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Exposure to Ionizing Radiation and Risk of Dementia: A Systematic Review and Meta-Analysis

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Abstract

The number of people living with dementia is rising globally as life expectancy increases. Dementia is a multifactorial disease. Due to the ubiquity of radiation exposure in medical and occupational settings, the potential association between radiation and dementia, and its subtypes (Alzheimer's and Parkinson's disease), is of particular importance. There has also been an increased interest in studying radiation induced dementia risks in connection with the long-term manned space travel proposed by The National Aeronautics and Space Administration (NASA). Our aim was to systematically review the literature on this topic, and use meta-analysis to generate a summary measure of association, assess publication bias and explore sources of heterogeneity across studies. We identified five types of exposed populations for this review: 1. survivors of atomic bombings in Japan; 2. patients treated with radiation therapy for cancer or other diseases; 3. occupationally exposed workers; 4. those exposed to environmental radiation; and 5. patients exposed to radiation from diagnostic radiation imaging procedures. We included studies that considered incident or mortality outcomes for dementia and its subtypes. Following PRISMA guidelines, we systematically searched the published literature indexed in PubMed between 2001 and 2022. We then abstracted the relevant articles, conducted a risk-of-bias assessment, and fit random effects models using the published risk estimates. After we applied our eligibility criteria, 18 studies were identified for review and retained for meta-analysis. For dementia (all subtypes), the summary relative risk was 1.11 (95% CI: 1.04, 1.18; P = 0.001) comparing individuals receiving 100 mSv of radiation to those with no exposure. The corresponding summary relative risk for Parkinson's disease incidence and mortality was 1.12 (95% CI 1.07, 1.17; P <0.001). Our results provide evidence that exposure to ionizing radiation increases the risk of dementia. However, our findings should be interpreted with caution due to the small number of included studies. Longitudinal studies with improved exposure characterization, incident outcomes, larger sample size, and the ability to adjust for effects of potential confounders are needed to better assess the possible causal link between ionizing radiation and dementia.

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INTRODUCTION

An estimated ten million new dementia cases occur worldwide every year (1). In 2020, there were 55 million patients living with dementia globally, and this number is expected to more than triple by 2050 (2). Dementia is an incurable and debilitating condition (3) that can bring distress and isolation to patients (4), as well as high healthcare costs that burden patients' families and caregivers (5). The most common type of dementia is Alzheimer's disease (AD), which accounts for approximately two-thirds of all cases (6), followed by Parkinson's Disease (PD) (7, 8). Dementia (unspecified), AD and PD share similarities in underlying biological mechanisms (9, 10) and are frequently grouped together.

Age is the most important risk factor for dementia, followed by other determinants such as poor nutrition; low physical activity; and genetic, socioeconomic and environmental factors (11). Ionizing radiation can modify cognitive functions (12-14) and affect neurological integrity (15, 16), and has been linked with an increased risk of dementia (17). While radiation is one of the most studied carcinogens (18), more recent studies have suggested that exposure increases the risk of adverse non-cancer outcomes, particularly with cardiovascular diseases such as ischemic heart disease (19, 20) and stroke (21, 22).

Few epidemiological studies have examined the effects of radiation on dementia, primarily because the majority of studies has focused on cancer or cardiovascular outcomes using incidence or mortality data (18). Death certificates often do not include dementia as the underlying cause of death and the accompanying under-ascertainment of mortality can introduce bias, and reduce study power when investigating the effects of radiation on dementia (23). Despite these challenges, there have been more recent investigations on this topic including a recent meta-analysis by Lopes et al. (24). The Lopes et al. meta-analysis examined radiation risks for a broad grouping of non-malignant diseases of the central nervous system that also included PD (24). There is a growing need for understanding the health effects from exposure to low dose radiation, including dementia, in view of NASA's long-term space travel plans (25). While space radiation is primarily composed of galactic cosmic rays (GCR) and solar particle radiation (26, 27), which differ from radiation exposures on Earth, epidemiologic research on any form of radiation can inform NASA's risk mitigation strategy (25, 28, 29). A 2012 literature review suggested that there were few studies of radiation exposure and increased risk of dementia and related outcomes, and their findings were equivocal (17). Hence, we undertook this review to provide a current synthesis of published findings on this topic, and to explore drivers of differences in the strength of association reported across studies. Our study complements the recently published review by Lopes et al. (24) by assessing issues related to publication bias and heterogeneity, as well as presenting summary measures of association specific to dementia.

METHODS

Protocol and Registration

We conducted this systematic review in accordance with PRISMA guidelines (30). We registered the protocol for the review on PROSPERO [CRD42021260596], on September 17, 2021.

Exposure Definition

Radiation can be in the form of electromagnetic waves that include gamma rays and X rays, or particles such as alpha or beta particles (31). In this review, we examined the effects of both low (10 to 100 millisievert (mSv) and high (over 100 mSv) doses of external and internal radiation exposures to all forms of radiation at all dose-rates on dementia outcomes. We included both full-body and brain doses of radiation in the study but made no distinction when combining them in the meta-analysis.

Outcome Definition

The grouping "dementia" includes Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), Normal Pressure Hydrocephalus (NPH), vascular dementia, mixed dementia, dementia with Lewy bodies, frontotemporal dementia, and Creutz-feldt-Jakob Disease (32). Of these, we studied dementia (unspecified), AD and PD in this review. We defined the outcomes based on ICD-9 (33) and ICD-10 (34) codes as shown in Table 1.

Study Populations

Five different study populations cover the majority of identified exposure scenarios. These populations were: 1. survivors of atomic bombings in Japan; 2. patients treated with radiation for cancer and/or benign diseases; 3. occupationally exposed workers; 4. populations exposed to environmental radiation exposures, including background and accidental radiation; and 5. patients exposed to diagnostic radiation imaging procedures such as X rays, CT scans, etc.

Eligibility Criteria

The following inclusion criteria were used for search string development, abstract screening, and full-text review:

- Studies published in English and indexed in PubMed between 1/1/2001 and 11/7/2022. We selected this period because of improvements in dosimetry and outcome classification in the last two decades (35-38). Before 2000, dementia outcomes were not as well-defined using ICD-9 codes (39). To ensure that previous published studies of high quality were not missed, we also reviewed citation lists in all selected articles.

- Observational studies with human participants exposed to ionizing radiation that reported outcomes of incidence or mortality due to dementia, AD or PD.

- Radiation therapy exposure studies that included subgroup(s) receiving radiation therapy exclusively, regardless of other groups receiving concomitant chemotherapy.

For the full text review, the inclusion criteria were further expanded to the following:

- All the conditions for abstract screening along with articles that mentioned dementia, AD or PD in the full text or supplementary tables.

- Studies that published measures of association, such as excess relative risk (ERR) per unit of radiation dose, odds ratio (OR), hazard ratio (HR), standardized mortality ratio (SMR), or standardized incidence ratio (SIR).

The following exclusion criteria were applied to shortlist studies for meta-analysis:

- Studies that were clinical trials, surveys, descriptive or ecological studies, commentaries, or editorials.

- Studies that did not have any mention of radiation or only studied non-ionizing radiation.

- Previous studies from the same cohort that had a subsequent update published for similar outcomes or used similar methodology.

- Studies with participants exposed to ionizing radiation who did not have individual level dose estimates and/or did not report individual outcomes of incidence or mortality due to dementia, AD or PD.

- Studies that did not report a risk measure of association per unit of radiation dose for dementia/AD/PD outcomes.

Search Strategy

A combination of Medical Subject Headings (MeSH) and keywords associated with dementia and radiation were used to identify relevant publications on ionizing radiation and dementia. We placed no restrictions on the location of the study with our search, however, we restricted to English language publications. We searched PubMed [that indexes most published research articles, including those found in MEDLINE (40) and Cochrane Central (41)] for articles relevant to the topic. We built the search string using five substrings, each of which corresponded to a different patient population as defined under the exposure definition, with outcome as any or all among dementia, PD and AD. We used the Covidence® platform for systematic reviews to manage search results (42).

