genes associated with both hypothyroidism and lung cancer, especially in the LSCC group, were enriched in the PI3K/Akt signaling pathway and oxidative stress response. However, genes linked to hypothyroidism and LUAD did not exhibit this enrichment. We speculated that the above-mentioned pathway may have contributed to the association

between hypothyroidism and lung cancer risk and may explain differences in the association among various types of lung cancer.

Exercise regulates oxidative stress and PI3K/Akt signaling [[19,20]]; therefore, we further used MR to analyze whether exercise mediates the relationship between hypothyroidism and lung cancer. MR analysis results revealed that hypothyroidism is associated with reduced exercise, while exercise is related to a reduced risk of lung cancer among individuals of European ancestry. This suggests that the relationship between hypothyroidism and lung cancer is partially mediated by exercise, aligning with the previous results of transcriptome analysis.

An observational study in Taiwan found a connection between hypothyroidism and a reduced risk of rectal cancer [[30]]. An observational study in the US showed that patients with cutaneous squamous cell carcinoma were more likely to have a history of hypothyroidism than the general population [[31]]. In addition, a recent systematic review involving 367,416 patients with breast cancer revealed that hypothyroidism may reduce the risk of breast cancer in European populations (OR, 0.93; 95 % CI, 0.88–0.99) [[32]]. To our knowledge, no previous studies, including observational studies, prospective studies, or MR analysis, have investigated the association between hypothyroidism and lung cancer risk. Our MR study revealed that hypothyroidism is related to a decreased risk of lung cancer, aligning with previous observational studies associating hypothyroidism with a decreased risk of neoplasms, including breast and rectal cancers.

The precise mechanism by which hypothyroidism reduces the risk of cancer, including lung cancer, remains unclear. Hypothyroidism is also associated with increased oxidative stress [[33]], which refers to an imbalance in the oxidation process in the body [[34]]. Reactive oxygen species production is elevated and antioxidant systems are impaired in patients with hypothyroidism [[35]]. Experimental hypothyroidism induces oxidative stress in the breast [[36]]. Oxidative stress and the consequent damages are important factors that are involved in lung cancer development [[37,38]]. PI3K/Akt pathway activation has been observed in breast tumors of rats with hypothyroidism [[39]]. The PI3K/Akt pathway is also activated in lung cancer [[40]]. Consistent with previous findings, our two-disease transcriptome analysis results also showed that the association between hypothyroidism and lung cancer may be associated with the oxidative stress response and PI3K/Akt signaling pathway. In addition, MR analysis revealed that both hypothyroidism with or without myxoedema and LSCC risk had lower OR than hypothyroidism and lung cancer risk. Further enrichment analysis results suggested that the association between hypothyroidism and lung cancer risk may be due to oxidative stress response and PI3K/Akt signaling pathway. The oxidative stress response is higher in patients with squamous cell carcinoma than in the general population [[41]], further suggesting that the reduced risk of lung cancer is partly associated with hypothyroidism, which regulates the oxidative stress response and PI3K/Akt signaling pathway.

In addition, a recent systematic review showed that the risk association between hyperthyroidism and breast cancer may be mediated by the treatment received, such as radioactive iodine treatment [[42]]. A matched case-control study comprising 2,566 pairs of colorectal cancer samples showed that levothyroxine use was related to a statistically significant lower relative risk of colorectal cancer (OR, 0.59; 95 % CI, 0.43–0.82; $P = 0.001$) [[43]]. A case-control study including 20,990 patients with colorectal cancer and 82,054 controls showed that long-term administration of thyroid hormone replacement therapy for five to 10 years (OR, 0.88; 95 % CI, 0.79–0.99; $P = 0.03$) and more than 10 years (OR, 0.68; 95 % CI, 0.55–0.83; $P < 0.001$) were related to a reduced risk of colorectal cancer [[44]]. Levothyroxine replacement improves oxidative status in patients with primary hypothyroidism [[45]]. Therefore, we hypothesized that hypothyroidism partly reduces lung cancer risk due to the use of levothyroxine. However, due to the lack of GWAS data on the use of levothyroxine, we could not investigate its association with lung cancer using MR analysis.

However, our study has certain limitations that cannot be ignored. First, the GWAS data used were mainly based on European populations, which limits the applicability of our findings; therefore, verifying this conclusion in other populations is necessary. Second, our findings confirmed a causal relationship between hypothyroidism and the risk of lung cancer; however, identifying a definite causal relationship between hypothyroidism and the risk of lung cancer may need further studies, such as prospective large-scale longitudinal cohort studies. Third, we found that the relationship between hypothyroidism and reduced lung cancer risk may be mediated by the oxidative stress response and PI3K/Akt signaling pathway, and identified exercise as a mediator; however, this needs further mechanistic experiments.

4. Conclusion

In summary, our MR study provided genetic evidence for a significant association between hypothyroidism and the risk of lung cancer, and the results of transcriptome analysis suggested that these effects were likely mediated by the oxidative stress response and PI3K/Akt signaling pathway. In addition, we found that thyroxine replacement therapy might partially contribute to this phenomenon. Therefore, our study suggests that further investigating into the potential factors and viable etiologies causes of hypothyroidism that may be linked to risk of developing lung cancer is important.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Wei Liu: Writing – review & editing, Writing – original draft, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fei-Hang Zhi:** Validation, Data curation. **Shao-Yi Zheng:** Validation, Data curation. **Hao-Shuai Yang:** Validation, Data curation. **Xi-Jie Geng:** Validation, Data curation. **Hong-He Luo:** Visualization,

Supervision. **Yan-Fen Feng:** Writing – review & editing, Visualization, Validation, Supervision. **Yi-Yan Lei:** Writing – review & editing, Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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