Exposure to low-dose radiation in occupational settings and ischaemic heart disease: a systematic review and meta-analysis

Cheryl E Peters,1,2,3 Emma Kathleen Quinn,4 Laura Andrea Rodriguez-Villamizar,4,5 Heather MacDonald,6 Paul J Villeneuve

ABSTRACT

Ionising radiation is a human carcinogen, but the evidence is less clear that exposure to low-dose ionising radiation (LDIR) increases the risk of adverse cardiovascular outcomes. We synthesised the literature of chronic occupational exposure to LDIR and cardiovascular disease, particularly for ischaemic heart disease (IHD).

The literature search was conducted using three databases including studies published between 1990 and 2022. A quality assessment of the studies was completed using the Office of Health and Assessment and Translation Risk of Bias Rating Tool. We conducted meta-analyses for IHD mortality using random effects models using measures of excess relative risk per sievert (ERR/Sv) obtained from internal cohort comparisons, as well as with standardised mortality ratios (SMRs) from external cohort comparisons.

We identified 2189 articles, and of these, 26 provided data on IHD and were retained. Most studies were classified as having a ‘moderate’ level of risk of bias. Fourteen and 10 studies reporting external radiation doses were included in meta-analyses using SMR and ERR/Sv, respectively. The meta-summary SMR was 0.81 (95% CI 0.74 to 0.89) with evidence of reduced risk but high heterogeneity across studies. For internal cohort measures, the summary ERR/Sv for a lagged exposure of 10 years was 0.10 (95% CI 0.01 to 0.20) with low heterogeneity. The subgroup analysis by lagged exposure time showed the strongest association were for the 15 and 20 years lag.

Our findings suggest that occupational exposure to LDIR increases the risk IHD mortality and highlight the relevance of internal cohort comparisons.

INTRODUCTION

Ionising radiation is an established human health hazard and is well-characterised for the physical harms it causes, and its role as a carcinogen.4 The classification of ionising radiation as a human carcinogen is based on animal studies, as well as evidence provided by studies of survivors of nuclear events, those with occupational exposures and patients treated with low doses and there is recent evidence of cancer risk related to low-dose ionising radiation (LDIR) exposure.5,6

There is an increased recognition of the adverse impacts of therapeutic or other LDIR exposure on the heart and coronary arteries.7 A systematic review by Little et al8 concluded that, at low or moderate doses, ionising radiation increases the risks of developing ischaemic heart disease (IHD) and cerebrovascular disease (CeVD). However, they also noted that the ‘patterns of risk reported are not straightforward’. While their review did not undertake a meta-analysis, an earlier paper by the same authors reported a statistically significant excess relative risk (ERR) per Gy for IHD (0.082 9% CI 0.057 to 0.106).9 Analysis of the International Nuclear Workers Study (INWORKS) cohort, a study of nuclear energy workers, also found
excess risks for circulatory system diseases. Workers exposed to low-dose radiation represent an important study population to evaluate cardiovascular outcomes because of their large numbers and relevance for the extrapolation of risks to the general population. According to the United Nations Scientific Committee on the Effects of Atomic Radiation, approximately 24 million workers worldwide are exposed to ionising radiation, and 48% of them are exposed from anthropogenic sources. Despite previous attempts to characterise cardiovascular risks across diverse study populations there are remain several uncertainties due to heterogeneity in published risk estimates.

This heterogeneity may be due to a number of factors, including different effects by disease subtype (eg, heart disease, stroke, cardiovascular disease), sources of ionising radiation and nature of exposure (ie, acute vs chronic), study populations and quality of the exposure assessment. Some reviews have combined populations with disparate exposure profiles (ie, Japanese atomic bomb survivors, radiotherapy patients and workers), which, while helpful to increase statistical power (ie, sample size) may introduce heterogeneity that could obscure possible effects.

The biological effects of ionising radiation on human organs differ depending on the irradiation doses, with higher doses typically producing more severe and/or immediate effects. While there are ongoing discussions about the definition of low-dose radiation, it is typically considered as doses under 0.5 Gy, and the molecular mechanisms that are generated in response to low-dose radiation exposure are not well understood.

