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ORIGINAL RESEARCH

The Relationship Between Hypothyroidism and Pneumonia and Possible Prevention and Treatment Measures

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Background: Epidemiological study has confirmed an association between hypothyroidism and pneumonia, but the causal relationship between the two remains unclear.

Methods: The National Health and Nutrition Examination Survey (NHANES) data were used to confirm the correlation between hypothyroidism and pneumonia. Mendelian randomization (MR) studies were conducted to explore the potential causal relationship. Co-expressed differential genes were used to identify potential mechanisms and potential drugs for pneumonia treatment, CCK8 and qPCR were used to detect the safety and efficacy of potential drugs. Molecular docking and Western blot assays were used to explore potential underlying mechanism of pneumonia treatment.

Results: The NHANES and MR (Training set: OR=47.88, 95% CI: 8.432–271.8, P=1.3e-5; Test set: OR=1.849, 95% CI: 1.029–3.323, P=4.0e-5) analyses indicated that hypothyroidism may increase the risk of pneumonia. Moreover, increasing the usual walking pace was associated with a reduced risk of pneumonia, and sensitivity analysis indicated these results were robust. Hypothyroidism may increase the risk of pneumonia through the JAK-STAT signaling pathway. Garcinol was identified as a compound that attenuates lipopolysaccharide (LPS)-induced pneumonia via inhibiting the expression level of p-STAT1.

Conclusion: Hypothyroidism may elevate the risk of pneumonia, highlighting the need for preventive measures among hypothyroid patients, such as increasing walking pace. Additionally, garcinol shows potential therapeutic effects for pneumonia management.

Plain Language Summary:

Why was the study done - The clinical, economic, and humanistic burdens caused by pneumonia have always been a concern. It is particularly important to further analyze the potential risk factors, protective factors and therapeutic drugs of pneumonia.

What did the researchers do and find - There is a potential causal relationship between hypothyroidism and the risk of pneumonia, increasing the usual walking pace may help reduce the risk of pneumonia, and garcinol may have a therapeutic effect on LPS-induced pneumonia by reducing the phosphorylation level of STAT1.

What do these results mean - The relationship between hypothyroidism and pneumonia will receive further attention and increased walking speed and garcinol may play a further role in the prevention and treatment of pneumonia.

Keywords: hypothyroidism, pneumonia, mendelian randomization, nhanes, walking, garcinol

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Introduction

Hypothyroidism is a common clinical disease characterized by a deficiency of thyroid hormones, and if not treated in time, it may cause serious adverse health effects on multiple organ systems.[1] A meta-analysis conducted in 2019, which aggregated results from 20 surveys across Europe, indicated that approximately 4.7% of the population suffers from undiagnosed hypothyroidism.[2] Although levothyroxine, one of the most prescribed medications worldwide, is effective for most patients with hypothyroidism, its bioavailability is reportedly influenced by many factors, including interfering drugs or foods and concurrent diseases. Moreover, a minority of patients still experience symptoms after their serum thyroid-stimulating hormone (TSH) levels return to normal with medication.[3,4] Previous studies have suggested a close association between hypothyroidism and pneumonia, such as the risk of pneumonia,[5] ventilator-associated pneumonia (VAP),[6] covert pneumonia risk in elderly diabetic patients,[7] and mortality risk in interstitial pneumonia with autoimmune features.[8] Those evidences suggesting an urgent need to conduct screening for hypothyroidism and its complications.

Pneumonia is a lower respiratory tract infection involving the lung parenchyma, typically caused by respiratory viruses and various bacteria. Pneumonia caused by bacteria can be further divided into community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP).[9] It is estimated that 1.5 million adults in the United States are hospitalized annually due to CAP, with the burden of HAP accounting for about 1.5% of all hospital admissions in the UK.[10,11] The development of pneumonia is influenced by a variety of factors, including host susceptibility, pathogen virulence, and the microbial inoculum reaching the lower respiratory tract.[12] Although CAP has traditionally been viewed as an acute pulmonary disease, the current understanding is that it is a multisystem disease, and further insights into it are warranted. Besides this, the causal relationship between hypothyroidism and pneumonia remains unclear.

Furthermore, due to the inherent flaws in traditional designs, existing observational studies cannot completely rule out the possibility of reverse causality and confounding factors, which may lead to biased associations and conclusions.[13] MR is a method that uses genetic variations as instrumental variables (IVs) to help uncover causal relationships in the presence of unobserved confounding and reverse causality.[14] The MR design helps to reduce the confusion of environmental factors because alleles are randomly assigned at conception and genotypes are not affected by diseases, thus avoiding reverse causality bias.[15,16] Therefore, the aim of this study is to conduct a dimensional analysis of the relationship between hypothyroidism and pneumonia, including the correlation, causal relationship and potential mechanisms between hypothyroidism and the risk of pneumonia, and to seek corresponding preventive measures and therapeutic drugs.

Methods

This study is conducted based on STROBE_checklist_case-control and STROBE-MR-checklist, and related files have been uploaded as Supplementary Materials 1 and 2. According to Article 32, Paragraph 1 and Paragraph 2 of the "Measures for the Ethical Review of Life Science and Medical Research Involving Human Subjects" promulgated by China on February 18, 2023, the data used in this study come from public databases and does not involve identifiable content related to the privacy of the subjects. Therefore, it is exempt from ethical review.

Correlation Analysis of Hypothyroidism and Pneumonia

The data used for the correlation analysis were derived from the NHANES database for the years 2007–2012. The specific information extracted included gender, age, race, education level, poverty index, BMI, serum cholesterol content, serum TSH content, smoking status, drinking frequency, diabetes status, and HSQ520 (influenza, pneumonia, and ear infection). The exclusion criteria were as follows: (1) race as Hispanic (to categorize participants into white, black, and others); (2) unknown or missing information; (3) age without a precise value (recorded as 80 in the database for ages ≥80); (4) hyperthyroidism patients (TSH < 0.34 mIU/L). The flowchart is shown in Figure 1. Education level was categorized into three groups (below high school, high school, and above high school), poverty index into three groups (<1, ≥3, between 1–3), BMI into three groups (less than 25 kg/m², 25–30 kg/m², greater than 30 kg/m²), and thyroid function into two categories (TSH of 0.34–5.6 µIU/mL considered normal, and TSH greater than 5.6 µIU/mL regarded as hypothyroidism).