We constructed the literature search string in three phases (Appendix - Text Box 1). The first phase involved searching the titles and abstracts using the search strings for the five exposure scenarios. Following this, we conducted a manual search of citation lists of these published articles and identified relevant additional articles that we imported into Covidence®. The third phase expanded on the search eligibility criteria, by including studies on community residents and studies on cancer treatment using radiotherapy where dementia was reported as one of the outcomes. The third phase also excluded published systematic reviews, meta-analyses, retracted publications, corrigenda on trials, protocols, editorials, and overview articles.

In addition, an independent investigator (TB) blinded to our search strategy validated the search results by querying MEDLINE (40), Embase (43), APA PsycINFO (44), Cochrane Central (41), CINAHL (45), and Web of Science (46), followed by a manual search of Google scholar (47), and reference lists of articles with similar topics. These additional search results matched all relevant studies obtained via our primary search strategy, except

for one that did not yet have full text published but was listed as a conference abstract and was, therefore, excluded during the full text review.

Abstract Screening and Full Text Review

The abstract screening and full text review were conducted in accordance with our established inclusion criteria. Each article was independently screened by two reviewers, and conflicts were discussed between the reviewers with any remaining conflicts resolved by a senior author (LZ).

Data Abstraction

We used a standardized data abstraction form that included the following elements: publication details [author(s), year], study settings, population characteristics, radiation source, dose, type of exposure, dosimetry, duration, and units (effective or absorbed), outcome (incidence or mortality), and measures of association for dementia, PD and AD. Two reviewers independently abstracted the data from each study into a template that was compared for possible conflicts. The reviewers resolved the conflicts between themselves through discussion, and any remaining conflicts were resolved by LZ.

Risk of Bias Assessment

We conducted risk of bias assessments for each study by using the Office of Health Assessment and Translation (OHAT) guidelines (48). Two reviewers independently rated each study using a standardized protocol. Any conflicts were resolved by the reviewers or LZ through discussion. LZ reviewed the final assessments. We implemented a four-point rating scale while assessing the risk for selection bias, confounding, effect modification, attrition/data exclusion, bias in exposure classification, outcome assessment, reporting of outcome measures, and other threats to internal validity.

Meta-Analysis

The primary outcomes were incidence or mortality of dementia/AD/PD. We fit a random effects model to generate a summary measure of association that accounted for both within- and between-study variability in measures of association. Funnel plots were created and Egger's test was applied to assess publication bias (49). We assessed heterogeneity using the Cochrane Q-statistic and reported it in the form of the percent variation across studies (I^2) (50). Using STATA 17.0, we conducted a meta-analysis for studies that reported an excess relative risk (ERR = Relative Risk - 1) (51). We assumed that 1 Gy = 1 Sv = 1,000 mSv and converted measures of association reported per 1 Gy or 1 Sv to per 100 mSv for consistency across studies. We converted the reported ERRs into relative risk (RR) estimates that we then imported into STATA. We used STATA to estimate standard errors and natural log of relative risks from the relative risk estimates, and to perform the meta-analysis.

RESULTS

Literature Search

In the first phase of the search strategy (PubMed search) where we screened the abstracts, we identified 195 articles that satisfied the eligibility criteria for screening abstracts. The manual search of article references in the second phase resulted in the addition of ten new articles. The third phase (detailed previously) yielded 348 articles. Out of a total of 543 articles identified from all three phases, we found 119 to be duplicates we removed before screening. Of the remaining 424 articles, we found 305 to be irrelevant or not satisfying our inclusion criteria. After the abstract screening, 118 articles were shortlisted for the full text review. An inter-rater Kappa of 0.74 indicated substantial agreement between reviewers (52). After the full-text review was completed, 18 studies (26, 53-71) met the eligibility criteria for data abstraction (Table 2), which included a total of 853,821 participants. Figure 1 shows the PRISMA flowchart.

Out of the 18 studies included in the final set for abstracting (Table 2), 13 studies looked at the effects of occupational exposure (26, 53-62, 66, 68, 72), three studies examined the effects in atomic bomb survivors (64, 65), and 2 studies examined the effects of therapeutic radiation exposure (63, 67). We found 8 of these 18 studies to be eligible for meta-analysis (representing about 730,000 individuals) as they had similar definitions of the outcome, predictor, measure of association, sample type, and temporal characteristics (54-56, 59, 60, 62, 68, 69, 72). All 8 shortlisted studies (Table 3) provided a measure of association (or risk estimate) between occupational exposure to radiation and dementia. The Los Alamos study (54) presented risk estimates for dementia/AD, as well as separately for PD. We included only the latter in the meta-analysis.

In addition to the 8 studies selected for meta-analysis, the other 10 abstracted studies (53, 57, 61, 63-66, 66, 67, 71) did not report risk estimates per unit of radiation dose and thus were not included in the meta-analysis. The heterogeneity in outcome definitions (in some cases, lack of reporting of relevant outcomes), study designs, and age distribution of study populations as well as the potential for bias further led to these 10 studies being excluded. A qualitative review of these studies produced inconclusive evidence with regards to the effects of radiation on dementia.

Meta-Analysis

Six (26, 54-56, 59, 67, 68, 70, 72) of the eight studies included in the meta-analysis reported findings that were not statistically significant (Table 3). The Mound workers study reported a non-statistically significant result for deaths attributed to dementia outcomes and motor neuron disease (72). The Los Alamos study reported null results for both outcomes: dementia (ICD-9: 290-319) and AD (ICD-9: 331) combined, and PD (ICD-9: 332), separately (54). The study of medical radiation workers reported no statistically significant association between radiation and dementia incidence (55). The authors combined dementia (ICD-9: 290-319), AD (ICD-9: 331), PD (ICD-9: 332), and motor neuron disease (ICD-9: 290, 331, 332; 335.2) for analyses, but they also reported the measures for PD separately. The nuclear power plant workers study found no statistical

significance for the association between radiation and PD mortality (59). The Mallinckrodt workers study grouped dementia, AD, PD, and motor neuron disease and reported a lack of evidence for an effect of radiation on these outcomes (56). The industrial radiographers study also reported a positive but not statistically significant effect of radiation on the risk of dementia (26, 68).

Two of the eight selected studies reported statistically significantly increased radiation risks of dementia outcomes (60, 62). The INWORKS study reported a statistically significant risk estimate (ERR/Sv = 1.30; 90% CI 0.23, 2.72) for the broad category of deaths from "mental disorders" (ICD-10 F00-F99), of which only 53% were due to dementia-related outcomes (62). The study did not report measures of association for dementia/PD/AD. The Mayak workers study reported a statistically significant increased risk of PD from radiation exposure, with ERR/Gy = 1.02 (95% CI 0.59, 1.63) (60).

An overall meta-analysis of the risk estimates from eight studies for all types of dementia/AD/PD (Fig. 2) resulted in a positive and statistically significant risk of dementia/AD/PD from low-to-moderate dose chronic radiation, with a relative risk of 1.11 (95% CI: 1.04, 1.18) per 100 mSv. The measures of association from the individual studies exhibited heterogeneity (I^2 = 37.1%). While the funnel plot (Fig. 3) indicated the possibility of publication bias due to a lack of smaller studies, the Egger's test for publication bias was not statistically significant (P = 0.339).

