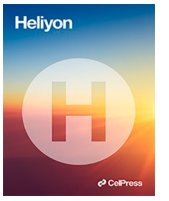
Heliyon 10 (2024) e40439

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Indoor radon exposure: A systematic review of radon-induced health risks and evidence quality using GRADE approach

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A R T I C L E I N F O

Keywords:
Indoor radon exposure
Lung cancer
Chronic obstructive pulmonary diseases (COPD)
Leukemia
Evidence quality

A B S T R A C T

Background: Radon (Rn) is a radioactive gas with well-established carcinogenic properties. It is a significant contributor to natural background ionizing radiation exposure, accounting for over 50 % of human exposure. Prolonged exposure to radon gas has been conclusively linked to various health issues such as lung cancer, leukemia, and Chronic Obstructive Pulmonary Diseases (COPD). Despite this, there is a scarcity of comprehensive studies examining the quality of evidence establishing an association between indoor radon exposure and these health problems.

Objective: We performed a systematic review of peer-reviewed research articles to explore the current evidence on the potential association between residential radon exposure and human health, specifically focusing on lung cancer, COPD, and leukemia.

Methods: A comprehensive search was conducted on PubMed and Google Scholar using MeSH terms and keywords (*residential radon, radon AND lung cancer, radon AND COPD, radon AND leukemia*). The inclusion criteria focused on studies that analyzed the link between residential radon exposure and lung cancer, leukemia and COPD. We searched for peer-reviewed studies published from 2010 to 2024. Studies carried out in occupational settings were not considered. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to select relevant studies. Reviewers independently collected data, resolving disagreements through discussion. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate evidence quality, and the study was registered with PROSPERO, CRD42024550735.

Results: The evidence indicating an associative or causal link between indoor radon and lung cancer was found to be of high quality or conclusive, particularly with stronger support from case-control studies. The findings for COPD and leukemia were inconclusive, indicating that additional research is necessary to establish a definitive link between residential radon exposure and these health outcomes. These associations was deemed moderate or inconclusive primarily due to methodological shortcomings, conflicting findings and the prevalence of weak study designs and poor exposure data. The existing evidence on the potential connection between residential radon exposure and the risk of COPD and leukemia is currently limited. In order to definitively confirm or disprove this association, more studies are needed. Further research is crucial to elucidate these relationships and to guide the development of effective public health interventions.

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https://doi.org/10.1016/j.heliyon.2024.e40439
Received 25 May 2024; Received in revised form 9 November 2024; Accepted 13 November 2024
Available online 14 November 2024

Conclusion: The review found that the association between radon exposure and lung cancer was consistent with existing scientific knowledge. However, the evidence for association between indoor radon exposure and COPD was inconclusive. Additionally, evidence linking indoor radon exposure to leukemia was uncertain. Future research should use more robust study designs (cohort and case control studies) and directly measure long-term radon levels to investigate the potential association between residential radon exposure and COPD and leukemia.

1. Introduction

Radon (Rn) and its progenies are the primary source of natural background ionizing radiation, accounts for around a half of all human exposure to radiation. This radioactive gas is present in all types of buildings and homes, making it the largest source of background radiation exposure to the public [1–5]. The average total annual dose from all sources of ionizing radiation for the world's population is 3.0 mSv, with over 80 % of this coming from natural sources [6,7]. Rn is the heaviest noble gas that originates from the natural radioactive decay chain beginning with uranium-238 [8]. This prevalent naturally occurring radioactive material (NORM) exists in soil, rocks, and even building materials [9]. While typically trapped within these solids [10,11], Rn can accumulate in enclosed spaces, reaching concerning concentrations indoors [11]. Due to its high density, Rn tends to settle in basements and other low-lying areas, unlike outdoor radon which disperses rapidly [11,12]. Indoor radon levels tend to be higher in poorly ventilated spaces [13], in cold climates, especially during winter [14], in areas reliant on groundwater sources [15] and are influenced by building materials and characteristics [16]. This accumulation of indoor Rn presents a significant health risk, warranting attention and mitigation strategies.

Radon (Rn) has several isotopes, but Rn-222, also known as radon, is the most common and has significant implications for public health [8,17,18]. Compared to other radon isotopes, Rn-222 has a longer half-life of 3.82 days. It is the only radioactive gas in the uranium decay series, and it is the heaviest and most stable member of the inert gas family [19]. Similar to Uranium-238 and Radium-226, its precursors, radon also undergoes radioactive decay, leading to the formation of radon progenies. Rn progenies (also known as radon daughter or radon decay products), specifically polonium-218 (^{218}Po) and polonium-214 (^{214}Po), account for more than 90 % of the radiation dose resulting from radon exposure [11,12,20,21]. However, the concentration of radon gas is used as a reliable indicator of the concentration of radon decay products in indoor radon measurements [22]. Adverse health effects from radon exposure come from its decay products, often attached to dust particles, which can be inhaled and deposited in the lungs [7,23,24]. The inhalation of radon can lead to the deposition of its radioactive decay products on the bronchial mucosa. This causes sustained cellular irradiation [13]. The heavy charged particles released by radon can result in cellular damage and death as they move through lung tissue [19]. Damage to Deoxyribonucleic Acid (DNA) from radon decay products can disrupt the helical structure, potentially leading to uncontrolled cell proliferation and the formation of bronchopulmonary tumors [13]. Although the body has repair mechanisms, persistent damage can overwhelm these processes, increasing the risk of lung cancer [12,13,24]. The International Agency for Research on Cancer (IARC), World Health Organization (WHO), and United States Environmental Protection Agency (EPA) has reported indoor radon exposure and its decay products as the most important cause of lung cancer after smoking [13].

Multiple studies have confirmed the correlation between prolonged exposure to Rn and the risk of developing lung cancer [25–29]. Rn is a known human carcinogen that can cause lung cancer [2,23]. It is recognized as such by multiple international organizations such as the IARC, WHO, and EPA [2,30]. Radon's carcinogenic effects has been confirmed mostly from experimental animal studies and occupational studies involving underground miners [31,32]. Lung cancer is one of the most common cancer type, responsible for approximately 1.6 million annual deaths worldwide [33]. It has been estimated that between 3 and 14 % of lung cancer fatalities globally may be attributed to indoor radon exposure [22,33]. Radon exposure is a significant public health concern linked to an increased risk of lung cancer [34]. However, the adverse health effects of radon extend beyond respiratory disease. Epidemiological studies have demonstrated a positive association between indoor radon levels and leukemia incidence [16,22,35]. Notably, natural background radon is estimated to contribute to a 20 % increase in childhood leukemia cases [36,37]. While the etiology of childhood leukemia is complex, involving both genetic and environmental factors, radon emerges as a critical environmental risk factor. The precise mechanisms by which radon induces leukemogenesis remain to be fully elucidated, although it is hypothesized that inhaled radon can reach the bone marrow, causing DNA damage and cause leukemia [37].

