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Source: Radiation Research, 196(6) : 574-586

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RADE-21-00078.1

RADIATION RESEARCH **196**, 574–586 (2021)
0033-7587/21 $15.00

DOI: 10.1667/RADE-21-00078.1

Quantitative Bias Analysis of the Association between Occupational Radiation Exposure and Ischemic Heart Disease Mortality in UK Nuclear Workers

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de Vocht, F., Martin, R. M., Hidajat, M. and Wakeford, R. Quantitative Bias Analysis of the Association between Occupational Radiation Exposure and Ischemic Heart Disease Mortality in UK Nuclear Workers. *Radiat. Res*. 196, 574–586 (2021).

The scientific question of whether protracted low-dose or low-dose-rate exposure to external radiation is causally related to the risk of circulatory disease continues to be an important issue for radiation protection. Previous analyses of a matched case-control dataset nested in a large cohort of UK nuclear fuel cycle workers indicated that there was little evidence that observed associations between external radiation dose and ischemic heart disease (IHD) mortality risk [OR = 1.35 (95% CI: 0.99–1.84) for 15-year-lagged exposure] could alternatively be explained by confounding from pre-employment tobacco smoking, BMI or blood pressure, or from socioeconomic status or occupational exposure to excessive noise or shiftwork. To improve causal inference about the observed external radiation dose and IHD mortality association, we estimated the potential magnitude and direction of non-random errors, incorporated sensitivity analyses and simulated bias effects under plausible scenarios. We conducted quantitative bias analyses of plausible scenarios based on 1,000 Monte Carlo samples to explore the impact of exposure measurement error, missing information on tobacco smoking, and unmeasured confounding, and assessed whether observed associations were reliant on the inclusion of specific matched pairs using bootstrapping with 10% of matched pairs randomly excluded in 1,000 samples. We further explored the plausibility that having been monitored for internal exposure, which was an important confounding factor in the case-control analysis for which models were adjusted, was indeed a confounding factor or whether it might have been the result of some form of selection bias. Consistent with the broader epidemiological evidence-base, these analyses provide further evidence that the dose-response association between cumulative external radiation exposure and IHD mortality is non-linear in that it has a linear shape plateauing at an excess risk of 43% (95% CI: 7–92%) on reaching 390 mSv. Analyses of plausible scenarios of patterns of missing data for tobacco smoking at start of employment indicated that this resulted in relatively little bias towards the null in the original analysis. An unmeasured confounder would have had to have been highly correlated ($r_p > 0.60$) with cumulative external radiation dose to importantly bias observed associations. The confounding effect of "having been monitored for internal dose" was unlikely to have been a true confounder in a biological sense, but instead may have been some unknown factor related to differences over time and between sites in selection criteria for internal monitoring, possibly resulting in collider bias. Plausible patterns of exposure measurement error negatively biased associations regardless of the modeled scenario, but did not importantly change the shape of the observed dose-response associations. These analyses provide additional support for the hypothesis that the observed association between external radiation exposure and IHD mortality may be causal.

INTRODUCTION

At high radiation doses of approximately 5 Gy and above, direct damage to organs and tissues occurs, with damage to the heart and large arteries appearing within months of exposure (*1*). There is, however, epidemiological evidence of excess circulatory disease associated with doses below 0.5 Gy (*2*), although the evidence is not entirely consistent and patterns of risk are not straightforward (*3*). Plausible, if not completely understood, mechanisms exist by which acute high doses can affect the circulatory system (*4*) and result in heart disease (*5*), including damage to the structure of the heart and arteries (*6, 7*). For low-dose or low-dose-rate exposures, biological mechanisms, in which inflammatory and oxidate responses play an important role, have been proposed (*8, 9*).

Important evidence on the risk of diseases of the circulatory system from low-dose or low-dose-rate exposure

Editor's note. The online version of this article (DOI: https://doi.org/10.1667/RADE-21-00078.1) contains supplementary information that is available to all authorized users.