Worldwide, there are a variety of occupational cohorts exposed to ionising radiation that vary substantially by size, geography and data quality, and particularly the characterisation of exposure. These include studies of nuclear workers, uranium mining and processing, the cleanup workers from Chernobyl disaster, and medical diagnostics. Dose limits set for workers have typically been based on the risk of various cancers that are known to arise from ionising radiation exposure, and these limits tend to rely on linear non-threshold models that relate to DNA damage and mutagenesis. However, the increasing evidence building for diseases of the circulatory system speaks to additional human biological processes and there is a need to better understand the possible relationship between LDIR exposure and harms to the circulatory system to protect workers.

IHD is a leading cause of death worldwide, affecting an estimated 126 million people worldwide (1.7% of the world’s population). Indeed, cardiovascular diseases account for an estimated one-third of deaths globally, and among cardiovascular illnesses, IHD is the most common death. There are a variety of risk factors for IHD, but from a biological perspective, it arises from atherosclerosis or inflammation of the arteries.

The occurrence of IHD is higher in populations with metabolic syndrome and with advancing age, and these factors are thought to be driving the rapid increase in the global prevalence of IHD in recent decades.

The overall aim of this review was to synthesise previously published risk estimates of occupational LDIR exposure and cardiovascular disease using a systematic review and meta-analysis (SRMA) methodology. As previously mentioned, there is evidence to suggest that doses in excess of >0.5 Gy, both in occupational settings and from studies of nuclear accidents, increases the risk of developing cardiovascular disease. To date, however, it is unclear whether LDIR exposure (<0.5 Gy) increases the risk of cardiovascular disease, and an ongoing debate surrounding the dose threshold for circulatory disease, particularly since the ICRP’s report in 2012 suggesting a threshold of 0.5 Gy. Also, there are uncertainties about the shape of the dose-response curve. These research gaps motivated our present SRMA, as the prevalence of workers exposed below this threshold is high. Therefore, summarising findings from occupational cohorts is important from the perspective of radiation protection, and relevant for advancing our understanding of the relationship between LDIR and IHD.

METHODS
Search strategy and selection process
We developed a rigorous search strategy in collaboration with a librarian (HM) and systematically searched PubMed, SCOPUS and Web of Science for peer-reviewed papers published in English between 1990 and 31 December 2022. The full list of terms used to search the databases is provided in online supplemental material. In brief, we searched for terms related to ionising radiation (including its various forms), a specifier for low dose or moderate dose, terms related to job or occupation, and cardiovascular disease (including IHD, stroke and CeVD). In particular, we were interested in doses below 0.5 Gy, and the characterisation of risks for exposures less than 0.1 Gy, where possible. The review was registered with Prospero (the International Prospective Register of Systematic Reviews) with the identification number of 268885. Due to the wide variety of exposure sources and disease outcomes included in this study, we grouped analyses into subreviews; this study provides the results for occupational LDIR exposure and subsequent risk of IHD. Studies were identified, screened for eligibility and included in accordance with adapted Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

We implemented screening procedures using the Covidence systematic review software (http://www.covidence.org). We applied a predesigned screening tool to guide the reviewers through including or excluding abstracts. Eligibility criteria included that the paper was written in English; that it included data on cardiovascular disease, IHD, stroke or CeVD; that the exposure of interest was ionising radiation; that the setting of exposure was occupational in nature; that the paper reported risk estimate(s) for cardiovascular disease based on exposures less than 0.5 Gy; and that the study design was either cohort, case-control or cross-sectional. If it was not evident that all these criteria were satisfied following a review of the abstract, the paper was retained for a full text review. Abstracts were screened in duplicate by independent reviewers (EKQ and CEP), and conflicts were resolved by consensus. Full text review was also completed in Covidence and if the paper was later discarded, the reason for excluding was noted. This step was accomplished by using a second screening tool with ordered reasons for exclusion to ensure each reviewer considered the exclusion criteria in the same order. Any conflicts at this stage were resolved by consensus with the input of a third reviewer (PJV), if necessary. We compare responses between independent reviewers using Cohen’s Kappa. Our literature search identified multiple publications of the same study population. When this occurred, we prioritised publications of the same study population if they had longer follow-up and more cases, or if they included more detailed breakdowns of radiation dose at lower levels, or if they had more detailed information on confounders.