The exposure to indoor radon has been associated with an increased risk of COPD, although the exact relationship is not entirely understood [38–40]. COPD is a significant global health problem, affecting hundreds of millions of people worldwide and leading to considerable morbidity, mortality, and economic costs [41,42]. Although smoking is the primary risk factor, the prevalence of COPD among individuals who have never smoked emphasizes the importance of non-smoking causes, including environmental factors like radon. Further research is necessary to clarify the role of radon in the development of COPD [41]. Given the substantial health risks associated with indoor radon exposure, leading international organizations, including the WHO, EPA, and IAEA, have established reference levels to mitigate public health impacts. The World Health Organization (WHO) recommends a reference level of 100 Becquerels per cubic meter (Bq m^{-3}) to evaluate radon exposure· [22]. However, recent research indicates that there may not be a safe level of exposure to this radioactive gas [22,43]. Studies examining the association between Rn exposure and chronic diseases such as COPD [39,40] and leukemia [22,37] have produced conflicting results, highlighting the need for further investigation. The relationship between radon exposure and most health outcomes remains inconclusive due to inconsistencies across previous studies [22]. Heterogeneity in study design, population, and methodology has hindered robust evidence evaluation. To address this, this systematic

review aimed to synthesize recent research (past 14 years) to provide a more comprehensive understanding of radon's health impacts. This systematic review was conducted to assess the quality of evidence regarding the link between residential Rn exposure and the development of lung cancer, COPD, and leukemia. The strength of this evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. The GRADE approach improves transparency in evaluating environmental and public health questions. It involves a comprehensive process that starts with defining specific questions, assessing the certainty of the evidence, and then developing recommendations [44]. GRADE is extensively utilized globally in clinical medicine, public health, and health policy, and is employed by reputable organizations such as the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) [44]. The objective of this systematic review was to answer the following questions.

a) Does the existing body of evidence, assessed for its quality, support a conclusive or inconclusive association between residential radon exposure and the development of lung cancer?
b) Does the existing body of evidence, assessed for its quality, support a conclusive or inconclusive association between residential radon exposure and the development of chronic obstructive pulmonary disease (COPD)?
c) Does the existing body of evidence, assessed for its quality, support a conclusive or inconclusive association between residential radon exposure and the development of leukemia?

2. Methods

2.1. Study design

We used the PECO (Population, Exposure, Comparison and Outcome) to frame our research question. Our focus was on residents exposed to indoor radon and whether they had a higher risk of developing lung cancer, COPD or leukemia compared to those living in areas with lower Rn exposure. We conducted a systematic review of scientific literature to investigate this relationship.

Applying the PECO approach to our review, we focused on the following.

✓ Population (P): Residents exposed to high indoor radon concentrations
✓ Exposure (E): Indoor radon exposure
✓ Comparison (C): Residents exposed to lower indoor radon concentrations
✓ Outcome (O): Lung cancer, Leukemia and COPD

2.2. Protocol and registration

This systematic review protocol was created and registered with the Faculty of Health Sciences Research Ethics Committee (REC) under Clearance Number REC-1889-2023. The protocol of this systematic review was registered with the PROSPERO (CRD42024550735). Furthermore, the PRISMA checklist was utilized to structure the content of this systematic review.

2.3. Information sources and search strategy

Three researchers conducted independent searches of electronic databases, including PubMed (last screened or consulted March 30, 2024) and Google Scholar (Last screened and consulted, May 15, 2024), for peer-reviewed research articles. The search criteria were applied using Medical Subject Headings (MeSH) and involved specific key words and phrases such as *residential radon, radon and lung cancer, radon and COPD, and radon and leukemia* in various combinations. In addition, we meticulously examined the reference lists of the selected articles to discover other relevant research articles. The search was limited to research articles written in English and published between 2010 and 2024. The focus was on identifying research articles relevant to the researchers' specific questions, and the keywords were refined during the search process.

2.4. Selection and data extraction process

2.4.1. Study selection

This systematic review focused exclusively included all studies published between 2010 and 2024 that evaluated the adverse health effects, particularly lung cancer, leukemia and COPD associated with residential radon exposure. All studies regardless of the study design to be eligible had to compare adverse health effects between individuals who were exposed to high indoor radon concentrations against the control group or individuals who were exposed to lower indoor radon concentrations. We included studies that directly compared cases (individuals with either lung cancer, leukemia or COPD) and control (individuals without either lung cancer, Leukemia or COPD) and assessed if indoor radon concentration level was high amongst the cases. No restrictions were applied on how results were reported, as we considered the results that were reported as percentage, odds ratio and relative risk. Furthermore, we considered studies that reported the adverse health effects using either incidence and mortality. In cases where both incidence and mortality were reported, the incidence was considered. To ensure comprehensive coverage, targeted searches were conducted using keywords, publication dates, and reference lists of selected articles. Studies with indoor radon concentration measurements and health outcome assessments were included, regardless of location, and demographics.

Excluded studies did not meet the inclusion criteria, such as those on non-humans, in vitro experiments, unpublished works, occupational settings (i.e studies conducted amongst miners), and other studies format like systematic review, abstracts or commentaries. Duplicate articles were also excluded. Furthermore, studies that evaluated an association between radon in water and lung cancer, leukemia or COPD were excluded. This was done because radon in drinking water is associated with an increased risk of developing other organ cancers, primarily stomach cancer [37,45]. The systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology, detailed in Fig. 1. Eligibility assessment of the research articles found in electronic databases began with evaluating the research article's title to determine its relevance to the review's objective. This led to the exclusion of some research articles. Relevant articles from the title screening were then subjected to abstract screening, resulting in the inclusion of some articles and the exclusion of others due to irrelevance. Both the title and abstract needed to discuss indoor radon concentration and its associated health problems, specifically lung cancer, COPD, or leukemia. Potentially relevant studies were then retrieved for full evaluation. Discrepancies regarding decision to include or exclude research article were resolved through a collaborative process involving multiple reviewers. When disagreement arose among the initial three reviewers, a fourth reviewer was consulted to provide additional input and facilitate a consensus-based decision. In rare cases where consensus could not be reached, majority voting was used as a final resort.

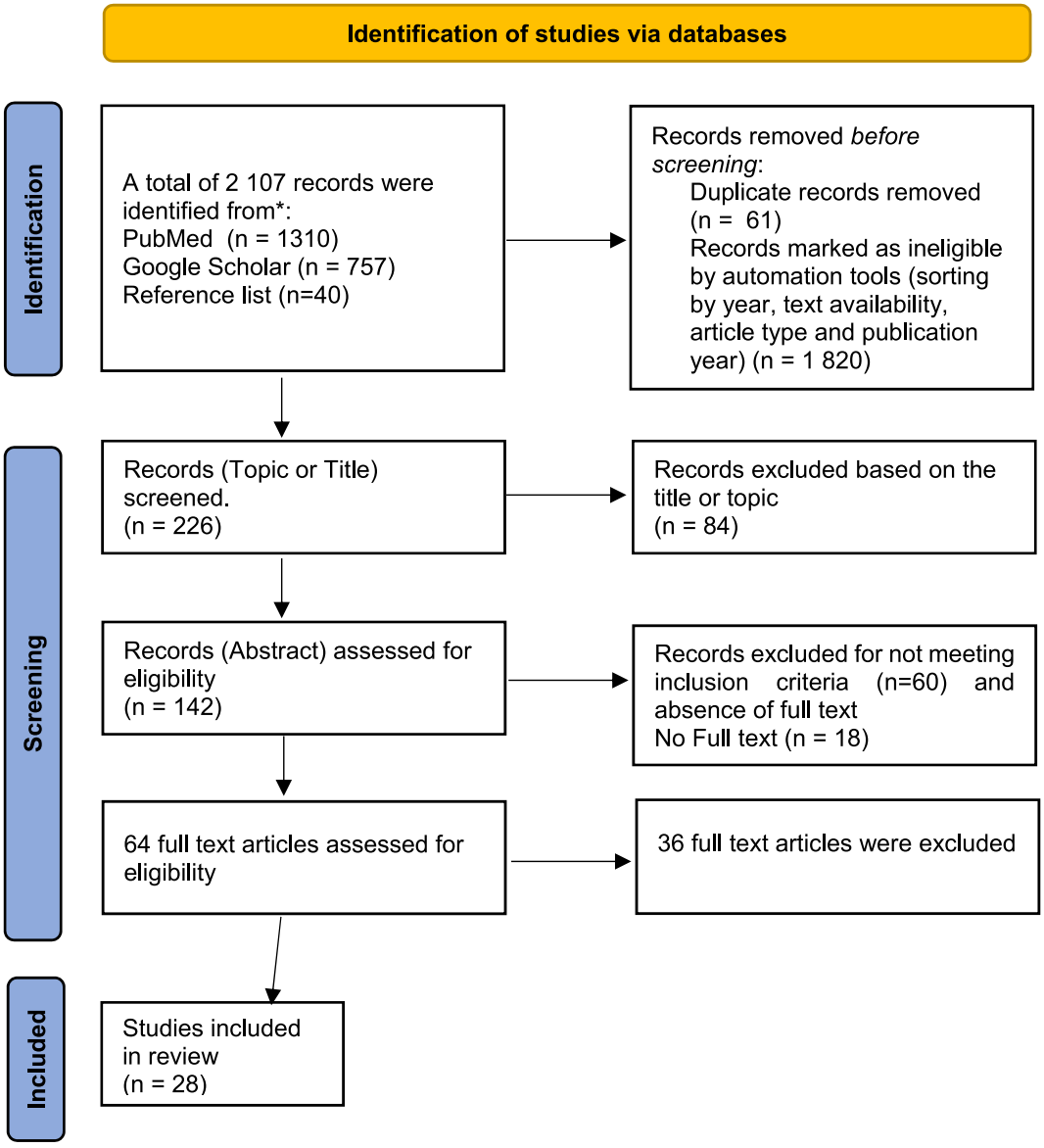

Fig. 1. Flow diagram of systematic literature search.