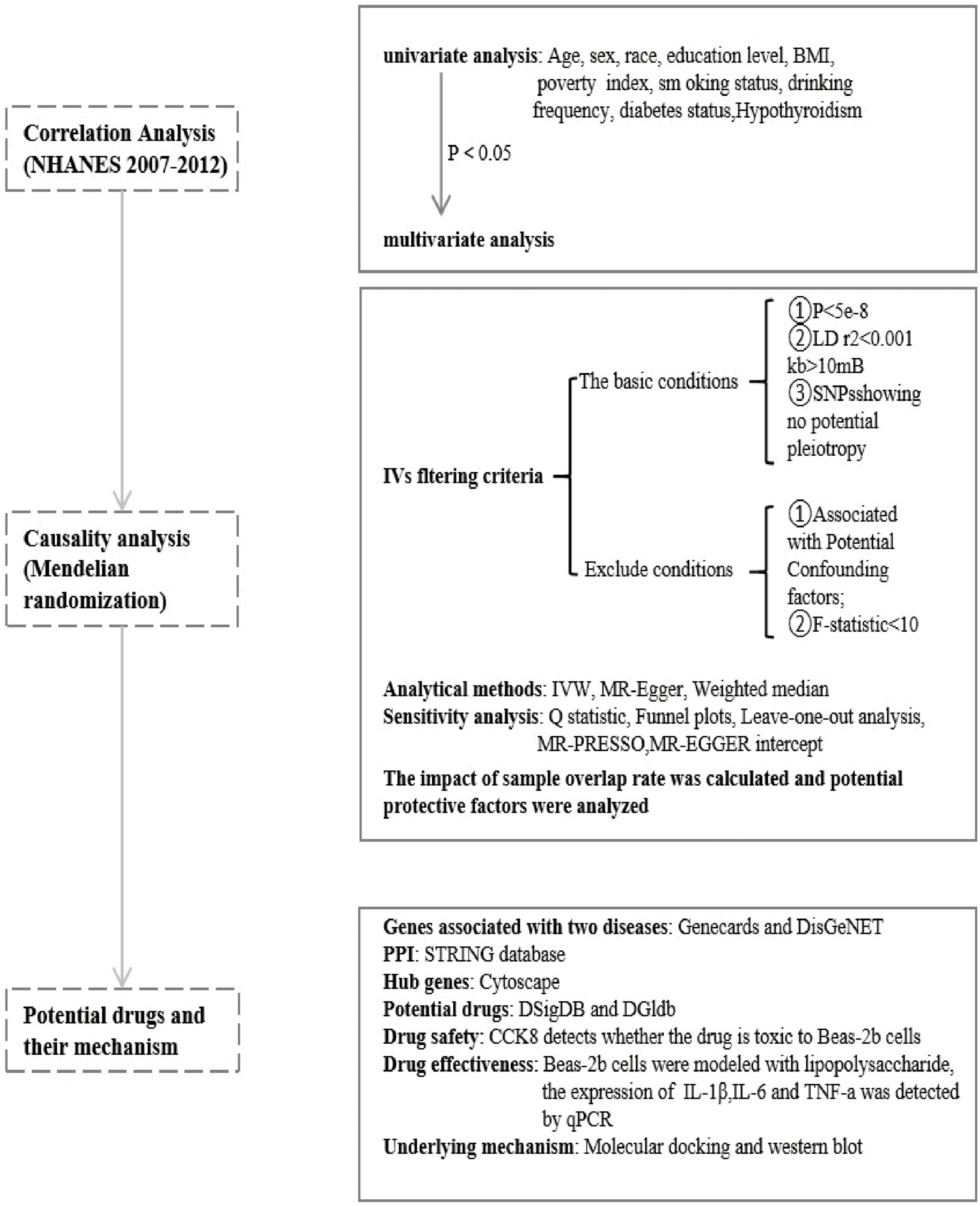

Figure 1 The flowchart of NHANES database.

Descriptive statistical measures were calculated to characterize the study cohort related to the demographic and influencing factors of interest. The receiver operating characteristic (ROC) curve and the Youden index were used to determine the optimal cut-off values for the analysis of related variables. After categorizing each variable, the Chi-square test was used to analyze the potential correlation of each factor with pneumonia, and variables with a P value < 0.05 were included in the binary logistic analysis to further clarify the potential risk factors for pneumonia. All p values are two-sided, and $p < 0.05$ is considered significant.

Mendelian Randomization

Data Source

We searched for summary statistics from GWAS conducted within the IEU OpenGWAS project. The summary statistics for hypothyroidism were derived from the MRC-IEU (including 463,010 participants, of which 9,674 had hypothyroidism) and Neale Lab (including 337,159 participants, of which 16,376 had hypothyroidism), the summary statistics for pneumonia were from the UK Biobank (including 486,484 participants, of which 22,567 had pneumonia) and NA (including 480,299 participants, of which 16,887 had pneumonia), and the summary statistics for usual walking pace were from Neale Lab (including 335,349 participants) and MRC-IEU (including 459,915 participants). All the aforementioned participants were of European descent. Detailed information about the data is shown in Supplementary Table 1.

The Rest of the Content

The IVs for the target phenotype were identified based on the following criteria proposed by Martin Bahls et al: (1) single nucleotide polymorphisms (SNPs) at a genome-wide significant level ($P < 5\times10–8$); (2) SNP clumping using the PLINK algorithm (LD $r2 < 0.001$, distance kb >10 mB); (3) exclusion of SNPs showing potential pleiotropy.[17] The strength of the correlation between SNPs and different target phenotypes is represented by the F-statistic.[18] Overall, an F-statistic >10 indicates a strong correlation between IVs and each phenotype.