Data extraction and risk of bias assessment
Data extraction was completed using standardised forms and a detailed instruction manual. Three independent reviewers (CEP, EKQ and LAR-V) extracted all study data. Data elements
abstracted included: author, study design, methods to characterise exposure, and identify outcome, sample sizes, number of cardiovascular events, exposure profile, and measures of association. Reviewers again resolved disagreement to reach consensus.

The quality of data retrieved from the individual studies was assessed using the Office of Health and Assessment and Translation (OHAT) Risk of Bias Rating Tool for Human and Animal Studies. This assessment was carried out by two reviewers (EKQ and CEP). The studies were classified into tiers based on the following criteria: Tier 1 includes studies where key study elements (selected as control of confounding, strength of the exposure assessment and accuracy/completeness of the health outcome assessment) were rated as ‘low’ or ‘probably low’ risk of bias and had most other OHAT tool items answered as ‘low’ or ‘probably low’ risk of bias; Tier 2 includes studies where neither the criteria for tier 1 or tier 3 were met; and tier 3 includes studies where key study elements were rated as ‘high’ or ‘probably high’ risk of bias and have most other OHAT tool items answered as ‘high’ or ‘probably high’. Any disagreements in bias assessments classification were resolved between the reviewers afterwards, and if a resolution could not be reached, were resolved by the senior author (PJV).

Statistical procedures
Following the data extraction and quality assessment steps, we carried out two separate meta-analyses. The first used standardised mortality ratios (SMRs) as measures of associations that are based on external cohort comparisons. Usually, this involved comparing mortality rates for cardiovascular disease in the occupational cohort to the general population. The second meta-analysis was based on summary measures of excess of relative risk (ERR) per unit (Sv/Gy) of radiation exposure based on internal cohort comparisons. We used ERR/Sv as most studies reporting risk estimates for whole-body or organ-specific external radiation doses used equivalent dose (Sv) measures. We included studies reporting risk measures in Gray (Gy) such as ERR/Gy or mGy as unweighted absorbed doses in Gy are very similar to equivalent doses in Sv. For internal meta-analysis we excluded measures from Azizova et al., as this study reported information for liver as exposed organ and the study from Azizova et al. was already included and provided similar information for the same cohort while using whole body dose exposure. We fit random-effects models that used the inverse variance method to generate forest plots and summary measures of association with 95% CIs. The F statistic was used to evaluate heterogeneity, considering F>75% as high heterogeneity. For the studies reporting internal comparisons (ERR/Sv), a subgroup exploratory analysis was conducted using different lags of exposure (5, 10, 15 and 20 years) to explore the effects of latency. We evaluated the potential for publication bias using funnel plots and Egger’s test. The ‘trim-and-fill’ method was applied to correct the summary measure of association when publication bias was found. All analyses were conducted in Stata V.13.

RESULTS
Selection and characteristics of studies
We identified 2189 papers in our initial search from which 59 were ultimately deemed relevant to be retained. Specific reasons for the exclusion of studies are provided in figure 1. Of the 59 retained studies, 26 included data on IHD and were included in the present paper. At abstract screening, the proportionate agreement between the two reviewers was 0.96, with a Cohen’s Kappa of 0.68, indicating substantial agreement. For the full-text screening, the proportionate agreement was 0.73, with a Cohen’s kappa of 0.47, indicating moderate agreement, though all conflicts were ultimately resolved. Except for three studies that evaluated incidence, all other included studies were based on IHD mortality outcomes. Most studies reported external cumulative whole body dose and nine studies reported organ-specific external or internal doses to the lung, liver, heart or other organs. Online supplemental table S1 documents relevant details of the 26 included studies (see online supplemental file 1). Characteristics of the studies including estimates of measures SMR or ERR were included online supplemental table S2.