2.4.2. Data extraction

The selection and screening process was carried out by three independent reviewers, with a fourth reviewer providing additional input and peer review as needed. Reviewers independently extracted data and then collaboratively discussed their findings, compared search results, and agreed on which articles to include based on pre-established criteria. Key study details, such as country, purpose, methodology, and relevant findings, were carefully extracted and compiled into a Microsoft Excel spreadsheet. The quality of evidence was collectively assessed using criteria outlined in Tables 1 and 2. The review team made decisions through a consensus-based approach facilitated by the fourth reviewer, and in rare instances of disagreement, majority voting was used, with further consultation sought if necessary. The selection and assessment led to the inclusion of 28 research articles.

2.4.3. Search results

We found a total of 2107 records through PubMed (1,310), Google Scholar (757), and article reference lists (40). We removed 61 duplicates and excluded 1820 records based on publication year, article type, or full-text availability, leaving us with 226 for title screening. Out of the remaining 226 studies, we excluded 84, because their titles were not relevant to the present study objectives, and the remaining 142 underwent abstract assessment. In the initial screening, we excluded 78 records: 60 for not meeting the inclusion criteria and 18 due to the unavailability of the full text. This left us with 64 full-text articles for further assessment of their eligibility for inclusion. Following a comprehensive review of the full texts, we excluded 36 articles for not meeting the inclusion criteria, ultimately resulting in the final selection of 28 studies for the current systematic review. Please refer to Fig. 1 below for a visualization of this process. Tables 3–5, presents key information on numerous studies, such as author(s), publication year, country of origin, study purpose, methodology, and findings.

2.5. Rating the quality of evidence

This systematic review utilized the Grading of Recommendations Assessment, Development and Evaluation (GRADE) principles to assess the quality of evidence regarding the correlation between health problems and residential radon exposure [44,72]. The assessment of evidence quality is mainly dependent on the study design, with randomized trials generally being the gold standard. However, in fields like environmental exposures where randomized trials are scarce, reliance on observational studies has become more prevalent, leading to the application of the GRADE methodology in these areas [73]. In the context of indoor radon exposure, the evidence available is solely observational, involving population-based studies such as cohort, case-control, ecological and cross-sectional designs. Factors outlined in Tables 1 and 2 were used to assess five domains for downgrading the certainty of evidence and six domains for upgrading the certainty of evidence. The assessment of evidence quality encompassed multiple factors, including study design, sample size, confounding variables, and potential biases. The impact of these factors on evidence quality has been extensively documented in scholarly literature [44,46,48].

Observational studies, such as cohort and case-control studies, were considered to potentially upgrade the quality of evidence due to their ability to establish a link between diseases and exposures compared to cross-sectional and ecological studies [22,46,48,73,74]. These studies, namely cohorts and case-control studies have been shown to produce results similar to randomized controlled trials, demonstrating their value as a research tool [47,73]. Exposure assessment reliability was determined based on the criteria in Tables 1 and 2 Direct, long-term indoor radon measurements were considered superior to short-term or retrospective assessments, as well as predictive exposure models [44,75]. The evaluation of exposure assessment techniques' employed was based on their ability to predict long-term radon exposure and to capture seasonal variation, taking into account the extended latency period for radon-induced health effects [22,29,76]. The GRADE rating reflects the degree of confidence in the estimated exposure and associated health issue for a given conclusion statement. Overall, the quality of evidence was assessed as high (conclusive) if the conclusion statements were consistently reported across multiple studies with robust study designs and exposure assessments [46,47,73]. In Table 1, a comprehensive ranking of the quality of evidence is presented, providing a clear and concise representation of the strength of the evidence. Meanwhile, Table 2 provides a detailed breakdown of the various factors that were considered when determining the quality of the evidence, allowing for a deeper understanding of the evaluation process.

Table 1
Rating the quality of evidence.

Quality level	Description
High (Conclusive)	We are highly confident that the actual effect is very close to the estimated effect. Further research is unlikely to alter our confidence in the conclusion statement. Multiple well-designed studies with strong exposure assessment, consistent findings, and large sample sizes are required [44,46]
Moderate (Inconclusive)	While the estimate is likely to be accurate, there is a chance that the true effect could be significantly different. Additional research may be necessary to increase our confidence in the conclusion, particularly considering studies that have used moderate to high exposure assessment and/or yielded inconsistent results [44,46]
Low (Inconclusive)	The level of confidence we have in the estimated effect is constrained. It is possible that the actual effect may differ significantly from the estimated effect. Our confidence in the conclusion statement is expected to be revised with additional research due to the limited number of studies or studies that have weak exposure assessments or inconsistent results [44,46].

1. Adapted from Balshem et al., 2011 [46]; Debia et al., 2016 [47].

Table 2
Factors influencing evidence downgrade and upgrade.

Downgrading factors	Upgrading factors
1 Small sample size (<200)	1 Large sample size (>200)
2 Inconsistent finding	2 Consistent findings
3 Confounding not controlled	3 Confounding controlled
4 Cross-sectional, ecological and case-series studies	4 Case-control and cohort studies
5 Direct short term radon measurements (including grab sampling)	5 Direct long-term indoor radon measurement (including the use of personal samplers)
6 Using geological radon data (i.e. regional average, radon maps, predictive models) from other sources	

Modified from Dijkers, 2013 [48].

2.6. Risk of bias among selected studies

The potential for bias in the selected studies was assessed by evaluating the methodology used, including the measurement of indoor radon gas as a risk factor and its impact on health outcomes. Each study was rated based on specific criteria outlined in the quality of evidence section. We expanded our search strategy to include research published from 14 years ago (between -2010 -2024) and encompassed studies from various geographical locations to minimize bias. However, we acknowledge that publication bias may have influenced the overall evidence presented in this study. Additionally, we only extracted results relevant to our systematic review, ensuring that the omitted findings did not impact the cumulative evidence. It's worth noting that different studies used varying statistical methods to report their findings, such as percentages and odds ratios, limiting the comprehensive analysis of results. Nevertheless, the reviewers were able to extract key findings from individual studies to draw definitive conclusions about the evidence. Due to insufficient numeric data and heterogeneity across the selected studies, no further analyses, such as subgroup analyses and meta-analysis were conducted.

2.7. Data analysis

The data extracted from multiple research articles was reviewed by three individuals. In rare instances where reviewers disagreed with the suggested conclusion, a fourth reviewer was consulted for guidance. The systematic review used the GRADE approach to evaluate the certainty of evidence regarding the association between residential radon exposure and various health outcomes. The assessment considered key factors such as study design, sample size, and consistency of findings to classify the evidence as high (conclusive), moderate (inconclusive), or low (inconclusive).

- ➢ High-Quality Evidence: This category was assigned when multiple well-designed studies with robust exposure assessments and large sample sizes consistently reported the association.
- ➢ Moderate-Quality Evidence: Moderate certainty indicated that the estimated effect is likely accurate, but further research might be necessary, particularly for studies with moderate exposure assessment or inconsistent results.
- ➢ Low-Quality Evidence: This category suggested limited confidence in the estimated effect due to a small sample size, few studies, weak exposure assessments, or conflicting findings.