Sensitivity Analyses

We assessed the individual impact of studies on the overall meta-analytic summary effect (Fig. 4). We found the Golden et al. study (56) had the largest – albeit still modest – influence on the overall risk estimate. Specifically, the overall estimate increased marginally to 1.12 (95% CI: 1.07, 1.16) when the Golden et al. study was removed. We also conducted sensitivity analysis restricting studies based on different classifications of outcomes. A Meta-analysis using a random effects model for studies reporting only mortality outcomes (Fig. 5) yielded an overall relative risk of 1.11 (95% CI 1.01, 1.22; P = 0.024) per 100 mSv. While a subgroup analysis for studies reporting on PD (Fig. 6) resulted in a summary relative risk of 1.12 (95% CI 1.07, 1.17; P < 0.001) with no heterogeneity.

Excluded Studies

In addition to the eight studies selected for the meta-analysis, the other ten abstracted studies provided mixed evidence related to the association between radiation exposure and dementia. However, these studies were determined to have a potentially high risk of bias, and/or not report a risk estimate per unit of radiation dose. Due to these limitations, we did not include them in the meta-analysis, but rather present a narrative review of them below.

    1.   The Paducah study reported a statistically significant SMR = 2.16 (95% CI: 1.38, 3.21) for the "other motor neuron disease" category that included the outcomes of AD, PD, and amyotrophic lateral sclerosis (ALS) (61). The study compared the worker cohort (1952–2003) with the US population (1940–2002), which also included World War II mortality and therefore, findings may be

distorted due to selection bias. No exposure range was listed, and granular data for dementia/PD/AD mortality were not presented.

2. The nuclear weapons test study found a statistically significant SMR = 0.90 (95% CI: 0.86, 0.95), indicating slightly lower dementia mortality rates as a result of being exposed to radiation (57). However, over 99% of the study cohort consisted of military men who were compared to the general male US population. This led to a considerable risk of selection bias, which prevented the inclusion of this study in the meta-analysis. Additionally, this study did not report individual radiation exposure estimates.

3. The U.S. and Canada study presented pooled cohort profiles of early uranium processing facilities, with a statistically significant SMR = 1.29 (95% CI: 1.04, 1.54) in males indicating an increased risk of dementia-related mortality in males from radiation exposure (58). This study did not report an ERR per unit radiation dose and thus it was excluded from the meta-analysis.

4. The female nuclear weapons workers study found that radiation doses higher than the baseline range of 0.0–4.9 mSv led to greater odds of death from dementia with both maximum annual (OR = 2.11, 95% CI: 0.98, 4.40) and total lifetime radiation doses (OR=2.09, 95% CI: 1.02, 4.29) (53).

5. The nasopharyngeal cancer (NPC) study conducted using Taiwan's Longitudinal Health Insurance Database reported a statistically significant adjusted hazard ratio (HR) = 1.91 (95% CI 1.42, 2.51) of dementia incidence among NPC patients receiving radiotherapy compared to non-NPC participants (63).

6. Based on a stratified analysis of the risk of dementia in colorectal cancer (CRC) patients receiving chemotherapy compared with the non-chemotherapy group, the CRC cancer study from 2022 found an adjusted HR = 1.16 (0.75–1.81) that was not statistically significant (67).

7. The Tennessee Eastman Corporation study, published in 2022, reported a statistically significant increased risk of dementia and AD among uranium processing workers with a SMR = 1.42 (95% CI 1.35, 1.49) while no statistically significant excess was found for PD disease (SMR = 1.13, 95% CI 0.96, 1.32) (66). This study also did not report an ERR per unit radiation dose and was excluded from the meta-analysis.

8. Using Poisson regression, the 2009 Japanese A-bomb publication found no association between radiation exposure and the incidence of dementia or any of its subtypes (64). The relative risks for all dementia among those exposed to relatively low doses (5–499 mSv) and those exposed to relatively high doses (500 mSv) compared to unexposed participants were 0.82 (P = 0.24) and 0.94 (P > 0.5), respectively.

9. The 2016 A-bomb study employed cognitive scores – as defined by the authors – collected before dementia onset and used an adjusted mixed effects model to estimate radiation effect on the long-term changes in cognition (71). The

study did not find a statistically significant association of radiation and cognitive decline.

10.	After performing an adjusted regression analysis, the A-bomb study published in 2022 found no evidence of radiation effect on cognitive function (65). The mean cognitive function score – as defined in the study – for participants subjected to radiation doses of less than 5 mSv, 5–250 mSv and greater than or equal to 250 mSv were 92.0, 90.9 and 91.0 (P = 0.32), respectively.

The heterogeneity in outcome definitions in the additional studies (in some cases, lack of reporting relevant outcomes), outcome measures, study designs, and study population age groups, as well as potential bias, led to these nine studies being excluded from the meta-analysis. However, a qualitative review of the excluded studies produced inconclusive evidence of the impact of radiation on dementia.

Risk of Bias Assessment

Table 4 details the risk of bias assessment under the OHAT guidelines (48) for the eight studies in the meta-analysis. Selection bias was present in all studies, primarily in the form of the healthy worker effect (due to the utilization of occupational cohorts) and unmeasured confounding. Apart from the INWORKS study (62) that had higher risk, all studies had a very low risk of attrition bias, and low risk of selection bias, exposure and outcome misclassification, measurement bias, and other threats to validity. The INWORKS study (62) had a moderate risk of bias in most categories. The Mayak workers study (60) had very low or low risk of bias in most categories, leading to an overall low risk of bias assessment. The other seven studies had an overall moderate risk of bias. These studies, while meeting our eligibility criteria for a random effects model for meta-analysis, suffered from the greatest shortcoming in the form of unmeasured confounding, followed by selection bias, specifically the healthy worker effect.

DISCUSSION

This systematic review sought to synthesize evidence from epidemiological studies published in the last 22 years on ionizing radiation and dementia, including AD and PD subtypes. Current evidence came from mainly small-scale observational studies whose primary objectives were outside the scope of dementia-related outcomes. Aside from the recently published systematic review on the radiation-associated risk of non-cancerous central nervous system diseases, including a subgroup analysis on PD (24), no systematic literature review investigating the effect of radiation on the risk of dementia incidence and mortality has been published. Our article presented a comprehensive analysis evaluating this specific relationship.

Based on the publications included in the final meta-analysis, we found evidence of a positive association between radiation and the risk of dementia/AD/PD. The observed summary effect measure was statistically significant (P = 0.001), indicating an association of low-to-medium dose of ionizing radiation with dementia/AD/PD incidence and mortality. Both the I^2 of 37.1% and the lack of a statistically significant Cochrane's Q statistic (P = 0.133) indicated modest heterogeneity across the sample of studies. This resulted from

dissimilar outcome definitions (dementia, PD, AD, motor neuron diseases or a combination of these), demographics, and other unknown factors, despite all having the exposure within occupational settings. Risk factors such as age, sex, education and employment type were adjusted for most of the included studies to produce risk estimates (54-56, 59, 60, 62, 72). However, with only eight studies finalized for the meta-analysis, Cochrane's Q test, the funnel plot and the overall meta-analysis estimate of radiation risks should be interpreted with caution.

While age has been established as the most important risk factor for dementia, other modifiable risk factors such as poor nutrition; low physical activity; and genetic, socioeconomic and environmental factors need further exploration for the prevention and treatment of dementia (11). Furthermore, the underlying molecular mechanisms regarding the association between radiation and cognitive disorders have not been fully understood. AD manifests mainly as a result of intraneuronal accumulation of beta-amyloid and neurofibrillary tangles in the brain (73). This accumulation is linked to inflammation, oxidative stress, and the apoptosis and necrosis of neural tissue (15, 17, 74), which leads to brain cell death or loss of function . Often AD patients struggle with markedly poor quality of life (76). Pathologically PD is marked by neuronal loss in the substantia nigra, and elsewhere is associated with ubiquitinated protein deposits in the cytoplasm of neurons (Lewy bodies) and proteinaceous inclusions within Lewy neurites (8). Radiation is now an established factor for premature aging (15, 77) through the production of reactive oxidative stress (77). Low and high doses of radiation may cause dementia (15, 16) as both can alter brain cell and cognitive functions (12-14) and also affect neurological integrity. However, studies investigating this topic are few, employ heterogenous exposure settings (78, 79) and/or animal or clinical models (80, 81), lack statistical power, and suffer from bias.