Risk of bias assessment
A high-level summary of the OHAT Risk of Bias analysis is depicted in figure 2, while a detailed summary for each domain of bias for each paper is provided in online supplemental figure S1. Overall, the risk of bias across our included studies was moderate, with only two studies falling in tier 1 and the remaining falling in tier 2 in terms of quality (ie, none of our studies fell into the lowest tier—tier 3—with respect to risk of bias). Most of the risks of bias found in our study subset were around the control of confounders and the quality of the exposure assessment, which is typical for observational studies. Selection bias was also of ‘probably high’ concern for approximately 31% of our included studies.

Association between occupational LDIR exposure and IHD mortality
There were 14 studies that reporting comparisons of the IHD mortality in populations occupationally exposed to LDIR with the general or another reference population used to derive the SMR. The summary results of these studies comparing exposure with general population are presented in figure 3. The overall SMR was 0.81 (95% CI 0.74 to 0.89) suggesting a reduced risk compared with general population but with a high degree of heterogeneity across studies (F=97.8%, p<0.01). The study from Zablotska et al., in Canadian uranium processing workers compared with general Canadian population, was the only study that reported a SMR above one, however, this finding was not statistically significant.

There were 20 studies that reported results for internal comparisons of the exposed populations reporting results for external doses, 1 study reporting results for internal doses only and 4 studies reported both external and internal doses. The reports are given in terms of ERR, risk ratios (RRs) or HR; however, the categories used for doses response assessment (RR and HR) differed widely across studies which made it impossible to produce summary meta-analysis estimates across different dose categories. Results were more uniformly reported for cumulative exposure using ERR/Sv-Gy as an effect measure and usually these estimates were based on an exposure with a 10-year lag.

There were 10 studies reporting internal comparisons of the IHD mortality in populations occupationally exposed to LDIR using ERR/Sv-Gy as the measure of association. The summary results of these studies regarding external exposure with by 5 years of lagged exposure time are presented in figure 4. The overall ERR/Sv for 10-year lag exposure was 0.10 (95% CI 0.01 to 0.20) with very low non-statistically heterogeneity across
the nine studies ($I^2=14.7\%$, $p=0.280$). The studies from Kreuzer et al, in the cohort of German uranium miners, from Boice et al, in the US cohorts of nuclear plant workers and medical workers, and the multicountry study of Vrijheid et al, reported a reduction in risk (negative coefficient) which were not statistically significant. The subgroup analysis for lagged exposure time found that the summary effect sizes were similar for 5-year and 10-year lags and increased about three times for the 15 and 20 years lags (ie, ERR/Sv measures of 0.09, 0.10, 0.023 and 0.24 with lags of 5, 10, 15 and 20 years, respectively). This analysis suggests that the IHD mortality risk increase over time of exposure, however, the 95% CIs overlap among these lag categories which suggest these differences in risks were not statistically significant (figure 4).

The funnel plot suggested some modest asymmetry in the published SMR estimates (see online supplemental figure S2). The Egger’s test, however, was not statistically significant for the SMR measure (bias coefficient=4.85, $p=0.139$) or the ERR/Sv measure (bias coefficient=0.41, $p=0.346$), and therefore, we did not correct the summary measure for publication bias.

**DISCUSSION**

In this updated systematic review of occupational radiation exposure and cardiovascular disease mortality that included published studies through 2022, we derived summary measures of association using meta-analysis. We found a statistically significant excess of risk for IHD mortality among workers exposed to low doses ionising radiation when risks based on internal cohort

Figure 3  Meta-analysis of association between ischaemic heart disease mortality and low-dose occupational radiation exposure expressed as standardised mortality ratio (SMR) with comparisons to general population.
comparisons were used. In contrast, for published measures of association between exposed workers and the general population, we found a statistically significant lower mortality ratio among exposed workers. This SRMA included exposed populations of energy nuclear workers, uranium miners, nuclear weapons workers, medical and radiological technologists. Additionally, a wide spectrum of occupational activities and cumulative external doses (dose ranged between <0.005 and 0.5 Gy) were found within the studies included. Variations in follow-up periods reported allowed for analyses exploring lagged effects of up to 20 years that suggest a potential differences in dose-effect, still non statistically significant. This SR included 22 studies with IHD mortality compared with 10, 16 and 22 studies available included in Little’s previous SRMA in 2012, 2016 and 2023,5 9 50 which reported results combined for occupational studies and studies in atomic-bomb survivors.