The GRADE approach incorporates factors that can strengthen or weaken the confidence in the evidence. Upgrading factors included, strong study design (i.e cohort, case-control or pooling studies) large sample sizes, consistent findings, and well-controlled confounding variables. Conversely, downgrading factors include limitations like small sample size, inconsistent results, or weak study designs (e.g., ecological, cross-sectional studies). By employing the GRADE approach, this systematic review provides a transparent and structured assessment of evidence quality.

3. Results

3.1. Radon-induced health problems

3.1.1. Lung cancer

A systematic literature search was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search identified 28 studies, 10 of which specifically examined the relationship between indoor radon exposure and lung cancer. Table 3 presents a comprehensive overview of the studies that have investigated the link between indoor radon exposure and lung cancer risk. In most of the reviewed studies, indoor radon exposure was primarily assessed through direct long-term measurements using alpha track detectors deployed in participants' homes for over three months [19,51,52,54,55,57]. A smaller number of studies relied on regional radon data, primarily from nationwide radon surveys and radon maps, to determine individual radon exposure levels [49,50,53,56]. The majority (8 out of 10 studies) of the reviewed studies have demonstrated a strong correlation between indoor radon exposure and an increased risk of lung cancer. For instance, an Italian ecological study found that residential radon exposure accounted for 1.6 % (with a 95 % CI of 1.4–1.7) of lung cancer deaths, with a more pronounced effect in

Table 3
Association between radon exposure and lung cancer.

Author, Year	Location	Main purpose of the study	Methodology	Major findings
Association between radon exposure and lung cancer				
1 Gariazzo et al., 2021	Italy	To assess how radon exposure contribute to lung cancer risk.	This ecological study analyzed lung cancer deaths in 8000 Italian towns, factoring in radon exposure from regional maps and field campaigns, as well as smoking.	Radon exposure was found to be responsible for 1.6 % (95 % CI: 1.4, 1.7) of lung cancer mortality, with 3.9 % in males and 1.6 % in females [49].
2 Ha et al., 2017	South Korea	To evaluate the association between indoor radon concentration and risks of lung cancer.	An ecological study using national survey data on radon (5553 measurements), smoking, sex, and cancer incidence explored regional radon concentrations and potential cancer risks.	In male subjects, the relative risk of lung cancer per 100 Bq/m^3 increase was 1.01 (95 % CI: 1.00, 1.02), a statistically significant difference [50].
3 Moshupya et al., 2019	South Africa	To investigate the association between indoor radon exposure and lung cancer near mine fields.	In this cross-section study indoor and outdoor radon levels were measured in 16 homes for three months using 60 SSNTDs. Lung cancer data from NCR and SSA were also analyzed.	Exposed area with high indoor radon concentration had higher lung cancer mortality rates than control areas [51].
4 . Torres-Durán et al., 2014	Spain	To assess the effect of residential radon exposure on the risk of lung cancer amongst non-smokers.	In this case-control study radon levels were measured for 3 months using CR-39 detectors in a case-control study. Lung cancer statistics and data on environmental tobacco smoking were also collected. 521 individuals participated.	The odds ratio of lung cancer was 2.42 (95 % CI 1.45–4.06) for individuals exposed to ≥200 Bq·m (−3) compared with those exposed to <100 Bq·m(-3) [52].
5 Lee et al., 2015	Korea	To determine the percentage of lung cancer deaths attributable to radon exposure	In this ecological study, radon data from national surveys and lung cancer mortality statistics were analyzed using BEIR-VI and European Pooling models while controlling for smoking as a confounder.	The analysis revealed that radon was responsible for 8 %–28 % of lung cancer deaths, depending on factors like gender and smoking habits [53].
6 Lorenzo-González et al., 2019	Spain	To determine the relationship between residential radon exposure and lung cancer risk in never smokers.	In this pooling case-control study indoor radon were measured using alpha-track detectors. A total of 1415 individuals, 523 cases and 892 controls were included.	Lung cancer odds ratio of 1.73 (95%CI: 1.27–2.35) for individuals exposed to ≥ 200 Bq/m^3 compared with those exposed to ≤100 Bq/m^3 was observed [54].
7 Grzywa-Celińska et al., 2022	Poland	To assess the residential radon exposure of lung cancer patients in the Lublin region, Poland.	In this cross-sectional study of 102 lung cancer patients, radon levels were measured in patients' homes using passive radon detectors (CR-39) for 30 days.	The study found no statistically significant association between average radon exposure and the type of lung cancer developed by patients [55].
8 Hassfjell et al., 2017	Norway	To estimate the incidence of radon-associated lung cancer	In this pooling study radon data and lung cancer risks were gathered from European case-control studies. Radon measurements were corrected to estimate long-term concentrations in homes.	Residential radon exposure accounted for 373 cases of lung cancer, with an approximate 95 % confidence interval of 145–682 [56].
9 Kudo et al., 2021	China	This hospital based case-control study re-evaluated the association between lung cancer risk and residential radon exposure in a region previously identified with increased risk.	In this study lung cancer cases were compared with matched controls. Radon concentrations was measured in 69 participants' current and previous dwellings using discriminative detectors. Exposure assessment included a time-weighted average of radon concentrations across occupied dwellings.	This study revealed no significant increase in lung cancer risk associated with residential radon exposure [57].
10 Ozbay et al., 2021	Turkey	To investigate the association between indoor radon exposure and lung cancer risk in specific districts of Izmir.	This comparative study compared lung cancer patients with a control group. Indoor radon concentrations were measured using SSNTD detectors in 117 locations.	This study revealed a positive association between increased radon concentrations (269 Bq/m^3 in lung cancer group vs. 123 Bq/m^3 in the control group) and lung cancer risk, even when accounting for smoking [19].

males (3.9 %) [49]. Similarly, studies conducted in South Korea [50] and Spain [52,54] through ecological, case-control, and combined analyses, found that higher levels of Rn exposure (above 200 Bq/m^3) were linked to an increased risk of lung cancer. Moreover, a study conducted in Korea estimated that Rn exposure could account for a significant proportion (8 %–28 %) of lung cancer deaths in Korea, depending on factors such as smoking [53]. Additionally, a collaborative analysis in Norway found that a considerable number of lung cancer cases in Europe were attributable to Rn (373 cases), although the confidence interval was wide (95 % CI = 145–682) [56]. A case-control study conducted in Turkey revealed a positive association between increased radon concentrations (269 Bq/m^3 in

Table 4
Association between indoor radon exposure and COPD.