In contrast to the above findings, some studies have found low-dose radiation therapy to be protective against systemic amyloid deposits, as well as against chronic inflammatory diseases (82). There is interest in studying preclinical evidence for the reduction of amyloid plaques as it is associated with modulation of inflammatory and anti-inflammatory cytokines and cognitive improvement in AD (82). Overall, there is not enough evidence to conclude whether exposure to radiation causes dementia, AD and/or PD or if other factors influence the outcome(s).

The results from our review align with the conclusions of the recent meta-analysis by Lopes et al. which found a positive dose-response relationship between radiation exposure and the risk of PD incidence and mortality (24). The three studies from Lopes et al. were evaluated in this meta-analysis and an additional 5 studies reporting dementia-related outcomes were included (24). The key differences between the Lopes et al. (24) meta-analysis and this study was the outcome definition and the meta-analysis methodology used. The Lopes et al. (24) article explored the effect of radiation on the risk of a broad category of non-cancerous central nervous system diseases, with a sub-group meta-analysis on PD incidence and mortality. While there are strengths to having a broad outcome definition, especially as it increases the sample size of the synthesized studies, our article focuses on specific outcomes of dementia, AD and PD, as defined in Table 1. The latter approach is advantageous as broader definitions may result in challenges in standardizing inconsistencies in outcome

assessment, especially as future research may require further convergence on specific types of dementia. A broader outcome definition also directly increases heterogeneity, as observed from the $I^2 = 88.43\%$ in the Lopes et al. (24) article, compared to this meta-analysis at $I^2 = 37.1\%$. Our article also includes more comprehensive statistical analyses including forest plots for dementia-related outcomes, and an assessment of publication bias using a funnel plot and the Egger's test. Furthermore, this study includes detailed sensitivity analyses exploring the effect of individual studies and different outcome measure definitions (incidence versus mortality) on the overall estimate. While Lopes et al. (24) reported a meta-analysis of SMRs from three studies on PD, we included the studies that also reported ERRs as part of our meta-analyses. Both the Lopes et al. (24) review and ours performed subgroup analyses for PD outcomes with consistent results.

Our findings are also in agreement with the Russian Mayak workers study that found a harmful effect of radiation on the risk of PD (60), and a recent narrative literature review which showed that radon decay products could be a harmful factor in dementia/AD risk (83). However, the latter literature review was based on case reports, small-scale case-control and ecological studies. Thus, the evidence is not sufficient for establishing an association between radon and other forms of radiation exposure and dementia. The results of our meta-analysis deviate from those of studies examining survivors of atomic bombings in Japan (64, 65, 71) which reported null results. Our results are also different from the near-protective effect (not statistically significant) of radiation on dementia that Boice et al. found among nuclear weapons test participants (57).

Our systematic review has many strengths. It underscores a new perspective for research in the very important field of the impact of low and high doses of radiation on dementia. We considered radiation risks in five types of populations based on their source of radiation exposure whereas most of the literature has predominantly focused on accidental radiation or radiation encountered in occupational settings. Expanding the exposure settings to include therapeutic radiation, background radiation, and diagnostic radiation allows researchers the benefit of evaluating the effect estimate in a more holistic manner. Additionally, this review studies the composite outcome definition that includes dementia, AD and PD, which account for the majority of dementia-related diagnoses. Until now, these neurodegenerative outcomes have been largely treated as an afterthought in most observational studies. This review highlights these gaps and opens the field for future studies exploring the relationship of radiation with these increasingly prevalent neurodegenerative diseases. Another strength of this systematic review is the independent, blinded validation of all steps taken during the entirety of the project from the search strategy to the full text review, data abstraction, and risk of bias assessment.

This systematic review also has several limitations. This review is dependent on the available literature published in the last 22 years in English and indexed in PubMed (validated with MEDLINE, Embase, PsycINFO, Cochrane Central, CINAHL, Google Scholar, and Web of Science) investigating the relationship of radiation and dementia, which yielded few studies for assessment. We excluded studies published before 2000 because the outcomes of dementia, vascular dementia, PD and AD were ambiguously defined based only on ICD-9 codes; the advent of ICD-10 addressed this limitation. Upon manually examining the

citation lists of all identified studies, we only found one relevant study (84) published before 2000 and this study reported elevated proportionate mortality ratios (PMR) for presenile dementia, AD, PD and motor neuron disease, stratified by race, sex and occupation. The overall PMR was not reported, and we could not incorporate it into our meta-analysis. Due to this eligibility criterion of publication year, only 18 studies were found to satisfy the inclusion criteria, of which only eight qualified for meta-analysis. Because only eight studies were included in the final meta-analysis, we are limited to assessing and addressing the possibility of publication bias in this meta-analysis.

The overall risk of bias in seven of the eight studies included in the meta-analysis is moderate, with only one study having a low risk of bias (60). We looked at the studies with various radiation exposure scenarios, but all eight studies shortlisted for the meta-analysis were from the group of occupational exposures, and therefore, the overall effect estimate is generalizable only to this setting. However, there was significant heterogeneity in the radiation dose limits of the eight studies, with the upper limit ranging from 0.83 Sv to 8 Sv across studies. This highlights the dearth of reliable observational studies that assessed the dose-response relationship of dementia and exposure to radiation in settings outside of the work environment. This is further underscored by the fact that seven out of the eight studies had primary outcomes of interest that were not related to dementia or its subtypes. Further, there is heterogeneity in the outcome measurement between incidence and mortality: only one study (60) evaluated dementia incidence while all other studies reported mortality measures of association. Finally, the eight shortlisted studies also did not have consistency in the outcome definition: while one study (56) presented a composite point estimate for the risk of dementia, AD, PD and motor neuron disease (ICD-9 290.0–290.4, 331.0, 332, 335.2), these outcomes were reported additionally in only the studies on Mound workers (72), medical radiation workers (55) and the Los Alamos facility workers (54). Relevant to the research question of this systematic review, the INWORKS study (62) only reported the point estimate under a broader definition of mental health disease, where dementia cases accounted for only 53% of deaths. Two studies (59, 60) only reported PD outcomes. Lastly, given the limited research available, this review only examined dichotomized outcomes of mortality and incidence. Hence, there remains a lack of evidence evaluating the effect of radiation on the prognosis of dementia in terms of symptom severity, comorbidity development, and disability levels.

This systematic review aligns with NASA's Human Research Roadmap by: 1. characterizing the risk of adverse cognitive conditions (dementia, PD, and AD) and 2. describing the risk of adverse health outcomes due to long-term health conditions resulting from mission exposures (i.e., the category of ionizing radiation). While not explicitly evaluating exposure during space travel, the current findings suggest the need to further explore the connection between radiation and cognition.

The positive summary meta-analytic risk estimate produced by this review encourages further research in this increasingly important area of focus. Future investigations examining radiation and dementia-related outcomes could benefit from including specific data on different types of dementia as opposed to clustering them together, to allow for precise analyses for specific dementia outcomes. Additionally, converging on a standardized method

of outcome assessment will allow future meta-analysis of studies matching in methodology. Following the UNSCEAR criteria for epidemiologic research on radiation would improve consistency and homogeneity of the included studies (85). Direct risk comparisons between different exposure types (based on dose type, partial-/whole-body exposure, radiation subtypes, and exposure duration, etc.) could allow future meta-regressions to be conducted. Future research could also aim to conduct longitudinal assessments of dose-response relationships between radiation exposure and continuous measures of dementia experiences, such as symptom progression and severity. Finally, future studies could leverage one-payer systems for healthcare (e.g., Medicare and Medicaid in the U.S., Canadian Medicare, and NHS in the UK, among others) for more reliable diagnosis and prognosis data.

