

# Ionizing radiation exposure during adulthood and risk of developing central nervous system tumors: systematic review and meta-analysis

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## Supplementary data

Table S1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 checklist

Section and Topic	Item #	Checklist item	Reported on page
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	1
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4-6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-6

Section and Topic	Item #	Checklist item	Reported on page
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6-7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6-8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7-8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7-8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7-8
<b>RESULTS</b>			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7 ; Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	8-12, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8-12, Table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	8-12, Table 1

Section and Topic	Item #	Checklist item	Reported on page
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	13 ; Figure 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	13
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	13
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13-14
	23b	Discuss any limitations of the evidence included in the review.	14-18
	23c	Discuss any limitations of the review processes used.	14-18
	23d	Discuss implications of the results for practice, policy, and future research.	18
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	31
Competing interests	26	Declare any competing interests of review authors.	31
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

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 For more information, visit: <http://www.prisma-statement.org/>

Table S2: List of the causes of deaths studied and corresponding codes according to the International Classification of Diseases (ICD)

	Causes of death
<b>ICD 7 version</b>	
193	Malignant neoplasm of brain and other parts of nervous system
<b>ICD 9 version</b>	
191	Malignant neoplasm of brain
192	Malignant neoplasm of other and unspecified parts of nervous system
<b>ICD 10 version</b>	
C70	Malignant neoplasm of cerebral meninges
C71	Malignant neoplasm of brain
C72	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
D32	Benign neoplasm of meninges
D33	Benign neoplasm of brain and other parts of central nervous system
D42	Neoplasm of uncertain behavior of cerebral meninges
D43	Neoplasm of uncertain behavior of brain and central nervous system





First author, year	Country	Population	Design	Exposure assessment	Outcome(s)	Major results	NOS scores
Boice et al. 2021	USA	55,218 (M), 53,801 (F) medical and associated radiation workers	Cohort	Mean cumulative absorbed dose to the brain: 18.9 mGy (max: 1.08 Gy)	Brain, central nervous system cancer (ICD-9: 191, 192.0-192.1)	SMR (95% CI): 0.89 (0.76, 1.04), n <sub>deaths</sub> = 167	8
Lee et al. 2021	South Korea	53,582 (M) and 40,338 (F) diagnostic medical radiation workers	Cohort	Mean cumulative badge dose: 7.20 mSv (IQR 0.21-5.41 mSv)	Brain, central nervous system cancer (ICD-10: C70-C72)	SIR (95% CI): 1.45 (0.94, 2.24), n <sub>diseases</sub> = 43 (M/F) SIR (95% CI): 1.04 (0.72, 1.52), n <sub>diseases</sub> = 27 (M) SIR (95% CI): 1.61 (0.98, 2.62), n <sub>diseases</sub> = 16 (F)	8
Zielinski et al. 2009	Canada	23,580 (M), 43,982 (F) medical radiation workers	Cohort	Cumulative lifetime dose: 3.78 mSv	Brain, central nervous system cancer (ICD: NA)	SMR (90% CI): 0.61 (0.40, 0.90), n <sub>deaths</sub> = 19 (M/F) SMR (90% CI): 0.68 (0.39, 1.11), n <sub>deaths</sub> = 12 (M) SMR (90% CI) 0.52 (0.25, 0.98), n <sub>deaths</sub> = 7 (F) SIR (90% CI): 0.72 (0.52, 0.97), n <sub>diseases</sub> = 32 (M/F) SIR (90% CI): 0.95 (0.64, 1.36), n <sub>diseases</sub> = 22 (M) SIR (90% CI): 0.47 (0.26, 0.80), n <sub>diseases</sub> = 10 (F)	8
<b>Nuclear weapons test participants</b>							
Tao et al. 2022	USA	145,023 (M) shipyard radiation workers	Cohort	Mean lifetime dose: 15.4 mSv, median: 0.82 mSv.	1 - Brain, central nervous system cancer (ICD: NA) 2 - Benign neoplasm of the eye, brain, and other part	1 - SMR (95% CI): 0.81 (0.73, 0.89), n <sub>deaths</sub> = 372 2 - SMR (95% CI): 0.90 (0.55, 1.38), n <sub>deaths</sub> = 20	8
Gillies et al. 2022	UK	21,357 servicemen and male civilians from the UK who participated in the UK's atmospheric nuclear weapon tests and experimental programmes and 22,312 controls	Cohort	1,716 test participants had a non-zero recorded radiation dose: mean: 10 mSv, and 81 participants were recorded as having received 50 mSv or more.	1 - Brain and CNS tumors (ICD: NA) 2 - Benign brain and CNS (ICD: NA)	1 - SMR (95% CI): 1.02 (0.84, 1.22), n <sub>deaths</sub> = 116 1 - SIR (95% CI): 1.12 (0.95, 1.32), n <sub>diseases</sub> = 146 1 - RR <sub>mortality</sub> (90% CI): 0.99 (0.80, 1.22) 1 - RR <sub>incidence</sub> (90% CI): 1.05 (0.87, 1.27) 2 - SIR (95% CI): 2.08 (1.50, 2.80), n <sub>diseases</sub> = 43 2 - RR <sub>incidence</sub> (90% CI): 1.97 (1.29, 3.02)	8
Boice et al. 2020	USA	114,270 (M) military participants at eight aboveground nuclear weapons test series	Cohort	Mean gamma radiation dose: 6 mSv (max: 908 mSv)	Brain, central nervous system cancer (ICD-9: 191-192)	SMR (95% CI): 0.94 (0.86, 1.03), n <sub>deaths</sub> = 495	7
<b>Flight attendants</b>							
Dreger et al. 2020	Germany	6,006 (M) cockpit crew, 14,048 (F) cabin crew	Cohort	Median cumulative effective doses: 44.1 mSv (IQR: 30.5-54.1, max: 99.7) and 25.1 mSv (IQR: 10.5-46.6, max: 96.7) for male cockpit and female cabin crew respectively	Brain, central nervous system cancer (ICD: NA)	SMR <sub>c</sub> (95% CI): 2.01 (1.15, 3.28), n <sub>deaths</sub> = 23 (M); SMR <sub>c</sub> (95% CI): 1.26 (0.60, 2.36), n <sub>deaths</sub> = 14 (F)	8
Yong et al. 2014	USA	5,958 (M), 6 (F) cockpit crew	Cohort	Mean annual cosmic radiation dose: 1.4 mSv (median: 1.4 mSv, range: 0.0042-2.8 mSv)	Brain, central nervous system cancer (ICD: NA)	SMR (95% CI): 1.39 (0.95, 1.96), n <sub>deaths</sub> = 32	8