	Author, Year	Location	Main purpose of the study	Methodology	Major findings
Association between radon exposure and COPD					
1	Barbosa-Lorenzo et al., 2017	Spain (Galicia)	To evaluate the relationship between residential radon exposure and COPD.	An ecological study investigated potential associations between indoor radon levels (measured by CR-39 detectors for 3 months), COPD, and smoking habits in dwellings of COPD patients (49,393) compared to control surgery patients.	No association identified between indoor radon and COPD (RR = 0.95, 95 % CI: 0.92–0.97 per 100 Bq/m^3) [58].
2	Yitshak-Sade et al., 2019	US States	To assess the association between chronic exposure to indoor radon and mortality, with a specific focus on COPD as a potential cause of death.	This cohort study tracked mortality among over 13 million Medicare potential participants (age 65+) for over a decade (2000–2013), estimating their radon exposure based on county averages derived from ZIP codes.	Radon exposure was associated with up to 4.49 % (95 % CI: 3.69 %–5.30 %) of COPD deaths [59].
3	Pando-Sandoval et al., 2022	Spain	To investigate whether there is an association between residential radon concentrations and characteristics of COPD	This case-control study investigated indoor radon exposure in 189 hospitalized COPD patients (mostly male, average age 64) by measuring radon levels in their homes (using CR-39 detectors for 3 months) and collecting health data (i.e smoking habits, occupational exposures).	The findings suggest no significant influence of radon exposure on clinical characteristics in smokers and ex-smokers with COPD [41].
4	Ruano-Ravina et al., 2021	Spain	To determine an association between indoor radon exposure and COPD.	In this case-control study measured radon in homes of COPD cases (n = 189) and controls (n = 747) using CR-39 detectors (3 months), then analyzed the link between radon exposure and COPD adjusting for demographics and smoking.	No significant association between residential radon and COPD (OR = 1.12 (95%CI 0.41–3.06) for both higher (200Bq/m^3) and lower (5Bq/m^3) indoor radon exposure group [42].
5	Turner et al., 2012	US States	To assess the relationship between residential radon exposure and COPD	A prospective cohort study examined 1.2 million CPS-II participants, estimating radon exposure at enrolment based on county-level predictions and ZIP codes. The analysis also factored in smoking history.	Radon was significantly associated with COPD mortality (HR per 100 Bq/m^{-3} 1.13, 95 % CI 1.05–1.21) [38].
6	Wang et al., 2022	Eastern Massachusetts, United States	To study the link between brief exposure to particle radioactivity (PR) from radon decay products in PM2.5 and lung function in COPD patients	A year-long cohort study of 142 elderly COPD patients, the association between PR exposure and pulmonary function was analyzed using spirometry tests before and after bronchodilator administration, alongside weekly measurements of indoor and ambient PR and PM2.5. was conducted	Higher indoor PR exposure, especially in homes with low air infiltration, was linked to reduced pulmonary function in COPD patients, even after adjusting for PM2.5 and black carbon [60].

the lung cancer group vs. 123 Bq/m^3 in the control group) and lung cancer risk, even when accounting for smoking [19]. Additionally, reviewed studies have shown that the risk of radon-induced lung cancer is higher in males compared to females [49,53]. However, a cross-sectional study in Poland found no significant association between Rn exposure levels and the type of lung cancer developed in patients [55]. Additionally, a hospital-based case-control study conducted in China with 69 participants found no significant association between residential radon exposure and lung cancer risk [57]. Overall, numerous studies have reported a positive association between radon exposure and lung cancer, with most studies suggesting that radon exposure was responsible for lung cancer deaths [49,51,53].

3.1.2. Chronic Obstructive Pulmonary Diseases (COPD)

A thorough search of the literature was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. In total, 28 studies were found, with 6 of them specifically examining the relationship between indoor radon exposure and COPD. The reviewed studies investigating the association between indoor Rn exposure and COPD yielded mixed findings (See Table 4). Majority of studies used to explore the potential association between residential radon exposure and COPD utilized direct long-term indoor radon measurements to assess individual exposure, primarily employing passive alpha track detectors (CR-39) placed in participants' homes for over three months [41,42,58]. Several studies (3 out of 6) reported no significant association between radon and COPD. This includes a Spanish case-control study which found no association between indoor Rn levels measured by CR-39 detectors and COPD (RR = 0.95, 95 % CI: 0.92–0.97 per 100 Bq/m^3) [58]. Similarly, another case-control study conducted in Spain, measured radon levels in COPD patients' homes and observed no significant influence of Rn exposure on COPD characteristics amongst smokers and ex-smokers [41]. A third Spanish case-control study also reported a null association (OR = 1.12

Table 5
Association between radon exposure and leukemia.

Author, Year	Location	Main purpose of the study	Methodology	Major findings
Association between radon exposure and leukemia				
1 Zlobina et al., 2022	Russia, China, and France	Investigate link between radiation exposure and non-communicable diseases (i.e leukemia).	An ecological study measured radon (using Alfarad RRA-01M − 01) and ambient radiation to estimate regional annual radiation doses. Leukemia morbidity data was obtained from hospitals, and reports	Positive correlation between leukemia rates and radon volume activity (RVA) levels was observed ($p < 0.0082$) [61].
2 Oancea et al., 2017	United States of America	To investigate the potential link between residential radon exposure and leukemia	This ecological study investigated potential links between residential radon levels (using US EPA radon data) and leukemia risk. It analyzed data on 22,811 leukemia cases obtained from state registries.	Age-adjusted chronic lymphocytic leukemia (CLL) rates significantly correlated with residential radon ($p < 0.0001$) [62].
3 Berlivet et al., 2021	France	To investigate the association between residential exposure to radiation and the risk of childhood acute leukemia (AL).	This ecological study estimated radon exposure in municipalities using national survey data (10,843 indoor radon measurements) and grids (i.e 5x5 km20. It then analyzed childhood acute lymphoblastic leukemia (AL) cases (n = 6059) from the national registry.	No link found between childhood leukemia and radon exposure radon: IRR = 0.97, (95 % CI = 0.91–1.03 per 100 Bq/m^3) [63].
4 Demoury et al., 2017	France	To determine a link between radon exposure and leukemia risk.	This case-control study combined IRSN and Ministry data (10,843 measurements) to estimate radon exposure on a 1 × 1 km grid. This study had 9056 cases and 30,000 controls.	No statistically significant association SIR = 1.01 (95 % CI = 0.86, 1.19) was found [64].
5 Schwartz et al., 2015	US States	Evaluating the association between chronic leukemia and residential radon exposure.	This ecological study utilized data from EPA's long-term radon monitors placed in 5694 homes across the US to create the EPA Map of Radon Zones (MRZ). Leukemia statistics were obtained from a population-based registry and cancer registers.	A significant correlation ($p < 0.005$) was observed [65].
6 Del Risco Kollerud et al., 2014	Norway	To investigate association between residential radon exposure and childhood leukemia	This prospective cohort study followed 712,674 children from birth to age 15. While only 6 % had direct radon measurements, indoor radon data were estimated for the rest using nearby measurements and geological data.	No association was observed between radon exposure and leukemia (HR = 0.99, 95 % CI = 0.76–1–30) [66].
7 Nikkila et al. (2019)	Finland	To evaluate the potential association between residential radon exposure and childhood leukemia.	This retrospective case-control study used a model built with existing radon measurements (n = 244,059) to estimate radon exposure in 1093 childhood leukemia cases and 3279 controls identified from national registries.	Insignificant association found between high radon and leukemia increase OR 1.1–1.3, (95 % CI 0.79–1.77) [67].
8 Inamasu et al., 2018	South Africa	To investigate a link between living near gold mine tailings (radon source) and leukemia risk.	This retrospective analysis reviewed medical records of 1880 leukemia patients. It also analyzed demographics and residential locations of these patients. Radon levels were not measured.	Higher incidence rates observed near gold mines [68].
9 Espina et al., 2019	South Africa	To investigate a link between living near gold mine tailings (radon source) and leukemia risk.	This prospective study followed 556 patients diagnosed with haematological malignancies. Questionnaire was used to gather information on residential history, smoking and radiation exposure. Radon levels were not measured.	Higher incident rate was found in areas that are known to have elevated radiation (radon) exposure [69].
10 Kendall et al., 2013	Great Britain	Assessed the potential association between childhood leukemia and natural background radiation such as radon.	A record-based case-control study examined the association between leukemia and natural background radiation in over 63,000 children from the National Registry of Childhood Tumors in Great Britain between 1980 and 2006. Maternal radon exposure at the child's birth was estimated using national radon databases and a predictive radon map.	No significant association was found between radon exposure and any type of childhood cancer [70].

(*continued on next page*)

Table 5 (*continued*)

Author, Year	Location	Main purpose of the study	Methodology	Major findings
11 Hauri et al., 2013	Switzerland	This study evaluated the association between domestic radon exposure and the incidence of leukemia	In 2000, a nationwide cohort study was carried out to include all Swiss children under 16, and it continued until 2008. Radon levels in homes were estimated using a model that relied on 45,000 measurements.	Despite relatively high domestic radon levels in Switzerland, no association was found between radon exposure and childhood cancer [70].
12 Chen et al., 2019	Canada	This population-based study investigated the potential association between average radon concentrations and childhood leukemia and lymphoma incidence.	A long-term radon survey was conducted in 33 Canadian cities, covering 70 % of the population. The study linked city-level radon concentrations to leukemia rates in children from 2006 to 2015, analyzing six subtypes.	The estimated doses to red bone marrow from domestic radon exposure were low, and no significant association was found between radon exposure and childhood leukemia risk [71].