CONCLUSION

Although there are excellent studies exploring the association of ionizing radiation with cancer outcomes, there are far fewer such studies for dementia, and methodologically these studies have greater potential for bias. This is particularly relevant because of the negative outcomes associated with dementia that impact the patients and their caregivers (86). As life expectancy increases around the world, more people will experience this form of disease. This topic is gaining even more importance as humanity explores long-distance space travel to Mars associated with radiation exposure (27, 87). This systematic review and meta-analysis found a positive statistically significant association between the risk of dementia from radiation. However, future studies should evaluate this relationship by further evaluating other settings apart from occupational exposure and aim to build on the findings of this systematic review to better understand the risk of dementia and long-term cognitive harm as a result of radiation exposure.

ACKNOWLEDGMENTS

APPENDIX

Text Box 1:   Search String

Phase 1: Filters applied: English, from 2001/1/1 - 3000/12/12. – **195 results**

((((radiation[tiab] OR nuclear[tiab]) exposure) AND (occupation* OR worker*) AND (dementia OR parkinson* OR alzheimer*))

OR (((radiation[tiab] OR nuclear) AND (mortality[tiab] OR incidence[tiab]) AND worker*[tiab]) AND (dementia[All Fields] OR Parkinson*[All Fields] OR alzheimer*[All Fields]) AND ((cohort study) OR (case-control)))

OR ((nuclear weapons AND (worker* OR test*)) AND (mortality[ti] OR dementia OR parkinson* OR alzheimer*))

OR ((atomic[tiab] OR nuclear[tiab] OR radium[tiab]) worker[tiab] AND mortality[tiab] AND (dementia OR Alzheimer* OR parkinson*))

OR ((radiation atomic bomb survivors) AND (dementia OR parkinson* OR alzheimer*))

OR ((("X-ray imaging"[ti] OR "CT scan" [ti] OR "computed tomography" [ti]) AND (neurodegenerative[tiab] OR dementia[tiab] OR parkinson*[tiab] OR Alzheimer*[tiab])) AND ((cohort study) OR case-control OR (risk ratio) OR "ERR" OR (risk difference) OR (relative risk) OR (odds ratio) OR (hazard ratio)) NOT (PET OR photon[tiab]))

OR ((((radiation[ti] OR Chernobyl[tiab] OR Chornobyl[tiab] OR Fukushima[tiab]) AND (community residents OR environment*)) AND (neurodegenerative[tiab] OR dementia[tiab] OR Parkinson*[tiab] OR Alzheimer*[tiab])) NOT (PET OR mouse[ti] OR animal[ti] OR mice[ti])) OR (((radiation therapy[ti] OR cancer treatment[ti] OR radiation[ti] OR radiotherapy[ti] OR "radiation effects"[tiab]) AND (neurodegenerative[tiab] OR dementia[tiab] OR Parkinson*[tiab] OR Alzheimer*[-tiab]))) NOT (PET OR ultraviolet[tiab] OR Review[Publication Type] OR mouse[ti] OR animal[ti])

AND ((cohort study) OR case-control OR (risk ratio) OR "ERR" OR (risk difference) OR (relative risk) OR (odds ratio) OR (hazard ratio)))

Phase 2: Manual Reference Search – **10 results**

Phase 3: Filters applied: English, from 2001/1/1 - 3000/12/12. – **348 results**

((radiation[tiab] AND

(nuclear[tiab] OR atomic[tiab] OR weapon*[tiab])

AND (occupation*[tiab] OR worker*[tiab] OR person*[tiab])

AND (incidence[tiab] OR mortality[tiab] OR death*[tiab]))

OR ((radiation atomic bomb survivors) AND (dementia OR Parkinson* OR Alzheimer*))

OR (radiation[tiab] AND ("X-ray imaging"[tiab] OR "CT scan" [tiab] OR "computed tomography" [tiab])

AND (dementia[tiab] OR Parkinson*[tiab] OR Alzheimer*[tiab])

NOT ("PET" OR photon[tiab]))

OR (((radiation[tiab] OR Chernobyl[tiab] OR Chornobyl[tiab] OR Fukushima[tiab])

AND (community residents OR environment*)

AND (dementia[tiab] OR Parkinson*[tiab] OR Alzheimer*[tiab]))

NOT ("PET" OR mouse[ti] OR animal[ti] OR mice[ti]))

OR ((radiation[tiab] OR irradiat*[tiab])

AND (therapy[tiab] OR cancer[tiab] OR treatment[tiab] OR radiotherapy[tiab])

AND (dementia[tiab] OR Parkinson*[tiab] OR Alzheimer*[tiab])

NOT ("PET" OR ultraviolet[tiab] OR mouse[ti] OR animal[ti]))

AND (cohort[tiab] OR "case-control"[tiab] OR risk[tiab] OR "excess relative risk"[tiab]

OR "ERR" OR risk[tiab] OR "odds"[tiab] OR "hazard ratio"[tiab] OR

SIR[tiab] OR SMR[tiab]))

NOT ("review*"[ti] OR "review"[ptyp] OR meta-analysis[ptyp] OR meta-analysis[ti]

OR "systematic review"[ptyp] OR "retracted publication"[ptyp]

OR "retraction of publication"[ptyp] OR "retraction of publication"[-tiab]

OR "retraction notice"[ti] OR "retracted publication"[tiab]

OR corrigenda[tiab] OR corrigendum[tiab]

OR trial[ti] OR protocol*[ti] OR overview[ti] OR critique[ti])

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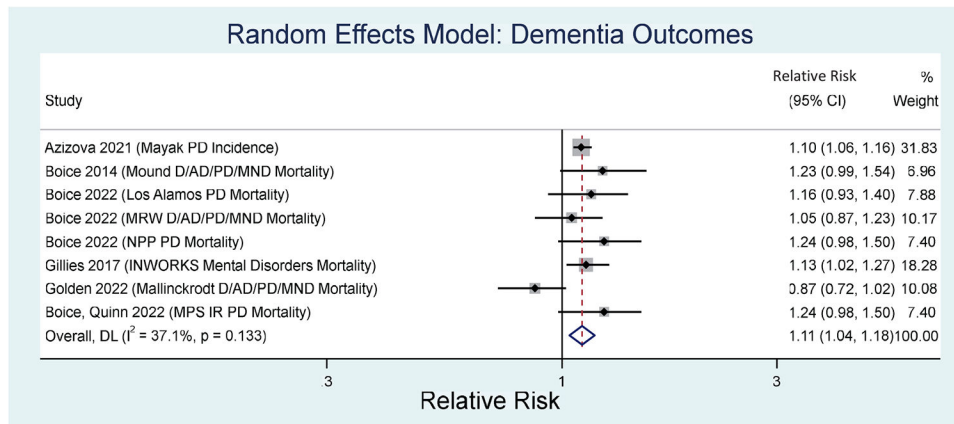
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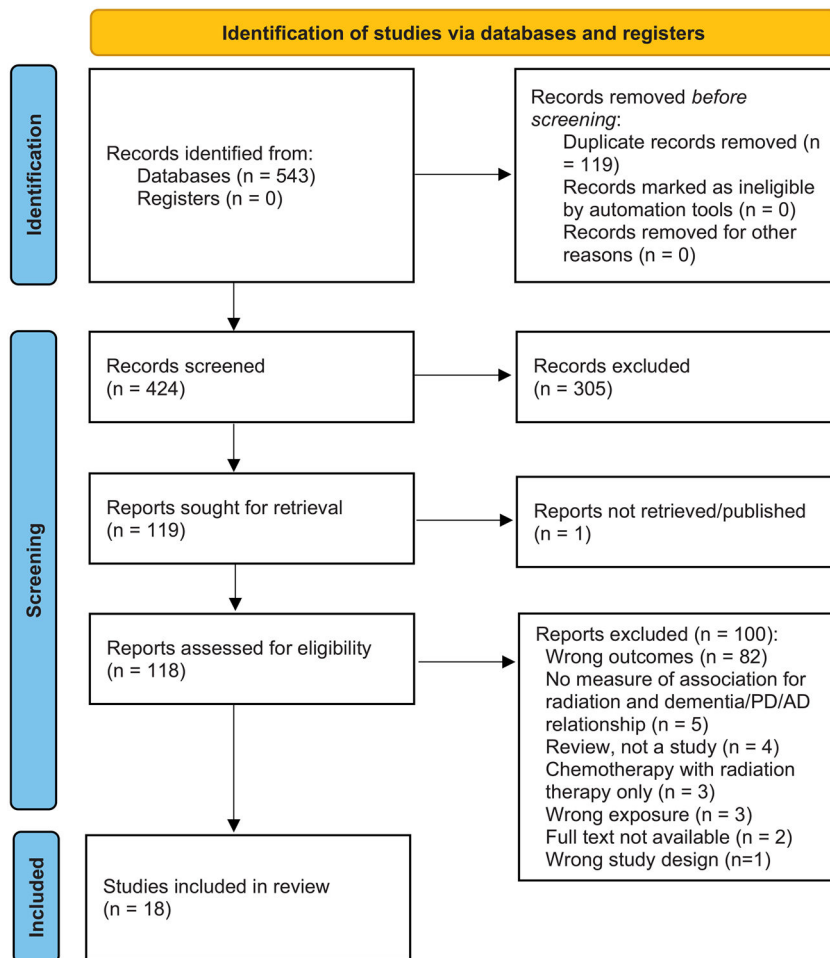
FIG. 1.
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. Used with permission from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. doi: 10.1136/bmj.n71.