Our finding of a reduced risk of IHD in exposed workers compared with the general population are consistent with the healthy worker effect.51 In our view, this is due to the distribution of different risk factors and health status itself that select people for certain jobs such as radiation-exposed jobs. The study from Zablotska et al was the only reporting an SMR above 1, but this result was not statistically significant.35 The effect of this study on the summary SMR is a potential explanation for the high heterogeneity found in this meta-analysis. Also, the characteristics of the specific cohorts of workers and the different mortality risks in the general populations across countries, might have an important effect in the heterogeneity of the SMR summary measure. Due to these substantial differences in background risk between workers in included studies and the general populations they were compared with, internal comparison of risks (ERR/Sv) within cohorts may be more informative, but do not represent the estimated risk for the general population exposed to any background LDIR, which under similar conditions might be higher.

Our meta-analysis findings that relied on internal comparisons of risk (ie, within worker cohorts) indicated an ERR of death from IHD of 10% per Sv (95% CI 1 to 20) for 10-year lagged exposure, which is similar when comparing to the previous meta-analysis reported by Little in 2012 (ERR/Sv=10% (95% CI 4% to 15%).50 Our summary estimate for 5-year lagged exposure was 9% of ERR/Sv, which was not statistically significant but similar to the estimate reported by Little in 2016 using mostly the 5-year lagged exposure (ERR/Gy=8.2%, 95% CI 3.7% to 10.6%). These previous meta-analyses included morbidity and mortality outcomes for IHD, as well as a combination of occupational exposure with those of the Japanese atomic-bomb survivors, for which ERR for IHD incidence was lower compared with most occupational cohorts.5 Our estimates for 10-year lagged exposure were slightly lower comparing to those reported by Little in 2023 for IHD mortality at doses <0.5 Gy (ERR/Gy=13% (95% CI 1.9% to 28%), but similar to our meta-ERR/Sv when
considering all lagged exposures (figure 4, ERR/Sv = 14%, 95% CI 7% to 21%)⁵; this study also included atomic-bomb survivors, environmental and occupational exposures combined. Our review focused only on those with low-dose occupational exposure and mortality outcomes which could explain some of the observed difference. Our study also conducted a subgroup analysis based on cumulated lagged dose that was not conducted in the mentioned previous meta-analyses. The summary ERR/ Sv might be sensitive to the characteristics of the newly added studies. A decrease of more than twice in the summary measures (ERR/Sv) were reported by Little et al, in a sensitivity analysis for risk of exposure to low/moderate dose on circulatory disease when including atomic bomb survivors and medical radiation studies to occupational studies.⁵²

The subgroup analysis explored summary effects for 5, 10, 15 and 20 years of latency. These findings showed no evidence of statistically significant heterogeneity within lagged groups of exposure and incremental excess of risk over length of lag. This finding points towards IHD being a late-effect risk after occupational LDIR exposure, however, the lagged categories were not statistically significantly different from one another. This analysis, however, was limited to the results from only two or three cohort studies for subgroups different to the 10 years lag, and future analyses as new or other available cohorts become more mature could provide more insight into the latency between LDIR exposure and risk of IHD.