(95%CI 0.41–3.06) for both higher (≥200 Bq/m3) and lower exposure (≤5 Bq/m3) [42]. In contrast, half of the reviewed studies (3 out of 6) conducted in the United States identified a positive correlation between Rn exposure and COPD. This includes a cohort study conducted in 2019, which found that radon exposure was associated with up to 4.49 % (95 % CI: 3.69–5.30) of COPD deaths [59]. Similarly, a prospective cohort study conducted in the US reported a significant association between Rn exposure and COPD mortality in a US prospective cohort study (HR per 100 Bq·m−3 1.13, 95 % CI 1.05–1.21) [38]. Furthermore, a year-long cohort study in Eastern Massachusetts revealed that higher indoor PR exposure from radon decay products in PM2.5, particularly in homes with low air infiltration, was associated with reduced pulmonary function in COPD patients [60].

3.1.3. Leukemia

A total of 28 studies were identified using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. Among these, 12 studies specifically focused on examining the relationship between indoor radon exposure and leukemia. Several epidemiological studies investigated the effects of residential radon (Rn) exposure on the risk of leukemia, yielding inconsistent findings (See Table 5). Majority of the reviewed studies analyzed regional radon data, including radon maps [63,64] and predictive models [61,66,67,70,71,77] to assess indoor radon exposure for individuals. Notably, none of the studies directly conducted long-term indoor radon measurements. A multi-national (Russian, China and France) ecological study reported a positive correlation between leukemia rates and radon volume activity (RVA) levels ($p < 0.0082$) [61]. Ecological studies conducted in the United States (US) found a significant correlation between residential Rn and leukemia [62,65]. Case-series studies conducted in South Africa found a higher incidence of leukemia among residents in areas with known elevated radiation exposure, but these studies did not measure Rn levels directly [68,69]. However, cohort and case-control studies did not find statistically significant associations between Rn exposure and leukemia risk [64,66,67]. This includes case-control studies conducted in France [64] and Finland [67], which reported no link between Rn exposure and leukemia (SIR = 1.01, 95 % CI = 0.86, 1.19; OR 1.1–1.3, 95 % CI 0.79–1.77 respectively). Likewise, prospective cohort studies in Norway found no significant association between Rn exposure and childhood leukemia (HR = 0.99, 95 % CI = 0.76–1.30) [66]. Three additional studies examined the potential association between childhood leukemia and radon exposure in Great Britain, Switzerland, and Canada. Despite varying study designs and sample sizes, all three studies found no significant association between radon exposure and childhood leukemia risk [70,71,77].

4. Discussion

4.1. Rn and lung cancer risk

The majority of the reviewed studies demonstrated a consistent positive association between indoor radon levels and lung cancer, with varying levels of evidence quality across different studies. Notably, three case-control studies [52,54,56] have provided high-quality evidence supporting this correlation. Specifically, a case control study conducted in Spain highlighted a positive connection between indoor radon exposure and an elevated risk of lung cancer among non-smokers [52]. In contrast, a case-control study in China with a very small sample size of 69 participants found no association between indoor radon exposure and lung cancer [57]. However, due to the small sample size in these case-control studies, their ability to definitively confirm or rule out an increased risk of developing lung cancer following prolonged exposure to elevated indoor radon levels was limited [22]. To obtain a more comprehensive estimate, scholars have aggregated data from multiple published studies. Recent collaborative analyses have further solidified the link between lung cancer and residential radon by analyzing combined data from numerous case-control studies [54,56]. This evidence strengthened the positive association previously identified through ecological studies and small-scale case control studies [22]. Generally, case-control studies are considered the most appropriate way to examine the association between lung cancer and residential radon exposure [22,29,74].

Suggestive, but lower quality evidence came from ecological studies. In addition to case-control studies, three ecological studies with large sample size and one cross-sectional study explored the association between residential radon exposure and lung cancer. These includes ecological studies conducted in Italy and Korea which has observed a positive association between lung cancer mortality and indoor radon exposure [49,53]. In most reviewed studies, smoking's influence on the relationship between radon exposure

and lung cancer risk was considered [49,50,52]. Furthermore, the risk of developing lung cancer following prolonged exposure to indoor radon exposure was prevalent amongst men compared to women [49,53]. The increased incidence of radon-induced lung cancer in men may be attributed to the synergistic interaction between radon (Rn) and smoking, as well as the predominance of male smokers compared to female smokers [78]. Furthermore, the risk of lung cancer was positively associated with being exposed to indoor radon levels above 200 Bq/m3 as compared to lower indoor radon concentration [19,52,54] However, this evidence does not suggest that lower indoor radon concentration does not pose a risk for developing lung cancer [22,76].

Although these ecological studies provided valuable contributions to the understanding of the relationship between radon exposure and lung cancer, they were not without their limitations. These limitations affect the validity and generalizability of the findings. Ecological studies, such as those conducted in Italy and South Korea, relied on aggregated data at the population level. Ecological studies are susceptible to ecological fallacy, where associations observed at the population level may not hold true for individuals [79, 80]. The majority of reviewed ecological studies relied on existing data, such as lung cancer morbidity and mortality data and nationwide radon data. Ecological studies, despite their convenience and cost-effectiveness, may yield misleading conclusions when investigating the relationship between environmental exposures and health outcomes. A study in Sweden compared the results of ecological and individual-level analyses of radon exposure and lung cancer risk. The study uncovered substantial discrepancies between the two approaches, with ecological models consistently underestimating or even indicating a protective effect of radon. In contrast, individual-level analyses consistently indicated a positive association between radon exposure and lung cancer risk [81]. These disparities were attributed to ecological bias, stemming from variations in the distribution of radon exposure and other risk factors across geographic regions, and effect modification, reflecting differing relationships between radon and lung cancer risk across populations with varying levels of other risk factors. These findings underscored the need for caution when interpreting ecological study results, particularly with weak associations. While ecological studies could offer valuable insights, they should not have been solely relied upon as conclusive evidence of a causal relationship. Early investigations into the risk of lung cancer from indoor radon exposure often employed ecological designs, examining the correlation between average radon concentrations and average lung cancer rates in different geographic areas. However, the World Health Organization (WHO) cautions that ecological studies can provide biased and misleading estimates of radon-related risks due to the lack of detailed individual information on residential histories, smoking habits, and other lung cancer risk factors [22]. Many of the reviewed ecological studies failed to account for these crucial factors, leading to potential limitations in their exposure assessment strategies [50,51,55]. Majority of the reviewed studies were further limited by retrospective exposure assessment, as they failed to properly account for an individual's residential history and mobility [50,53,54,56]. This could create uncertainties regarding the accuracy and reliability of the employed exposure assessment strategies. To estimate the average radon concentration that each person in the study has been exposed to over the past few decades, measurements of the radon concentration need to be taken in their current home. If the person has moved in the last few decades, measurements should also be taken in other homes where the individual has lived [22].