In addition, to make the conclusions as robust as possible, SNPS associated with potential confounders were also removed prior to the MR Analysis. Potential confounders associated with hypothyroidism include rheumatoid arthritis,[19] systemic lupus erythematosus,[20–22] body mass index (BMI),[23] education,[24] smoking, alcohol consumption, and diabetes.[25] Potential confounders associated with pneumonia include chronic obstructive pulmonary disease, smoking,[26] BMI,[27,28] alcohol consumption,[29] income,[30] education, and diabetes.[31]

To minimize the potential pleiotropic effects of genetic variations as much as possible, this study conducted three MR analysis methods to assess the causal effects of the exposure of interest and the target outcome. We applied the standard inverse variance weighted (IVW) estimation to the primary analysis, which combined the Wald ratio for each SNP on the outcome to obtain a pooled causal estimate. Additionally, MR-Egger regression and the weighted median method were used as supplements to IVW, as these methods can provide more reliable estimates under a broader range of scenarios. In brief, MR-Egger regression can provide a test for imbalanced pleiotropy and considerable heterogeneity,[32] and the weighted median method will provide a consistent effect estimate when the weighted variance provided by horizontal pleiotropy is at least half valid.[33]

To address the issue of horizontal pleiotropy, where genetic variants associated with the exposure of interest directly affect the outcome through pathways other than the hypothesized exposure, we further conducted a series of sensitivity analyses to detect the presence of pleiotropy and assess the robustness of the results. These included Cochran's Q statistic, funnel plots, MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO), leave one out analysis, and MR-Egger intercept test. Specifically, if the P-value of Cochran's Q statistic is less than 0.05, heterogeneity is considered present, and a random-effects model should be used. If the P-values of the MR-Egger intercept and MR-PRESSO are less than 0.05, horizontal pleiotropy is considered to be present. Additionally, to determine whether the causal estimates are driven by any single SNP, we performed the leave one out analysis. Finally, since all subjects come from Europe, to explore the potential impact of sample overlap rate on the conclusions, we used hypothetical odds ratios (OR) values to explore the possibility of Type I error at a sample overlap rate of 100% on the Bias and Type 1 error rate for Mendelian randomization with sample overlap (https://sb452.shinyapps.io/overlap/).

Mechanisms and Potential Drugs

Enrichment Analysis

The Genecards and DisGeNET databases were searched to obtain genes related to hypothyroidism and pneumonia. Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of core genes were performed using the clusterProfiler (4.2.2) package in R. Enriched GO terms and KEGG pathways with adjusted $p<0.05$ were selected.

Hub Genes Associated with Hypothyroidism and Pneumonia

The intersection of genes related to both diseases from the aforementioned databases and included them in the STRING database for constructing a protein–protein interaction (PPI) network. Subsequently, the results were saved in tsv format and imported into Cytoscape 3.9.0 software, where the CytoNCA plugin was used to calculate the degree and betweenness of each node. Targets with a degree and betweenness greater than the median were defined as key targets.

Analysis of Potential Drugs

DGIdb database (https://www.dgidb.org/) and DSigDB database (https://dsigdb.tanlab.org/DSigDBv1.0/) were used to find potential drugs by using the above hub genes. Drugs with interaction score less than 2 in DGIdb database were excluded and intersected with drugs in DSigDB database for subsequent analysis.

CCK-8

Cell viability was assessed using the CCK-8 (C0039, Beyotime) according to the manufacturer's instructions. In brief, 5×10^3 cells were seeded in 100 μL of medium in a 96-well plate and then treated with varying concentrations of potential drugs for an additional 24 hours. After treatment, 10 μL of CCK-8 solution was added to each well, and the cells were further incubated for 1 hour at 37°C and 5% CO2. The absorbance was measured at 450 nm using a SYNERGY absorbance reader (BioTek Instruments, Inc).

RT-qPCR

Total RNA was extracted from cells using the SteadyPure Quick RNA Extraction Kit (AG2102) according to the manufacturer's instructions (Accurate biotechnology). RNA was reverse-transcribed into cDNA using the Evo M-MLV RT Mix Kit with gDNA Clean for qPCR Ver.2 (AG1172). Quantitative PCR analysis was performed using the SYBR Green Premix Pro TaqHS qPCR Kit (Low Rox Plus) (AG11739) on the QuantStudio 5 (Thermo Fisher Scientific, USA). Primers were as follows: Human IL-1β: 5′-CCAGGGACAGGATATGGAGCA-3′ (primer F), 5′-TTCAACACGCAGGACAGGTACAG-3′ (primer R); Human IL-6: 5′-AAGCCAGAGCTGTGCAGATGAGTA-3′ (primer F), 5′-TGTCCTGCAGCCACTGGTTC-3′ (primer R); Human TNF-α: 5′-CTGCCTGCTGCACTTTGGAG-3′ (primer F), 5′-ACATGGGCTACAGGCTTGTCACT-3′ (primer R); Human β-actin: 5′-TGGCACCCAGCACAATGAA-3′ (primer F), 5′-CTAAGTCATAGTCCGCCTAGAAGCA-3′ (primer R).

qPCR conditions were as follows: pre-denaturation at 95°C for 30 seconds, followed by denaturation at 95°C for 5 seconds and annealing/extension at 60°C for 30 seconds, with 40 cycles. The relative expression levels of all genes were calculated using the $2-\Delta\Delta Ct$ formula.

Molecular Docking

The protein is downloaded from the PDB database, the water molecule and receptor protein are removed using PyMOL software, and saved in PDB format, then imported into the AutoDockTools software, followed by hydrogenation, calculation of charge, setting of atomic type, and output to the software's special format after completion. Chemdraw is used to draw the molecular structure of small molecules, and then the small molecules are imported into the Chemdraw 3D software to optimize the small molecule structure, and the output is completed in PDB format. Use the AutoDockTools software to open the small molecule file, perform the hydrogenation in turn, calculate the maximum number of rotating keys, and set the keys that can be rotated. Set as a ligand when done and export to a dedicated format.