First author, year	Country	Population	Design	Exposure assessment	Outcome(s)	Major results	NOS scores
Pinkerton et al. 2012	USA	1,701 (M), 9,610 (F) flight attendants	Cohort	Median estimated cumulative radiation dose: 12.7 mSv (range: 0.33-102 mSv)	Brain, central nervous system cancer (ICD: NA)	SMR (95% CI): 1.03 (0.56, 1.73), $n_{\text{deaths}} = 14$ (M/F) SMR (95% CI): 1.97 (0.72, 4.30), $n_{\text{deaths}} = 6$ (M) SMR (95% CI): 0.76 (0.33, 1.49), $n_{\text{deaths}} = 8$ (F)	7
Pukkala et al. 2012	Finland, Iceland, Norway, Sweden	1,559 (M), 8,507 (F) airline cabin crew	Pooled cohort	Estimated cosmic radiation dose (mSv) according to the percentage of cabin crew members: <5: 30%; 5-14.9: 34%; 15-34.9: 29%; $\geq 35$ : 6%.	Brain, central nervous system cancer (ICD-7: 193)	Entire follow-up: SIR (95% CI): 0.92 (0.60, 1.34), $n_{\text{diseases}} = 26$ Female are cabin crew: SIR (95% CI): 0.85 (0.52, 1.31), $n_{\text{diseases}} = 20$ Male cabin crew: SIR (95% CI): 1.28 (0.47, 2.79), $n_{\text{diseases}} = 6$	7
Pukkala et al. 2003	Denmark, Finland, Iceland, Norway, Sweden	10,051 (M) airline pilots	Pooled cohort	Estimated dose ( $\mu\text{Sv}$ ) according to the percentage of airline pilots: 1-2,999: 46%; 3,000-9,999: 15%; 10,000-19,999: 14%; $\geq 20,000$ : 11%.	Brain, central nervous system cancer (ICD: NA)	SIR (95% CI): 0.84 (0.50, 1.33), $n_{\text{diseases}} = 18$	7
<b>Chernobyl cleanup workers</b>							
Rahu et al. 2013	Estonia, Latvia, and Lithuania	17,040 Chernobyl cleanup workers (M)	Cohort	Average dose: 10.9 cGy (9.9 cGy, 11.8 cGy and 10.9 cGy in Estonia, Latvian, and Lithuanian sub-cohorts respectively)	1 – Brain, central nervous system cancer (ICD-10: C70-C72) 2 – Brain (ICD-10: C71)	1 – SIR (95% CI): 1.34 (0.92, 1.89), $n_{\text{diseases}} = 32$ 2 – SIR (95% CI): 1.25 (0.83, 1.81), $n_{\text{diseases}} = 28$	8