Cross-sectional studies conducted to explore the association between residential radon and lung cancer [51,55] offered weak generalizability due to small sample sizes and their inherent inability to establish causation. These studies offered a snapshot of the relationship between radon exposure and lung cancer at a single point in time, making it difficult to determine whether radon exposure preceded lung cancer development. Ecological studies [49,50,53] overestimated lung cancer risk compared to case-control and pooling studies [54,56]. This is likely due to their inability to control for confounding factors (i.e smoking) and use of regional indoor Rn data (including the use of radon maps) rather than individual data. This discrepancy may also be associated with the fact that the associations observed at the population level may not hold true for individuals [79,80]. Overall, this review strengthens the existing evidence by not only finding a positive association in weaker study designs, but also replicating similar results through more robust case-control and pooled analysis methodologies endorsed by WHO [22]. To address limitations associated with the reviewed studies, future studies should adopt prospective study design such as cohort study designs. How this approach may be costly because of the long latency period associated with radon induced lung cancer [76]. Consistent results observed from different study designs enhances the overall credibility of the evidence, potentially justifying why this evidence was classified as high-quality evidence. Additionally, this review aligns with previous systematic review that demonstrated a significant association between indoor Rn exposure and lung cancer risk [29, 37 63].

4.2. Rn and COPD

This systematic review was one of the initial reviews to investigate the potential link between residential radon exposure and COPD using the GRADE approach. Previous systematic reviews have primarily examined the relationship between radon exposure and COPD, incorporating both residential and occupational studies [39,40]. In previous systematic reviews, the presence of occupational studies may have led to biased results. This is because epidemiological studies involving miners may not accurately represent or apply to the general population. This is due to the differing occupational exposures compared to home environments, as well as the fact that the demographics of workers may not be representative of the general public [22]. Moreover, the positive association between radon and COPD observed in occupational studies could be influenced by other harmful exposures, such as silica, dust, diesel exhaust, and tobacco consumption [42]. Hence, the current systematic review focused on studies that were conducted amongst the general public. Based on the research articles reviewed in the present systematic review, no definitive conclusion could be drawn on the relationship between residential radon exposure and COPD. Multiple cohort studies conducted in the United States with a large number of participants (i.e 1.2 million) have suggested that exposure to radon in residential areas may result in increased COPD mortality [38,59, 60]. These studies have shown that residential radon exposure was associated with between 4 and 13 % rise in COPD mortality for each 100 Bq/m3 increase in radon concentration [38,59]. However, the evidence from these studies was considered moderate due to their

reliance on regional radon data and the lack of individual-level radon data. Additionally, the absence of adjustment for tobacco use in most of the studies was a significant limitation. Furthermore, these cohort studies were conducted following ecological approach of assigning residential radon concentrations to participants based on their country of residence. This approach may have introduced an ecological fallacy due to potential misclassification of residential radon exposure [42]. Contrastingly, studies conducted in Spain, including case-control and ecological studies, did not find a positive association between residential radon exposure and COPD, even among individuals exposed to elevated residential radon levels (above 200 Bq/m3) and active smokers [41,42,58] These Spanish studies had smaller sample sizes (less than 1000 participants) compared to the US cohort studies and involved direct long-term radon measurements in participants' homes. Additionally, the Spanish studies took into account the role of smoking in the relationship between radon and COPD [41,42,58].

Despite some positive associations found in cohort studies, particularly in a US study reporting a link between Rn and COPD mortality [38,59,60] the overall evidence for a causal relationship remains inconclusive. This was due to a lack of consistent findings across different study designs. Case-control studies [41,42] and an ecological study [58] failed to observe a significant association. This inconsistency aligns with previous reviews which highlighted the unclear nature of the association [39,40]. The use of an ideal control group in epidemiologic studies is seldom attainable. While hospital controls are often suitable in studies utilizing hospital cases, they may not accurately represent the broader population [80]. The exclusive recruitment of cases and controls from hospital settings raises concerns about selection bias in case-control studies. Although using hospital patients as controls may be logistically convenient, it is crucial to recognize that these patients may possess different characteristics compared to the general population. They may, for instance, exhibit higher rates of tobacco smoking. Moreover, their hospital admission may be linked to their exposure status, potentially leading to disparities in exposure measurements compared to the reference population. Consequently, this could result in a biased estimation of the association between exposure and disease. Similar to other systematic reviews, most studies included in the current systematic review lack of adjustment for tobacco smoking [39]. Limitations such as ecologically fallacy, inconsistent findings, and reliance on estimated Rn exposure levels further weaken the overall certainty of the evidence. Hence, the quality of this evidence was ranked inconclusive quality evidence. In addition, it has been challenging to conclusively prove the connection between exposure to indoor radon and COPD due to the limited number of studies on this topic [39,40]. The inconclusive findings regarding the association between radon exposure and COPD can be attributed to several methodological weaknesses in existing research. The presence of diverse study designs was identified as a notable constraint. Various study designs possess different advantages and drawbacks, and the diversity of study designs can lead to bias and hinder the capacity to make firm conclusions. Hence, collaborative analyses often concentrate on similar study designs, such as case-control studies, as was the case in radon and lung cancer pooling studies [54,56]. While some studies utilized cohort designs, providing stronger evidence of causation, others relied on case-control or ecological designs, which are more susceptible to confounding factors and biases. This resulted in the quality of evidence being downgraded. Furthermore, all the reviewed studies originated from Europe (specifically Spain) and the United States. This geographically limited scope underscores the necessity for additional research across various regions to determine if these findings hold true for populations worldwide. The cumulative impact of these methodological weaknesses has led to inconsistent findings. While some studies have indicated a link between radon exposure and these health conditions, others have not found a significant association. In the context of COPD, discrepancies in exposure assessment methods, follow-up durations, and statistical analyses impeded our capacity to establish conclusive findings regarding the correlation between radon exposure and the risk of developing the disease. Consequently, the overall evidence base remained insufficient to draw definitive conclusions. To address these methodological limitations and strengthen the evidence base, future research should prioritize well-designed cohort and case-control studies with large sample sizes, rigorous exposure assessment, and appropriate control for confounding factors, including occupational exposures and tobacco smoking. By rectifying these methodological shortcomings, future studies can contribute to a more definitive understanding of the potential health risks associated with radon exposure.

4.3. Rn and leukemia risk

Inconclusive evidence surrounds the link between indoor Rn exposure and leukemia risk. While few studies [61,62,65] hinted at a possible association, the majority [64,63,66,67,70,71,77] failed to find a significant association. The findings of the current review were inconsistent with other reviews which found that indoor Rn exposure was significantly associated with the risk of leukemia [37]. The inconsistency observed in the current review point to the low quality of the overall evidence. Various limitations may have contributed to this weakness. First, most studies relied on ecological designs [61,62,65], which struggled to isolate the true effect of radon exposure due to confounding factors. Second, the use of population-level mortality data, likely underestimated the risk, particularly for cancers like leukemia with lower fatality rates [22]. Studies are only as reliable as their exposure data. Most studies relied on indirect Rn measurements, such as regional data or estimates, to determine individual's residential radon exposure level [61, 62,65–67,70,71,77], while some did not measure indoor Rn concentrations [68,69]. Concerns around poor radon exposure data were observed across all study designs, suggesting that the overall findings on the association between residential radon exposure and leukemia may have been influenced by ecological fallacy.

For optimal accuracy in exposure assessment, it is recommended that studies directly measure radon (Rn) levels within participants' residences, including their previous residences if they have relocated [22,76]. Many studies did not directly measure long-term indoor radon levels, but instead relied on regional data to estimate residential radon exposure for participants. However, this approach has limitations due to uncertainties in measurement techniques and individual exposure patterns. Mäkeläinen et al. (2005) and European Commission (2001) have emphasized that individual radon exposure can vary significantly because of diverse daily activities, dwelling characteristics, ventilation habits, the amount of time spent inside the dwelling and different exposure levels in different

microenvironments, including at work, home and other premises [78,82]. Thus, relying solely on regional radon data may not accurately estimate individual exposure. According to the World Health Organization, it is recommended to integrate indoor radon data with individual mobility patterns to gain a more comprehensive understanding of radon exposure levels [22].