The active ingredient structure with the target molecular docking, using pyrx software (https://pyrx.sourceforge.io/) internal vina for docking. The Affinity (kcal/mol) value represents the binding capacity of the two, and the lower the binding capacity, the more stable the binding between the ligand and the receptor. It is generally believed that the docking energy value less than −4.25 kcal/mol indicates a certain binding activity between the two, less than −5.0 kcal/mol indicates a good binding activity, and less than −7.0 kcal/mol indicates a strong binding activity.

Finally, AutoDockTools is used to open it and output it as a pdb format file, and PyMOL is used to open it. The compounds were introduced into PyMOL, and the optimal model was selected from 9 small molecule conformations to analyze the interaction between the compounds and proteins.

Western Blot

RIPA lysis buffer (R0010-100mL), protease inhibitor (P6730-1mL), and phosphatase inhibitor (P1260-1mL) were all purchased from Solarbio. The primary antibodies p-STAT1(9167S), STAT1(9172S) and β-ACTIN (3700S) were purchased from Cell Signaling Technology. The prepared proteins were separated by gel electrophoresis and then transferred onto membranes. Secondary antibodies, including goat anti-rabbit IgG (LF102) and goat anti-mouse IgG (LF10), ECL detection reagent kit (SQ201), PAGE gel rapid preparation kit (PG212), electrophoresis buffer (PS105S), and transfer buffer (PS109S) were all purchased from EpiZyme. After blocking these membranes with BSA, they were incubated with the primary antibodies overnight at 4°C. After incubation, the membranes were incubated with the corresponding secondary antibodies for 60 minutes.

Statistical Analysis

Correlation analyses were conducted utilizing SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). MR analyses were performed using the software packages TwoSampleMR (version 0.5.6), gwasglue (version 0.0.0.9000), and VariantAnnotation (version 1.44.1) in R (version 4.2.2). The analysis and visualization of qPCR and WB results were performed using GraphPad Prism version 9.3.0 (GraphPad Software, LLC) (Supplementary Figure 5).

Results

Hypothyroidism Is Associated with the Increased Risk of Pneumonia

This study ultimately included 3,306 participants from the NHANES database, consisting of 1,794 males and 1,512 females, with ages ranging from 20 to 79 years. The racial distribution was 2,190 non-Hispanic whites, 847 non-Hispanic blacks, and 269 from other races. Education levels were categorized as follows: 526 with below high school, 739 with high school, and 2,041 with above high school. Poverty index categories included 562 with less than 1, 1,166 between 1 and 3, and 1,578 with greater than or equal to 3. Serum cholesterol levels ranged from 2.17 to 11.43 mmol/L. BMI categories were: 1,129 with less than 25 kg/m², 1,081 with 25–30 kg/m², and 1,096 with greater than 30 kg/m². Smoking history included 1,766 who had smoked at least 100 cigarettes in their lifetime and 1,540 who had smoked fewer than 100 cigarettes. Drinking frequency was categorized as weekly (1,492), monthly (828), and yearly (986). Diabetes prevalence included 272 with diabetes and 3,034 without diabetes. TSH levels were categorized as 3,227 with 0.34–5.6 µIU/mL and 79 with greater than 5.6 µIU/mL. The ROC curve and Youden index indicated the optimal cut-off values for age and serum cholesterol content were 52.5 years and 5.39 mmol/L, respectively (As shown in supplementary Figure 1). At these cut-off points, there were 2,108 participants under 53 years old and 1,198 participants aged 53 or older, and 2,134 with serum cholesterol levels below 5.39 mmol/L and 1,172 with levels at or above 5.39 mmol/L. Infections with influenza/pneumonia/otitis media were reported in 112 participants, while 3,194 participants had no such infections.

The results of the Chi-square test suggested that age, education level, poverty index, and serum TSH levels might be factors influencing influenza/pneumonia/otitis media, whereas gender, race, BMI, serum cholesterol content, smoking status, drinking frequency, and diabetes status might not be influencing factors for these infections. Subsequently, the four potential influencing factors were included in a multivariable binary logistic regression analysis. The results indicated that age and serum TSH levels (β=0.942, P=0.032) might be independent influencing factors for influenza/pneumonia/otitis media, education level is a potential influencing factor, and the poverty index (P=0.252) is not related. Detailed information and analysis results of the relevant data are shown in Supplementary Table 2.

Result of Mendelian Randomization

Instrumental Variable

To minimize the impact of sample overlap as much as possible, we selected datasets from different consortia for analysis in the MR analysis. Specifically, the datasets for usual walking pace, hypothyroidism, and pneumonia were ukb-a-513, ukb-b-4226, and ebi-a-GCST90018901 in the training set, and ukb-b-4711, ukb-a-77, and ieu-b-4976 in the validation set.

When ukb-a-513 was used as the exposure factor, there were 4 SNPs with an F-statistic less than 10. When ukb-b-4226 was used as the exposure factor, there was 1 SNP with an F-statistic less than 10. When ukb-b-4711 was used as the exposure factor, there were 10 SNPs with an F-statistic less than 10, and when ukb-a-77 was used as the exposure factor, there were 14 SNPs with an F-statistic less than 10. In addition, when hypothyroidism or pneumonia was the outcome variable, we excluded SNPS associated with confounders, respectively. In the training set, 8 SNPs were excluded when the usual walking pace was used as an exposure factor, and 7 SNPs were excluded when hypothyroidism was used as an exposure factor. In the validation set, 11 SNPs were excluded when the usual walking pace was used as an exposure factor, and 6 SNPs were excluded when hypothyroidism was used as an exposure factor. Detailed information on the excluded SNPs is shown in Supplementary Table 3. Detailed information on the IVs included in the final analysis is shown in Supplementary Table 4.