Random Effects Model: Dementia Outcomes

Study	Relative Risk (95% CI)	% Weight
Azizova 2021 (Mayak PD Incidence)	1.10 (1.06, 1.16)	31.83
Boice 2014 (Mound D/AD/PD/MND Mortality)	1.23 (0.99, 1.54)	6.96
Boice 2022 (Los Alamos PD Mortality)	1.16 (0.93, 1.40)	7.88
Boice 2022 (MRW D/AD/PD/MND Mortality)	1.05 (0.87, 1.23)	10.17
Boice 2022 (NPP PD Mortality)	1.24 (0.98, 1.50)	7.40
Gillies 2017 (INWORKS Mental Disorders Mortality)	1.13 (1.02, 1.27)	18.28
Golden 2022 (Mallinckrodt D/AD/PD/MND Mortality)	0.87 (0.72, 1.02)	10.08
Boice, Quinn 2022 (MPS IR PD Mortality)	1.24 (0.98, 1.50)	7.40
Overall, DL (I^2 = 37.1%, p = 0.133)	1.11 (1.04, 1.18)	100.00

FIG. 2.

Forest plot and summary of meta-analysis of all studies reporting ERR. This figure shows the meta-analysis of aggregate data using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau^2. Each row represents a different point estimate corresponding to the relative risk of disease outcomes from exposure to radiation with 95% confidence intervals. An overall random effects estimate is provided in the last line along with the test statistics. Our meta-analysis shows that the risk of dementia incidence or mortality in populations exposed to over 100 mSv is 1.11 (95% CI: 1.04, 1.18; P = 0.001) times the risk in those unirradiated. The width of the diamond represents the overall confidence interval from the meta-analysis and does not contain the null of 1. The heterogeneity present is low with I^2 = 37.1%, with Cochran's Q-test showing a lack of statistical significance at P = 0.133. Abbreviations: D: Dementia; PD: Parkinson's Disease; AD: Alzheimer's Disease; MND: Motor Neuron Diseases; MRW: Medical Radiation Workers; NPP: Nuclear Power Plant; MPS: Million Person Study; IR: Industrial Radiographers.

Funnel plot with pseudo 95% confidence limits
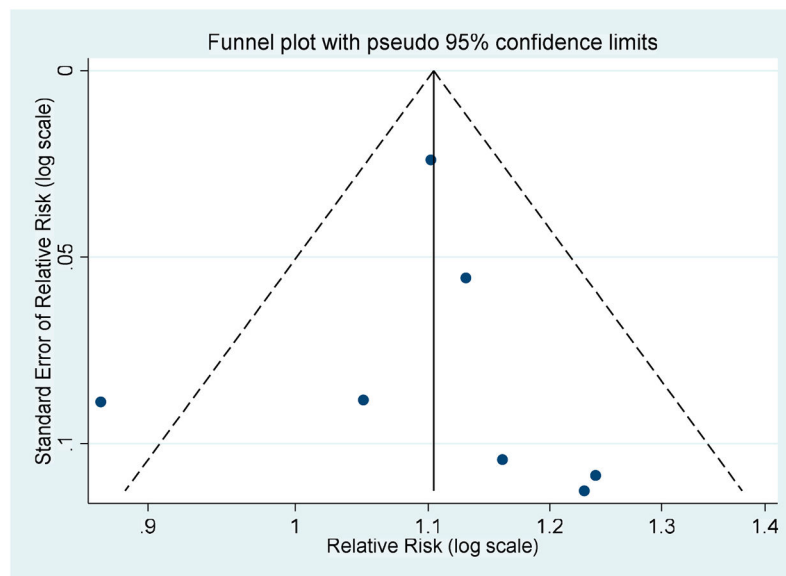
Egger's test for small-study effects:
Regress standard normal deviate of intervention
  effect estimate against its standard error

.
Number of studies = 8   Root MSE   = 1.352

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf. interval]	
slope	.0883597	.0452926	1.95	0.099	-.0224673	.1991867
bias	.2411526	.8274146	0.29	0.781	-1.783458	2.265763

Test of H0: no small-study effects   P = 0.781

FIG. 3.

Funnel plot and Egger's test for epidemiological studies on ionizing radiation and dementia.
Relative risk in the funnel plot above represents the ratio of the risk of dementia incidence or
mortality in populations exposed to over 100 mSv of radiation compared to the risk in those
exposed to lower doses of doses. The funnel plot shows slight asymmetry and thus may
imply the presence of publication bias. This was tested using the Egger's test that produced
no statistically significant evidence of publication bias with P = 0.781.