Furthermore, in the case of radon exposure and leukemia risk, limitations of ecologic studies are particularly serious because of the presence of smoking, which constitutes an overarching risk factor for leukemia than radon was not considered in the reviewed studies [22]. Literature suggests that leukemia risk due to indoor radon exposure is not easy to identify in a study without individual level data on smoking history and other potential risk factors [22]. The variability in study designs employed to investigate the relationship between indoor radon exposure and leukemia risk has significantly contributed to the inconclusive findings in this area. The dominance of ecological studies also introduced biases to a certain extent. The observed bias largely stems from the disparity between group and individual data. Regional radon levels and risk-modifying factors may not precisely represent the exposure levels of individuals who have developed leukemia [81,83,84]. Therefore, positive association between residential radon and leukemia observed in the reviewed ecological studies may not be able to show whether the exposure and outcome occur in the same subjects [81]. The probability of drawing a wrong conclusion from ecological studies is high, and this distorted correlation is often referred to as an "ecological fallacy" or ecologic bias [22]. Ecological studies are commonly used due to their convenience and cost-effectiveness, but caution must be exercised when interpreting study findings. Associations observed at the population level may not necessarily apply to individuals, as regional radon levels and other risk factors may not accurately reflect the exposure and risk factors for specific individuals who develop leukemia. The use of different study designs with varying strengths and weaknesses has led to inconsistent findings. Additionally, the conclusions of these studies varied in terms of effect sizes. Furthermore, the study population, setting, design, exposure measurement, and risk calculation methods were heterogeneous among studies, making it challenging to draw consistent conclusions [85]. Furthermore reviewed studies had several important limitations, mainly lack or poor adjustment for tobacco consumption. While some studies have hinted at a possible association between radon exposure and leukemia, others failed to find a significant link. This variability in results makes it difficult to draw definitive conclusions about the relationship between these two factors. Most of the studies conducted on the matter had a fairly large sample size, providing statistical power to identify real effects [63–67]. However, the limitations observed cannot be fully compensated by the sample size alone. Considering that limitations outweighed the strengths mentioned, the current evidence linking indoor Rn exposure to leukemia risk was classified inconclusive. To strengthen the evidence base, future research should prioritize well-designed cohort and case-control studies with direct and long-term radon exposure measurements at the individual level. These studies should also control for potential confounding factors, such as tobacco smoking and other lifestyle variables, to provide a more accurate assessment of the association between radon exposure and leukemia risk.

4.3.1. Research gaps and future Directions

Despite the potential benefits of using meta-analysis to consolidate evidence, conducting one proved unfeasible in this systematic review. The primary obstacle was the considerable heterogeneity among the included studies, which differed significantly in study design, strength and weaknesses, sample size, exposure assessment methods, and outcome measures. These discrepancies made it difficult to amalgamate the results meaningfully. It's important to recognize that ecological studies are inherently limited, particularly in their susceptibility to confounding factors and the potential for the "ecological fallacy" to influence geographical data interpretation. Consequently, cautious consideration is crucial when interpreting ecological studies. This was why previous systematic review have separately analyzed case-control studies and ecological studies [79]. Furthermore, the scarcity of studies on the relationship between radon exposure and COPD further impeded the possibility of conducting a meta-analysis. Conducting a robust meta-analysis typically necessitates an adequate number of studies with similar methodologies, which was not feasible in this case due to the limited number of studies and their inherent variability.

The link between indoor radon exposure and lung cancer is well-established, but there are still uncertainties that need to be addressed. To strengthen the existing evidence, there is a need large-scale population-based, long-term prospective studies with direct measurements of individual radon exposure. Utilizing improved exposure assessment methods, such as continuous radon monitoring and considering individual mobility patterns, can improve risk estimation. It's crucial to explore the interactions between radon and other risk factors, like tobacco smoking and occupational exposures. Additionally, examining geographic variations in radon-related lung cancer risk can help target prevention efforts. The association between radon exposure and COPD and leukemia was less definitive, with inconclusive findings from existing research base. In future research, it is essential to prioritize larger and more diverse populations to enhance statistical power and the ability to generalize findings for both health outcomes. The current research on the link between radon exposure and COPD has been limited to specific geographical areas, which represents a significant epidemiological constraint. The majority of studies in this area have been carried out in Spain and the United States, resulting in a substantial gap in knowledge regarding the potential health risks associated with radon exposure in other regions. Accurate and consistent measurement of radon exposure is essential for drawing reliable conclusions. This will enable meta-analyses, pooling findings from similar studies to arrive at more conclusive results, as has been done for studies linking radon exposure to lung cancer. Confounding factors, such as smoking and occupational exposures, must be carefully considered to isolate the specific effects of radon in both cases. Moreover, investigating geographic variations can provide valuable insights into potential regional differences for both COPD and leukemia. To advance our understanding of the potential health implications of radon exposure, future studies for all three health outcomes should focus on well-designed case-control and cohort studies with direct measurement of individual radon exposure. Improved exposure assessment methods, including continuous radon monitoring and consideration of individual mobility patterns, are crucial for all three. Additionally, investigating geographic variation in the association between radon and each of these health outcomes can provide valuable insights into potential regional differences. In the future, nationwide radon surveys should incorporate radon-induced health problems for all three outcomes to enhance our understanding of the prevalence and distribution of these issues

within populations. By integrating radon-related health data into broader public health surveillance efforts, is possible to develop more targeted and effective prevention and mitigation strategies for all three health outcomes.

4.4. Strengths and limitations

This systematic literature review strengths include a robust search strategy with multiple databases and reference list screening to minimize bias. It also employed a clear PECO framework and included quality assessment using the GRADE approach. The review included studies from various geographic locations and excluded irrelevant studies based on predefined criteria. The primary limitation arises from the diverse approaches and methodologies utilized in different studies, creating a barrier to conducting a meta-analysis. The lack of standardization in data collection and analysis procedures hinders the aggregation and comparison of results across studies. This variability in methodology complicates the process of synthesizing findings and drawing meaningful conclusions across the body of research. Nonetheless, limitations also stem from the exclusion of studies published more than 14 years ago and the dependency on reviewers' discretion for data extraction and quality assessment. Additionally, the studies included employed various methodologies with some studies lacking proper adjustment for confounding factors such as smoking. Reviewed studies primarily focus on Europe (Spain, Italy, France, Poland, Norway, Turkey), South Korea, China, Canada, Britain, United States (US), and South Africa. This limited geographical scope restricts the generalizability of the findings to these regions. Radon exposure levels and risk factors can vary significantly depending on geological formations, building practices, and environmental regulations. Studies from underrepresented regions, particularly Asia, Africa, and South America, are necessary for a more comprehensive understanding of the global impact of radon exposure. Overall, this review provides valuable insights into the association between indoor radon exposure and health risks, but further research with robust designs (ideally using prospective case-control and cohort studies) and long-term direct radon measurements is necessary for more conclusive evidence. In addition, the main limitation lies in the heterogeneity of the methodology used by the different studies, something that made it impossible to perform a meta-analysis.

5. Conclusions

In summary, this comprehensive review examined the evidence regarding the health hazards of indoor radon exposure, with a specific focus on lung cancer, COPD, and leukemia. The review revealed a significant positive correlation between radon exposure and lung cancer, which was supported by high-quality evidence from well-designed studies. However, the association between Rn and COPD remains inconclusive due to inconsistencies across various studies and limitations in their methodology. Additionally, the evidence regarding the connection between Rn and leukemia was deemed of low-quality, owing to conflicting results, methodological shortcomings in most studies, and the use of indirect exposure assessments. To conclusively establish the link between Rn exposure and COPD and strengthen the connection with leukemia, future research should employ more rigorous designs, direct radon measurements, and appropriate control for confounding factors.

CRediT authorship contribution statement

Khathutshelo Vincent Mphaga: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Wells Utembe:** Writing – review & editing. **Thokozani P Mbonane:** Writing – review & editing. **Phoka Caiphus Rathebe:** Writing – review & editing, Methodology.

Data and code availability

Data included in article/supplementary material is referenced in the article.

Additional information

This systematic review has no additional or supplementary information as all figures and tables are included in this manuscript.

Funding statement

Prof Phoka Caiphus Rathebe received funding from NRF (Support for Y-rated Researchers Programme (Grant number-CSRP23030380716).

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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