Hypothyroidism Is Causally Linked to a Higher Risk of Pneumonia and Increasing the Usual Walking Pace May Lower Pneumonia Risk

The results of the MR analysis indicated that hypothyroidism is associated with an increased risk of pneumonia and improving usual walking pace helps to reduce the risk of hypothyroidism and pneumonia (Figure 2 and Supplementary Figure 2). The results are shown in Supplementary Table 5. The two-step MR analysis process and calculation formulas are shown in Figure 3, indicating that in the analysis of the impact of usual walking pace on pneumonia, the mediating effect of usual walking pace on pneumonia risk through its effect on hypothyroidism was −0.147 in the training set, accounting for 16.5%, and −0.022 in the validation set, accounting for 2.2%.

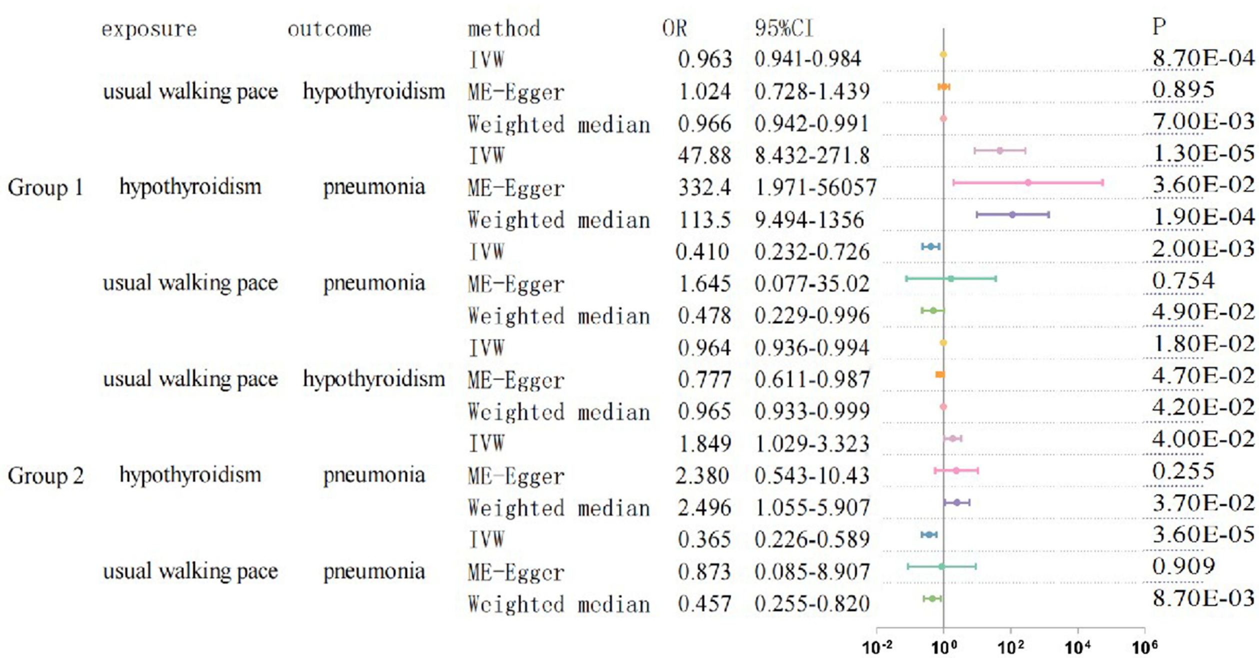

Figure 2 The forest map of MR results.

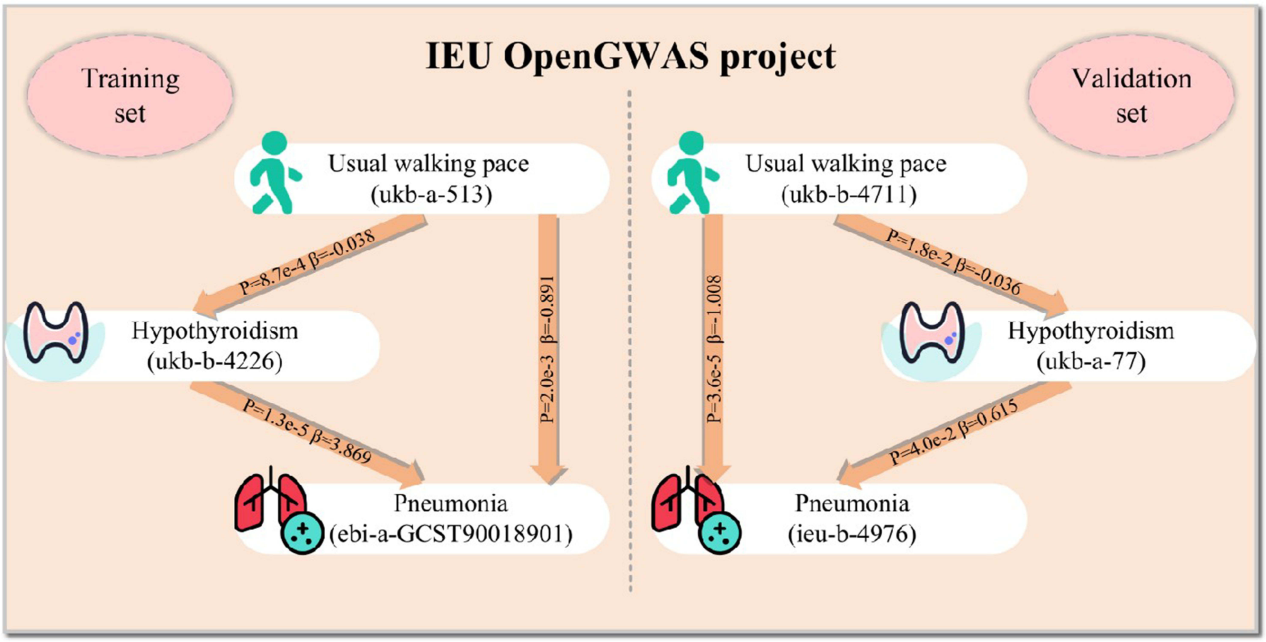

Figure 3 Two-step MR design.