Meta-analysis estimates, given named study is omitted
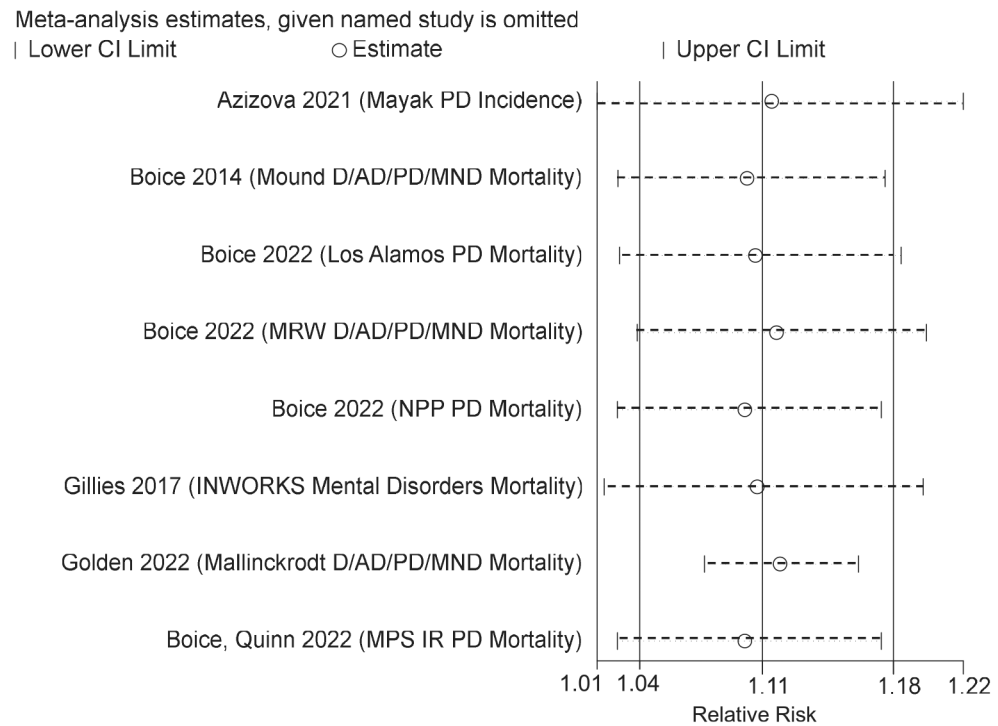
FIG. 4.
Influence of individual studies. The figure above shows the effect estimate and 95% CI every time an individual study (labeled on the left) is removed from the meta-analysis. The three vertical lines at 1.11, 1.04, and 1.18 correspond, respectively, to the overall relative risk estimate, and 95% CI lower and upper limits of the meta-analysis that includes all studies. Most of the included studies are consistent with the overall effect estimate determined by the meta-analysis. However, omission of the Golden et al. study raises the overall estimate and narrows the 95% CI owing to the study reporting an ERR estimate of −0.13 (95% CI −0.28, 0.02) at 100 mGy. All other studies upon individual omission overlap their 95% CIs with that of the overall meta-analysis estimate of relative risk = 1.11 (95% CI: 1.04, 1.18), and therefore, do not have a substantial impact in influencing the overall effect estimate. Abbreviations: D: Dementia; PD: Parkinson's Disease; AD: Alzheimer's Disease; MND: Motor Neuron Diseases; MRW: Medical Radiation Workers; NPP: Nuclear Power Plant; MPS: Million Person Study; IR: Industrial Radiographers
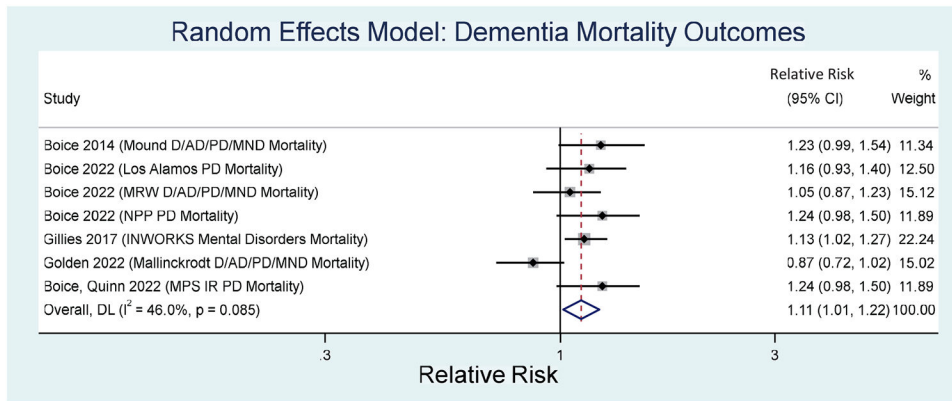
FIG. 5.

Meta-analysis of epidemiologic studies with only dementia mortality outcomes. This figure shows the meta-analysis of aggregate data using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau^2. Each row represents a different point estimate corresponding to the relative risk of disease outcomes after irradiation with 95% confidence intervals. An overall random effects estimate is provided in the last line along with the test statistics. Our meta-analysis shows that the risk of dementia mortality in populations exposed to over 100 mSv is 1.11 (95% CI: 1.01, 1.22; P = 0.024) times the risk in those unirradiated. The width of the diamond represents the overall confidence interval from the meta-analysis and does not contain the null of 1. The heterogeneity present is high with I^2 = 54.1%, tested with the Cochran's Q-test showing statistical significance with P = 0.042. Abbreviations: D: Dementia; PD: Parkinson's Disease; AD: Alzheimer's Disease; MND: Motor Neuron Diseases; MRW: Medical Radiation Workers; NPP: Nuclear Power Plant; MPS: Million Person Study; IR: Industrial Radiographers.
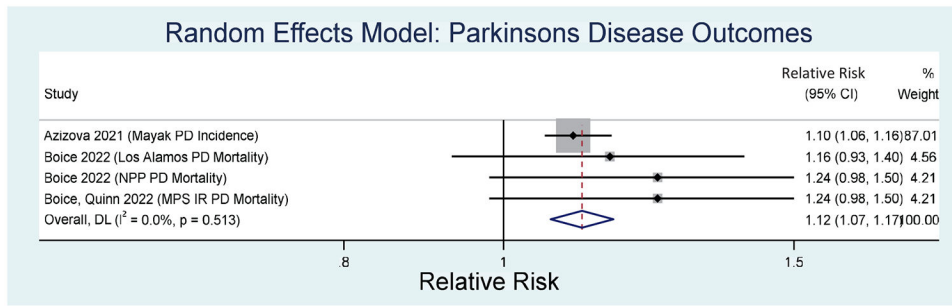
FIG. 6.

Meta-analysis of epidemiologic studies with Parkinson's disease outcomes. The figure shows the meta-analysis of aggregate data using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau^2. Each row represents a different point estimate corresponding to the relative risk of disease outcomes after exposure to radiation with 95% confidence intervals. An overall random effects estimate is provided in the last line along with the test statistics. Our meta-analysis shows that the risk of dementia incidence or mortality in populations exposed to over 100 mSv is 1.12 (95% CI 1.07, 1.17; P < 0.001) times the risk in those unirradiated. The width of the diamond represents the overall confidence interval from the meta-analysis and does not contain the null of 1. The heterogeneity present is absent with I^2 = 0%, and Cochran's Q-test showing a lack of statistical significance at P = 0.513. Abbreviations: PD: Parkinson's Disease; NPP: Nuclear Power Plant; MPS: Million Person Study; IR: Industrial Radiographers

TABLE 1

ICD Codes for Outcomes

Outcome	ICD-9 Codes (33)	ICD-10 Codes (34)
Dementia	046.1	G30.0–G30.9
	290.0–290.4	F0.0–F0.9
	294	F1.0–F1.9
	331.0	F2.0–F2.9
	331.1	F3.0–F3.9
	331.5	
Parkinsonism	332.0–332.1	G20.0–G20.9
		G21.0–G21.4
		G21.8–G21.9
		G22
		F02.3
Alzheimer's Disease	331.0	G30.0–G30.9
		F0.0–F.0.9