We observed low heterogeneity within subgroups of lagged exposure, which suggest that differences in the length/latency of exposure across cohorts is an important contributor to the heterogeneity of the ERR/Sv. More interestingly, this finding might also suggest that similar risk levels for each lagged exposure can be assumed for LDIR-exposed workers in different occupations as the cohorts for this analysis included nuclear workers, uranium miners and radiation workers.⁶ ⁴⁷ ⁴⁹ Increasing risk over time-since-exposure trends have been reported by Vrijheid et al in a multicountry nuclear workers study.⁴¹ The reports for the Japanese atomic bomb survivors exposed to LDIR have also indicated little evidence of nonlinearity in the dose-response curve for circulatory disease.⁵³ ⁵⁴ In contrast, the follow-up study in the Mayak Russian nuclear workers reported no differences in risk of IHD mortality (ERR/Gy) related to incremental length of exposure from 5 to 20 years.⁴³

We presented findings based mainly on whole-body cumulative external radiation and few studies reporting organ-specific cumulative external radiation and reporting IHD mortality as an outcome. The studies in uranium processing workers⁴⁶ estimated total (internal and external) dose to the heart finding a non-statistically significant excess of risk from IHD (ERR/100 mGy 0.13, 95%CI ~0.01 to 0.28). The studies in US medical radiation workers and power plant workers also estimated heart-specific external doses and found no evidence of statistically significant excess of risk from IHD (figure 4).³⁸ ³⁹ The study in nuclear weapons laboratory workers also estimated organ-specific internal doses finding no evidence of statistically significant excess of risk from IHD (ERR/100 mGy ~0.06, 95%CI ~0.16 to 0.04). Some studies reporting relative risks (RR) or HR for specific exposure dose categories were not included in our meta-analysis of internal comparisons as their categories were not comparable;⁴¹ ⁴⁶ ⁴⁷ ⁵⁵ ⁵⁶ the estimated risk for these studies were not statistically significant except for the study from X-ray workers in China that reported an RR 1.4 (95% CI 1.1 to 1.7).²¹ The study by Cha et al was excluded from meta-analysis as IHD mortality was not reported; this study reported IHD incidence for specific cumulative heart dose in a cohort of diagnostic radiation workers in South Korea, with reported ERR/100 mGy of 1.22 (95% CI −0.71 to 4.73), the highest risk level reported from the included studies.²⁰ Estimations of ERR based on radiation dose to the heart/brain have been higher compared with estimations obtained from mostly whole-body external radiation doses.³ Further analysis will be needed as more studies with organ-specific doses become available to have a better understanding of these risk compared with whole-organ external doses.

The literature suggests that there are common biological mechanisms for high and LDIR and the risk of cardiovascular diseases. At high doses exposure (>10 Gy) there is evidence of radiation-induced acute microvascular disease (injury of small vessels) and chronic macrovascular disease (affectation of coronary arteries). For both pathological processes, the main biological mechanism described is inflammation followed by proinflammatory signal cascades and atherosclerotic changes similar to the pathogenic process described for IHD from other exposures such as metabolic syndrome and ageing.²² ²⁷ Possible biological mechanisms of cardiovascular diseases related to moderate to low doses exposure (<5 Gy) include damage to endothelial cells and proinflammatory responses.²⁸ Less information from animal and human studies is available for understanding the biological mechanisms of exposure to LDIR, but recent data suggest the mechanisms may differ according to the dose and the state of the tissue irradiated.⁸ In the presence of healthy endothelial cells, the exposure to LDIR continuous of fractionated has shown to induce intracellular reactive oxygen species and oxidative stress that may accelerate vascular inflammation and atherosclerotic plaque formation. However, in the presence of endothelial cells that are already in an inflammatory state, LDIR seems to have an anti-inflammatory effect and low doses of irradiation therapy have been used in clinical treatments of non-malignant inflammatory and degenerative diseases.⁵⁷ Other biological mechanism of effect of LDIR is the direct damage to DNA with alterations of cell senescence and apoptosis that turns into epigenetic and metabolic changes and accelerated ageing.⁸ Further cellular, animal and human studies are needed to better describe and understand the biological mechanism of the effects of exposure to LDIR.