The Sensitivity Analysis Results Were Robust

In order to determine the correctness of the results of the MR Analysis, we performed a series of sensitivity analyses. The sensitivity analysis results were generally robust; however, the reliability of the causal relationship between usual walking pace and hypothyroidism remains uncertain. In short, except for the analysis of the usual walking pace and hypothyroidism risk, the results of Cochran's Q test, MR-Egger intercept test and MR-PRESSO all showed that P > 0.05. The Leave-one-out analysis results showed that the causal estimation is not driven by any single SNP, and the funnel plot is also symmetric. The results of the leave-one-out method and funnel plots are shown in Supplementary Figures 3 and 4, and the results of Cochran's Q test, MR-Egger intercept test, and MR-PRESSO are shown in Supplementary Table 6. In conclusion, these results corroborated that hypothyroidism increases the risk of pneumonia and that improving usual walking pace effectively reduces pneumonia risk. However, further studies are needed to elucidate the relationship between usual walking pace and hypothyroidism.

The Sample Overlap Rate Had No Significant Effect on the Conclusion

To explore the effect of sample overlap rate on MR Results, we analyzed the probability of type I errors with a sample overlap rate of 100%. Since previous studies have not explored the possible odds ratios between walking speed and pneumonia or hypothyroidism, we assumed the OR for potential protective factors to be 0.3 or 0.9, and the OR for potential risk factors to be 1.1 or 3.0. Under these circumstances, the probability of committing a Type I error in each analysis result is around 0.05, even at a sample overlap rate of 100%, suggesting that the relevant conclusions may not be affected by the sample overlap rate, as shown in Supplementary Table 7.

Potential Drugs and Mechanisms Underlying Hypothyroidism Induced Pneumonia

Potential Mechanisms by Which Hypothyroidism Increases the Risk of Pneumonia

In order to explore the potential mechanism by which hypothyroidism increases the risk of pneumonia, we analyzed the intersection genes of hypothyroidism and pneumonia. The Genecards and DisGeNET databases contain 5,259 and 613 genes associated with hypothyroidism, and 6,620 and 1,032 genes associated with pneumonia, respectively. A total of 108 genes are present in all four gene sets, as shown in Figure 4a. GO enrichment results (Figure 4b) showed that T cell activation and regulation of cell–cell adhesion are significantly enriched in BP. Cytoplasmic vesicle lumen and vesicle

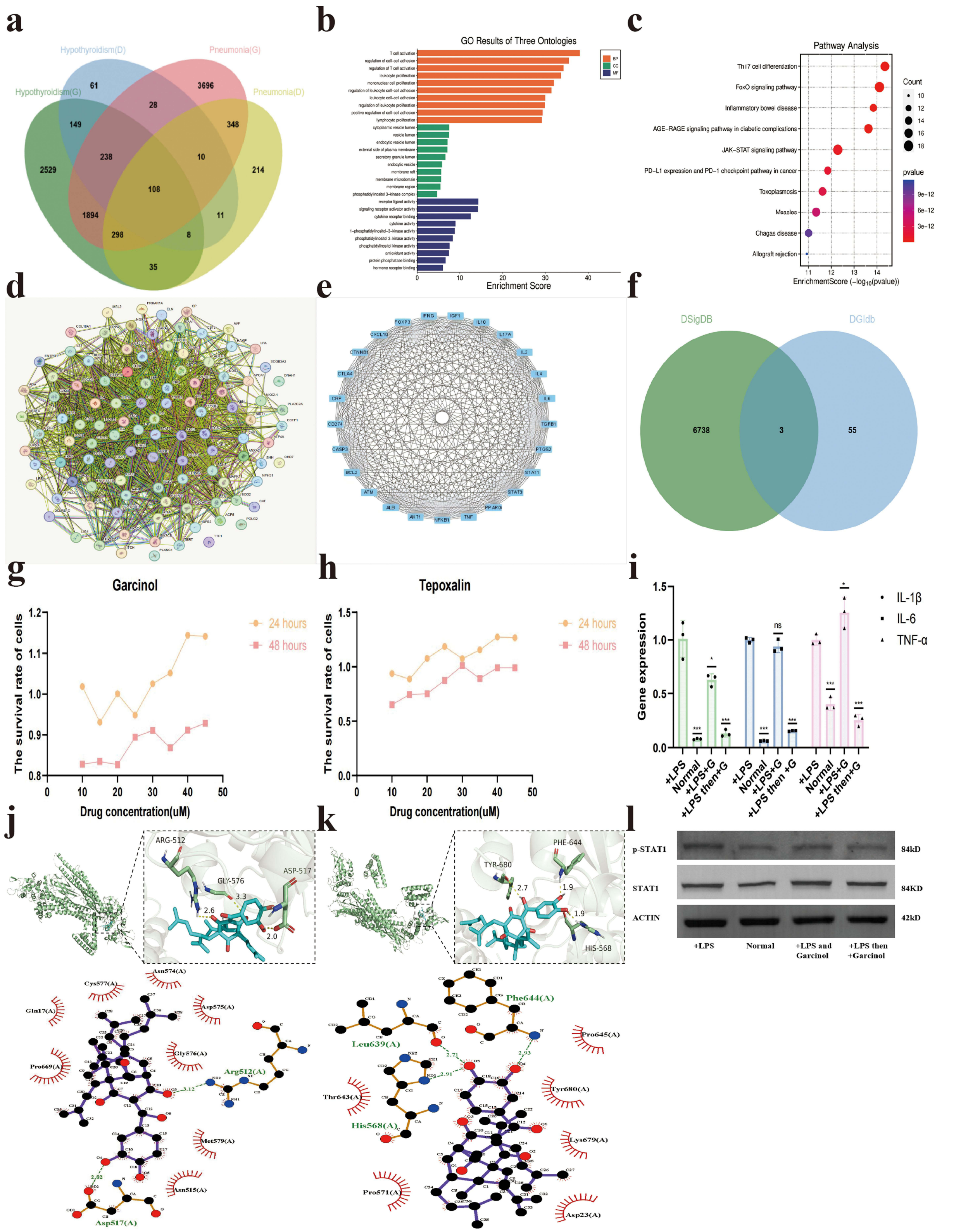

Figure 4 The results of potential mechanism analysis. (**a**) Intersection gene of hypothyroidism and pneumonia; (**b**) GO enrichment results of the intersection gene between hypothyroidism and pneumonia. (**c**) KEGG enrichment results of the intersection gene between hypothyroidism and pneumonia (**d**) The PPI network of intersection gene; (**e**) 24 hub genes; (**f**) Potential drugs; (**g**) Safety assessment of Garcinol; (**h**) Safety assessment of Tepoxalin (**i**). Effectiveness of Garcinol. * represents P < 0. 05, *** represents P < 0. 001. (**j**). Gaicinol and site 1 of STAT1 domain 2 have good docking efficiency. (**k**). Gaicinol and site 1 of STAT1 domain 2 have good docking efficiency. (**l**). LPS increases the level of STAT1 phosphorylation of BEAS-2B, and garcinol can reduce this effect.