TABLE 2

Studies Included in Full-Text Review

Study	Country of study	Study design	Number of subjects	Study follow-up	Mean length in years
Azizova 2020 (60)	Russia	Cohort	22,377	1948–2013	n/a
Boice 2014 (72)	U.S.	Cohort	4,954	1944–1979	40.4
Boice 2020 (57)	U.S.	Cohort	114,270	1945–2010	47
Boice 2022 (54)	U.S.	Cohort	26,328	1943–2017	44.9
Boice 2022 (55)	U.S.	Cohort	109,019	1965–2016	23.7
Boice 2022 (59)	U.S.	Cohort	135,193	1957–2011	30.2
Boice 2022 (66)	U.S.	Cohort	26,650	1943–2019	45
Boice, Quinn 2022 (26)	U.S.	Cohort	126,000 industrial radiographers	n/a	n/a
Chan 2010 (61)	U.S.	Retrospective cohort	6,759	1952–2003	n/a
Chiu 2022 (67)	Taiwan	Cohort	76,130	2007–2015	
Gillies 2017 (62)	France, UK, U.S.	Cohort	308,297	1944–2005	n/a
Golden 2021 (58)	U.S.	Cohort	2514	1942–2012	43.3
Golden 2022 (56)	U.S., Canada	Cohort	12,403	1930s–2017	37
Penn 2021 (63)	Taiwan, China	Retrospective matched-cohort	2,970	2000–2015	10.72 (calculated)
Sibley 2003 (53)	U.S.	Nested case-control	1,001	1943–1994	n/a
Yamada 2009 (64)	Japan	Cohort	2,286	1958–1996	5.9
Yamada 2016 (71)	Japan	Cohort	2,367	1992–2011	8.4
Yamada 2021 (65)	Japan	Case-control	303	2011–2015	n/a

Exposure source	Mean dose	Radiation type
Occupational	Males: 0.46 ± 0.67 Sv; females: 0.36 ± 0.56 Sv	Full body chronic external and internal exposure
Occupational	External: 26.1 mSv; external and internal combined: 100.1 mSv	Full body chronic external and internal exposure
Occupational	Males: 6 mGy	Full body chronic external exposure
Occupational	18.9 mGy	Full body chronic external and internal exposure
Occupational	28.6 mGy (weighted)	Full body chronic external and internal exposure
Occupational	33.2 mGy	Full body chronic external exposure
Occupational	591 weighted-mGy lung dose	Full body chronic internal exposure
Occupational	n/a	Full body chronic external exposure

Exposure source	Mean dose	Radiation type
Occupational	n/a	Full body chronic external and internal exposure
Therapeutic	n/a	Partial body acute internal exposure
Occupational	25.2 mSv	Full body chronic external and internal exposure
Occupational	37.2 mGy	Full body chronic external and internal exposure
Occupational	Males: 45.01 mGy; Females: 11.36 mGy	Full body chronic external and internal exposure
Therapeutic	n/a	Partial body acute internal exposure
Occupational	n/a	Full body chronic external exposure
A-bomb	<5 mGy: 0.5 mGy; 5–499 mGy: 186.4 mGy; > = 500 mGy: 1,330 mGy	Full body acute external exposure
A-bomb	434 mGy	Full body acute external exposure
A-bomb	n/a	Full body acute external exposure

TABLE 3

Studies Included in the Meta-Analysis

Study	Country of study	Study design	Subject count	Study follow-up	Mean follow-up length (years)	Exposure source	Cases	Deaths	Covariates	Result
Azizova 2021 (Mayak) (60)	Russia	Cohort	22,377	1948–2013	n/a	Occupational	300	n/a	Sex, attained age and duration of employment	Positive
Boice 2014 (72) (Mound)	U.S.	Cohort	4,954	1944–1979	40.4	Occupational	n/a	33	Sex, education, year of birth and year of hire	Null
Boice 2022 (Los Alamos) (54)	U.S.	Cohort	26,328	1943–2017	44.9	Occupational	n/a	735	Sex, education, year of birth	Null
Boice 2021 (MRW[d]) (55)	U.S.	Cohort	109,019	1965–2016	23.7	Occupational	n/a	326		Null
Boice 2022 (NPP[e]) (59)	U.S.	Cohort	135,193	1957–2011	30.2	Occupational	n/a	411	Sex, year of birth and occupational category	Null
Boice, Quinn 2022 (IR[f] (26)	U.S.	Cohort	123,556			Occupational	n/a		Sex, year of birth, and area-level education	Null
Gillies 2017 (INWORKS) (62)	France, UK, U.S.	Cohort	308,297	1944–2005	n/a	Occupational	n/a	705	n/a	Null
Golden 2021 (Mallinckrodt) (56)	U.S.	Cohort	2,514	1942–2012	43.3	Occupational	n/a	71 for dementia/AD/PD/Motor neuron disease and 50 for dementia/AD	Age, birth-cohort, gender, socioeconomic status, employment duration, employment facility / Pay type (hourly/salary) and year of birth	Positive / Null

Study	SMR[a] (95% CI)	HR[b] (95% CI)	ERR[c] at specified units (CI)
Azizova 2021 (Mayak)			ERR/Gy (95% CI): 1.02 (0.59, 1.63, P = 5.41×10^{-5})
Boice 2014 (Mound)	0.88 (0.61, 1.24)		ERR (95% CI) at 100 mGy: 0.23 (−0.01,0.54)
Boice 2022 (Los Alamos)	Dementia/AD: 0.92 (0.85, 0.98); PD: 1.16 (1.00, 1.34)	Dementia/AD: HR at 100 mGy: −0.99 (0.83, 1.18); PD: HR at 100 mGy: 1.18 (0.93, 1.49)	Dementia/AD: ERR (95% CI) at 100 mGy: −0.01 (−0.19, 0.16); PD: ERR at 100 mGy: −0.16 (−0.07, 0.40)
Boice 2021 (MRW)	0.70 (0.63, 0.79)	HR at 100 mGy: 1.05 (0.88, 1.25)	ERR at 100 mGy: 0.05 (95% CI: −0.13, 0.23)
Boice 2022 (NPP)	0.92 (0.84, 1.02)	HR (95% CI) at 100 mGy: 1.27 (0.98, 1.65)	ERR (95% CI) at 100 mGy: 0.24 (−0.02, 0.50)
Boice, Quinn 2022 (IR)	0.92 (0.84, 1.02)	HR (95% CI) at 100 mGy: 1.27 (0.98, 1.65)	ERR (95% CI) at 100 mGy: 0.24 (95% CI −0.02, 0.50)
Gillies 2017 (INWORKS)			ERR/Sv = 1.30; (90% CI: 0.23, 2.72)
Golden 2021 (Mallinckrodt)	Dementia/AD: 1.18 (0.88, 1.55); Dementia/AD/PD/Motor neuron disease: 1.17 (0.91, 1.48)	HR (95% CI) at 100 mGy: 0.91 (0.64, 1.29)	ERR (95% CI) at 100 mGy: −0.13 (−0.28, 0.02)

[a] Standardized mortality ratio (SMR).

[b] Hazard ratio (HR).

[c] Excess relative risk (ERR); We assumed that 1.Gy = 1 Sv = 1,000 mSv as a basis to convert ERR reported per 1 Gy or 1 Sv or 100 mGy to per 100 mSv appropriately for consistency across studies.

[d]Medical radiation workers.

[e]Nuclear power plant workers.

[f]Industrial radiographers study, as reported by the Million Person Study.

TABLE 4

OHAT Risk of Bias Assessment for Meta-Analyzed Studies

Study	Selection bias	Confounding and effect modification	Attrition bias	Exposure misclassification	Outcome misclassification	Measurement bias	Other threats to internal validity	Overall risk of bias
Azizova 2020 (Mayak)(60)	+	–	++	++	+	++	+	*
Boice 2014 (Mound) (72)	+	–	++	+	+	+	+	**
Boice 2022 (Los Alamos) (54)	+	–	++	+	+	+	+	**
Boice 2022 (MRW) (55)	+	–	++	+	+	+	+	**
Boice 2022 (Nuclear Power Plants) (57)	+	–	++	+	–	+	+	**
Boice, Quinn 2022 (IR) (26)	+	–	++	+	+	+	+	**
Gillies 2017 (INWORKS) (62)	–	–	–	–	+	–	+	**
Golden 2021 (Mallinckrodt) (56)	+	– –	++	+	+	+	+	**

Abbreviations key: ++ = Definitely low risk; + = Probably low risk; – = Probably high risk; – – = Definitely high risk

*
 = Low

**
 = Medium

***
 = High.