The risk of bias was low or probably low for nearly all studies across the domains of selective reporting bias, other statistical methods anomalies, outcome reporting bias, attrition/exclusion bias and any other source of bias. However, a significant proportion of our included studies were at high or probably high risk for selection bias (31%), detection bias (69%) and confounding bias (81%). However, these biases are known to be more prevalent in observational studies due to issues with designing and carrying out epidemiological investigations in large populations.⁶⁰ Examples of confounding bias detected in our studies included lack of adjustment for any factors beyond age and sex, such as socioeconomic status, smoking, alcohol consumption, dietary information, other occupational exposures or physical activity, which are all important risk factors for cardiovascular disease.⁶⁴ The ways in which occupational exposure to ionising radiation interacts with these risk factors has not been well studied, and indeed many of the occupational cohorts with data on ionising radiation exposure were unable to control for the effects of body size and other risk factors for IHD. A notable exception is the Mayak cohort of nuclear workers in Russia since it included information on confounding factors, and has information on both incidence and mortality.³¹ This study observed a statistically significant positive exposure–response relationship between increasing external radiation dose, and there was
limited impact on the estimates from the confounding factors. These sources of bias in our included studies are likely to have had some effect on the summary estimates that we produced across our two meta-analyses and it is possible that they could at least partly explain the modest effect sizes seen in our results.

Further analysis of radiation workers including other biological, clinical, lifestyle and behavioural risk factors will be needed to control for the effect of these exposures on IHD diseases and mortality. Using big data, linkage methods of records with administrative data, and other existing cohorts, is needed to rule out confounding and provide evidence for potential causation. Studies assessing internal organ-specific doses and their effects may assist in breaking down confounders, particularly through large cohort with individuals’ health records. Lastly, we recommend that studies that rely on incidence measures of cardiovascular mortality be carried out where possible, as they would be best capable to provide insights about the length of exposure latency period between time of first exposure and disease onset.

A key strength of this study was the comprehensive search of available literature in multiple databases and the use of the OHAT risk of bias assessment to study quality. All studies used standardised diagnostic codes appropriate for the time period of the cohort, often in combination with extensive quality checks across data sources (eg, cross-referencing medical records, case histories, autopsy report). As a result, the potential misclassification for the cause of death is lower than those that rely on morbidity as cardiovascular outcome. The detection of and registration of deaths, however, could differ across countries and over time, and thus is also a potential source of misclassification that cannot be ruled out from the original studies. However, most studies have been conducted in countries with strong vital statistics systems; and as a result, we expect the resulting bias to be minimal.

In conclusion, our systematic review and summary risk measures add to the existing literature investigating the potential association between LDIR and IHD mortality. An improved understanding of the risk of cardiovascular disease from LDIR exposure would be strengthened by investigations of more cardiovascular disease outcomes, such as ischaemic stroke. The inclusion of a range of occupational groups is useful to provide a more comprehensive view of the potential risk of IHD death after occupational LDIR exposure. The intersections between the biological mechanisms for LDIR exposure with other common risks for IHD mortality are challenging to investigate when data on other important risk factors for IHD were unable to be factored into the original studies. Our findings highlight a potential effect of occupational LDIR on IHD mortality, although it cannot be considered adequate evidence for causation. Further research will serve to support our understanding of the risk association with LDIR exposure for both occupational and environmental exposures, particularly regarding the risk of IHD.

**REFERENCES**


**Provenance and peer review** Not commissioned; externally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**

Emma Kathleen Quinn http://orcid.org/0000-0003-3130-259X
Paul J Villeneuve http://orcid.org/0000-0001-7786-7997

**Funding**

This project was funded by CANDU Owners Group Inc. Project No. SRD-734.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.
42

41

39

38

34

33

32

31

29

27

23

22

21

19

17


Although this document contains a variety of references to studies and reports, it does not appear to provide a coherent, focused analysis or review of any specific topic. The references are scattered and do not appear to form a logical sequence. The references include studies on the impact of radiation on various health outcomes, such as the risk of cardiovascular disease and cancer, as well as the epidemiology of ischemic heart disease. However, the document does not seem to present a comprehensive review or synthesis of these findings. It is possible that this document is a draft or preliminary version of a manuscript, and further work may be needed to organize the information and present it in a more coherent manner.

---

**Systematic review**

---