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lumen structures are significantly enriched in CC, receptor ligand activity and signaling receptor activator activity are significantly enriched in MF. In addition, KEGG enrichment results (Figure 4c) showed that the intersection genes of hypothyroidism and pneumonia were significantly enriched in Th17 cell differentiation and JAK-STAT signaling pathway. These results revealed potential mechanisms by which hypothyroidism increases the risk of pneumonia.

Potential Drugs for Pneumonia Treatment

In order to improve the accuracy of drug screening, we first analyzed the core genes between hypothyroidism and pneumonia. The PPI network visualized using the STRING database is shown in Figure 4d. After considering Degree and Betweenness, a total of 24 key targets were identified (such as CXCL10, AKT1, IL10, STAT1 and IL6), as shown in Figure 4e.

To further confirm the potential drugs for pneumonia treatment, we then analysed 1,164 potential drugs from the DGIdb database and 6,741 from the DSigDB database. After excluding data with an interaction score less than 2 from the DGIdb database, we identified 58 potential drugs by using the above 24 hub genes. Subsequently, by intersecting with the drugs from the DSigDB, we obtained three potential drugs, including 1,4-dichlorobenzene, tepoxalin, and garcinol. The VENN diagram is shown in Figure 4f. The potential targets for these three substances are CASP3, IL4, and STAT1, respectively.

To further explore the potential effects of the above three drugs on pneumonia, 10 μg/mL lipopolysaccharide (LPS) were treated to Beas-2b with for 24 hours to establish a pneumonia model. Because 1,4-dichlorobenzene is a pollutant, we did not analyze its potential in treating pneumonia. Subsequently, the cells were cultured with a certain concentration of potential drugs for an additional 24 hours. In addition, to explore whether drugs have a preventive effect on LPS-induced pneumonia, we added LPS and drugs to the culture medium for 24 hours at the same time.

CCK-8 results showed that garcinol had no obvious killing effect on Beas-2b at the concentration of 10–45uM; however, tepoxalin may have a certain killing effect on Beas-2b, as shown in Figure 4g–4h. RT-qPCR results showed that compared to Beas-2b cells, the expression of IL-1β, IL-6 and TNF-α increased in LPS-treated (10ug/mL) Beas-2b cells. Compared to the culture medium with only LPS added, added after obtaining the LPS-induced pneumonia model in the culture medium, garcinol inhibited the expression of IL-1β, IL-6 and TNF-α. However, when LPS and garcinol were added to the medium at the same time, garcinol had no preventive effect on LPS-induced pneumonia (Figure 4i). The above results suggest that garcinol may mitigate pneumonia induced by LPS.

Garcinol Inhibits STAT1 Phosphorylation by Binding with STAT1 SH2 Domain

Our results showed STAT1 was the potential target of garcinol, we then explored whether garcinol contributes co pneumonia treatment through regulating STAT1 expression.

To afford our interaction studies, the two putative binding pockets (site 1 and site 2) were considered.[34] Molecular docking results showed the binding energies of site 1 and site 2 of STAT1 with garcinol were −5.5 and −6.2 kcal/mol. Garcinol formed three hydrogen bonds with ARG-512, GLY-576 and ASP517 amino acids in STAT1 protein site 1 of SH2 domain (Figure 4j). Garcinol formed three hydrogen bonds with TYR-680, PHE-644 and HIS-568 amino acids in STAT1 protein site 2 of SH2 domain (Figure 4k). At the same time, the protein makes non-bonding contact with small molecules, forming a force represented by electrostatic potential energy and van der Waals force. In addition, WB results showed that LPS treatment increased the phosphorylation level of STAT1, whereas garcinol abolished the effect of LPS on p-STAT1 protein levels (Figure 4L). In conclusion, these results corroborated that garcinol contributes co pneumonia treatment through binding with STAT1 protein and inhibiting STAT1 phosphorylation.

Discussion

Although the potential relationship between hypothyroidism and the risk of pneumonia has been previously noted, no studies have been conducted to further analyze their potential causation, mechanisms, preventive measures, and therapeutic agents.

MR is a method that uses genetic variations as IVs to uncover causal relationships in the presence of unobserved confounding and reverse causality, it can reduce the impact of environmental factors, but also can effectively avoid reverse causal bias.[35] In addition, unlike typical observational studies, MR utilizes pooled estimates of exposure and outcomes from genetic databases from different sources to improve statistical power, thereby enhancing the assessment of causal effects between exposure and outcomes.[36] Generally speaking, the statistical power of the IVW method is significantly higher than other MR methods, particularly the MR-Egger. Thus, in MR analysis, IVW is commonly used as the primary method for screening potential significant results. Additionally, in most MR analyses, researchers emphasize the requirement for consistency in the direction of β across all MR methods, which was also applied in our study. Furthermore, to minimize the impact of different datasets, we selected various datasets for validation. Our results suggested a causal relationship between hypothyroidism and an increased risk of pneumonia that can be detected across different data sets.