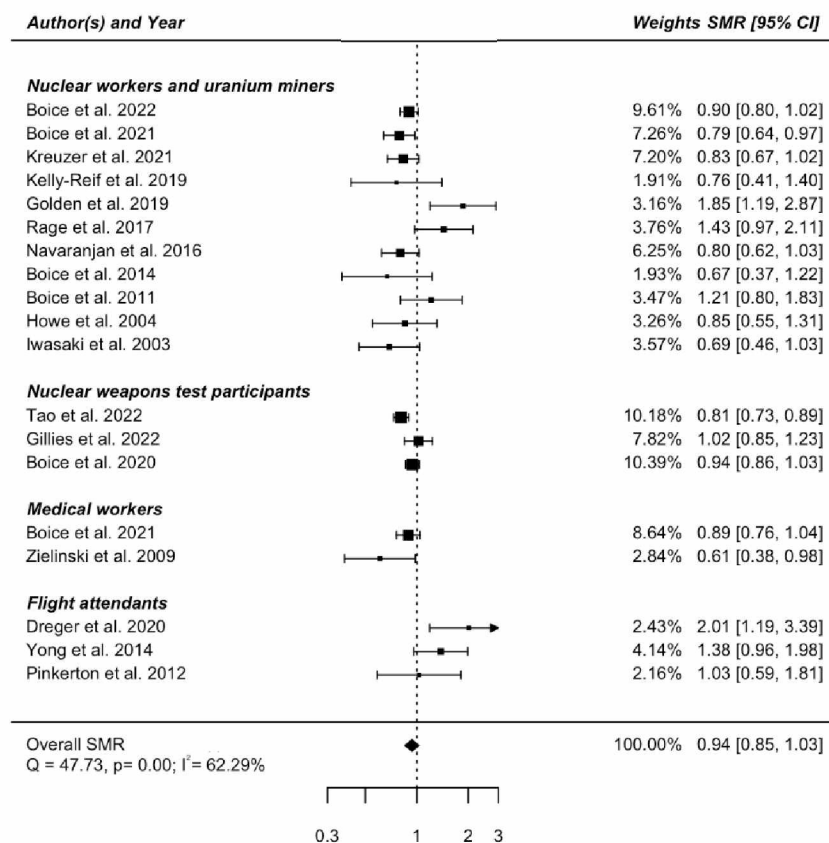


Figure S1: Standardized mortality ratio (SMR) and 95% confidence interval (CI) for brain/CNS tumors death in IR exposed populations compared with general populations as reference.

$SMR_{pooled}$  was calculated using both the natural logarithms of the SMRs and their standard errors for each included study. The standard error of log-SMR was estimated by  $\ln \left( \frac{SMR_{upper\ CI}}{SMR_{lower\ CI}} \right) / 3.92$ . The log-SMRs were then pooled together to generate and plot an overall effect size using the DerSimonian–Laird random-effect method. Lastly, the pooled log-SMRs were exponentiated as a back-transformation for interpretation. When only observed (D) and expected (E) numbers of deaths were reported in the studies, the SMR and associated lower and upper 95% CI-bounds were calculated as follows:  $SMR = D/E$ ,  $SMRL = SMR \times \left( 1 - \frac{Z\alpha}{2D^{1/2}} \right)^2$ , and  $SMRU = SMR \times \left( \frac{D+1}{D} \right) \times \left( 1 + \frac{Z\alpha}{2(D+1)^{1/2}} \right)^2$ , where  $Z\alpha$  is the  $100(1-\alpha/2)$  percentile of the unit normal distribution and  $\alpha=0.05$ .



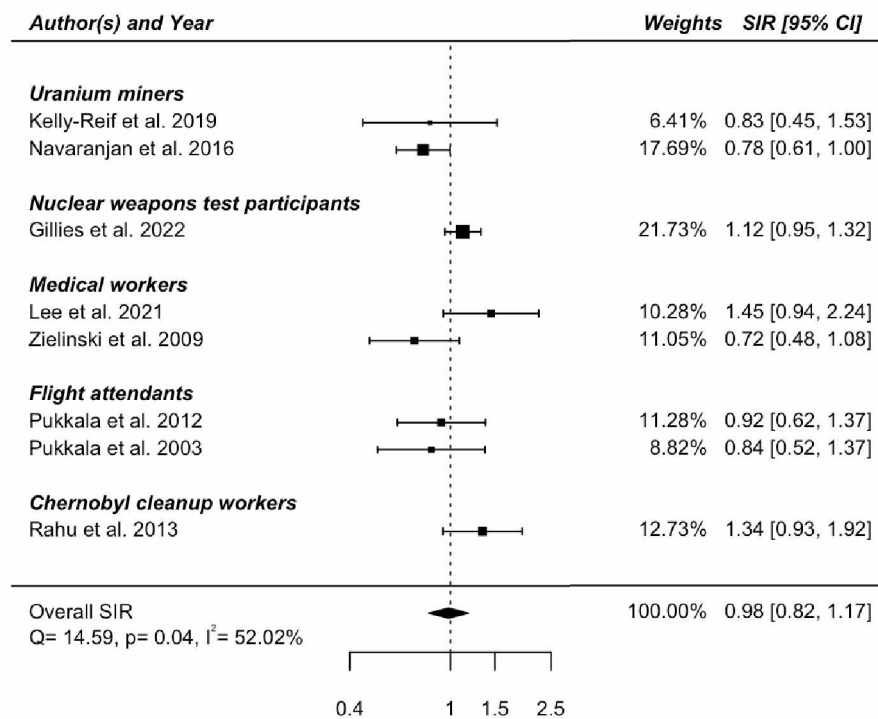


Figure S2: Standardized incidence ratio (SIR) and 95% confidence interval (CI) for brain/CNS tumors morbidity in IR exposed populations compared with general population as reference. The same statistical method as for the calculation of the SMR was performed.