Given that the etiological agents of pneumonia, such as bacteria, fungi, and viruses, are widely present in nature, and considering that many individuals may have risk factors such as weakened immunity, extreme age, or unsuitable living environments, the risk of pneumonia remains high for the general population. Moreover, despite government regulations, global air pollution levels continue to rise.[37] The clinical, economic, and humanistic burdens caused by pneumonia have always been a concern. It is known that pneumonia is a significant cause of morbidity and mortality in both the community and hospitals,[38] and CAP is a leading cause of death among infants, the elderly, and immunocompromised individuals.[39] Early respiratory infections in children, including pneumonia, result in over 40 million cases annually and lead to approximately 650,000 deaths.[40] Levothyroxine is the primary therapy for hypothyroidism, but its bioavailability can be hampered by a number of conditions, such as concomitant diseases, interference with medications and foods, brand switching, and nonadherence.[41–45] Therefore, exploring the potential risk and protective factors for pneumonia is increasingly important.

Previous studies have shown that faster walking has a special effect. Specifically, faster walking speed may be associated with a lower risk of specific death, including cancer specific death, cardiovascular specific death, and lung cancer specific death.[46–48] In addition, increasing walking speed may reduce the risk of certain diseases, such as lung cancer,[49] thyroid cancer,[50] and cardiovascular disease.[51] What's more, faster walking speed may slow the rate of disease progression and has a potential causal relationship with longer white blood cell telomere length.[52,53] However, it is not clear whether it is related to the risk of pneumonia. We analyzed the potential causal relationship using the MR study, and the results showed that increasing walking speed may help reduce the risk of pneumonia, which provides new insights into the prevention of pneumonia.

Despite innovative advancements in anti-infective therapies and vaccine development, CAP remains one of the most enduring causes of infection-related deaths globally.[54] Therefore, the search for new therapeutic targets and potential drugs is particularly important.

Multiple previous studies have shown that STAT1 play a role in the development of hypothyroidism and pneumonia.[55,56] Garcinol is a polyisoprenylated benzophenone found in the genus Garcinia, which is reported to regulate the metabolism of arachidonic acid by blocking the phosphorylation of cPLA2 and to reduce the protein level of iNOS by inhibiting the activation of STAT-1.[57] It can also exert anti-inflammatory activity in LPS-stimulated macrophages by inhibiting the activation of NF-κB and/or JAK/STAT-1.[57,58] These studies suggest that garcinol may be potential effective drugs for the treatment of hypothyroidism and pneumonia. Previous study has shown that garcinol exerts anti-inflammatory effects mainly by inhibiting STAT-1 nuclear transfer by binding to the SH2 domain of STAT1.[59] Our enrichment analysis results suggest that the JAK-STAT signaling pathway may play a key role in the mechanism by which hypothyroidism increases the risk of pneumonia, and the results of molecular docking also showed that garcinol had good binding activity with domain2 of STAT1. The results of this study suggest that garcinol has a potential therapeutic effect on pneumonia by inhibiting the activation of STAT1.

CASP3, as a core gene in apoptosis, plays a significant role in various physiological and pathological changes.[60] Previous studies have indicated that CASP3 is closely related to the occurrence and progression of pneumonia.[61–64] Pathogens, during infection, can promote their own replication and proliferation by regulating extrinsic death receptor and intrinsic mitochondrial apoptotic pathways.[65,66] Therefore, modulating the expression of genes involved in the apoptotic pathway may be a potential effective method of combating infections. Additionally, high expression of CASP3 may be associated with the development of papillary thyroid carcinoma, which carries a higher risk of lymph node metastasis, distant metastasis, and lower survival rates,[67] although current research lacks exploration of its association with hypothyroidism. 1,4-Dichlorobenzene is a typical volatile organic pollutant that can be transmitted through the atmosphere, with the main exposure coming from breathing polluted indoor air, posing a significant threat to human respiratory health.[68] Acute (short-term) exposure to 1,4-dichlorobenzene can cause irritation to the respiratory tract, skin, throat, and eyes. Chronic (long-term) human exposure to 1,4-dichlorobenzene can affect the liver, skin, and central nervous system (CNS).[69,70] It may be a potential risk factor for hypothyroidism or pneumonia. Tepoxalin may have the effect of regulating canine mast cell-mediated immune responses by blocking the production of arachidonic acid,[71] but there are currently no studies indicating its similar effects on pneumonia or hypothyroidism. The purpose of this study was to search for potential therapeutic agents, so we did not analyze the potential effect of 1, 4-dichlorobenzene. In addition, the findings suggest that tepoxalin may have an inhibitory effect on normal alveolar epithelial cells.

In exploring the potential mechanisms by which hypothyroidism increases the risk of pneumonia, we selected data from different databases to reduce potential errors. Furthermore, although previous studies have used datasets from the Gene Expression Omnibus (GEO) database to analyze DEGs between hypothyroid patients and normal individuals, after careful searches in GEO and PubMed, we found that those datasets might not be suitable. That is, apart from GSE103305, other datasets have various issues, such as some being derived from mouse studies, and others showing fewer than 10 DEGs after online analysis with the GEO2R tool.

However, there are some limitations that should be considered in our study. Firstly, only 79 individuals with TSH levels greater than 5.6 μIU/mL in the NHANES database, and the information on pneumonia was not clear, ie, the database grouped influenza, pneumonia, and ear infections under the same questionnaire code. Secondly, no external data were used for validating the correlation between hypothyroidism and pneumonia, which may necessitate further exploration in future large-sample prospective cohort studies. Thirdly, although the MR analysis showed a potential causal relationship, all participants were European, and applicability to other ethnic groups has yet to be tested. Finally, although the results of this study suggest that increasing walking speed may help reduce the risk of pneumonia and garcinol may be helpful in treating pneumonia, the relevant conclusions still need further verification.

Data Sharing Statement

All data used in this study came from public databases, meaning that no new data sets were generated in this study.

Ethics Approval Statement

According to Article 32, Paragraph 1 and Paragraph 2 of the “Measures for the Ethical Review of Life Science and Medical Research Involving Human Subjects” promulgated by China on February 18, 2023, the data used in this study come from public databases and does not involve identifiable content related to the privacy of the subjects. Therefore, it is exempt from ethical review.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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