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comes from cohort studies of radiation workers (*10–16*), but important limitations in these studies are known to hamper all observational epidemiology. These include measurement error in the (retrospective) assessment of exposure, residual confounding from occupational and non-occupational factors, loss to follow-up and other issues of missing data, and possible selection effects including collider biases (*17*) and prevent strong inferences about the potential causal association between protracted exposures to low doses or low-dose rates and circulatory disease risk (*8, 18, 19*). Different patterns of lifestyle factors between facilities have been suggested as possible contributions for observed variations in exposure-response associations (*10*).

We previously conducted a matched case-control study nested within a cohort of 64,937 nuclear fuel cycle workers employed at four sites operated by the former British Nuclear Fuels Ltd (BNFL) (*11*), and which in turn was included within the UK National Registry for Radiation Workers (NRRW) and INWORKS studies (*10, 12*). The analysis of the case-control study specifically aimed at assessing the effect on ischemic heart disease (IHD) mortality of several postulated known or suspected confounding factors (*11, 12, 16, 20, 21*) for which information was available for the cases and controls but not the full cohort (*22*). In our published nested case-control study, we observed a comparable association between IHD mortality and the dose from external sources of radiation to that observed for the cohort from which the case-control population was drawn, indicating that postulated over-matching, previously observed in a matched case-control study of leukemia in the same population (*23*), was not an important issue. We further observed that pre-employment body mass index (BMI), systolic and diastolic blood pressure, smoking status, occupational noise exposure and shiftwork were not important confounding factors. Being monitored for potential intakes of radionuclides, however, did affect the observed associations between external radiation exposure and IHD mortality; the association with external dose being weaker for those monitored for internal exposure. Nonetheless, there was no association between IHD mortality and the dose from internally deposited plutonium and uranium, the principal intakes of radioactive materials in these nuclear fuel cycle workers. Patterns of monitoring for internal exposures are complex and differ over time and between sites, and as such it remains unclear whether this effect is of biological origin or resulted from bias or confounding (*22*). The validity of any occupational epidemiological study is determined by the extent by which systematic errors (e.g., biases) have been avoided or minimized (*24*), and within this study there remain a number of limitations which reduced the strength of inferences that could be legitimately made from these data.

Quantitative bias analysis aims to estimate the potential magnitude and direction of non-random errors in epidemiological studies and to quantify the uncertainty about these biases. It incorporates sensitivity analyses and simulation of bias effects under plausible scenarios (*25*). Bias analysis should consider the possibility that results are affected by uncontrolled confounding, selection bias or measurement error. Simple or multidimensional bias analysis can be conducted if bias parameters are known with certainty (or modeled as if they are), but these only examine the bias conferred by a limited set of parameters. An extension is the use of probabilistic bias analysis, in which probability distributions for each bias parameter are developed and Monte Carlo sampling techniques are used to generate frequency distributions of corrected effect estimates, given a set of plausible assumptions about the distribution of bias parameters (*26*). Bias analysis, therefore, is an important epidemiological tool, especially where studies discuss the plausibility of causality of the observed associations and where such conclusions may impact on policy decisions, as is the case in the discussion of protracted exposure to low-dose or low-dose-rate ionizing radiation and circulatory disease risk (*3*).

In the current study we perform sensitivity and probabilistic bias analyses to assess whether the association between external radiation exposure and IHD mortality is robust to several assumptions made in the original matched case-control analyses. We investigate issues of non-linearity in the exposure-response associations, exposure measurement error, missing data and uncontrolled confounding. Issues of selection bias are not investigated in the current study because, as a case-control study nested in an occupational cohort, they are thought to be minimal.

MATERIALS AND METHODS

Population

The analyses in this study were based on a matched case-control population (n = 1,220 pairs) nested in a cohort of all male industrial (weekly-waged, blue-collar) workers who started work aged 50 years or less between January 1, 1950 and December 31, 1998 and had worked for at least 1 month at one of two nuclear sites in the UK formerly operated by BNFL (Sellafield and Springfields, in North West England). Workers had worked for 1 month to 42 years at either site (median, 8 years). This was the same study population that formed the basis for previous work on associations between IHD mortality risk and external and internal radiation exposure (*22*), as well as for associations with shiftwork (*27, 28*) and noise (*29*). The workers were involved in the production and manual skilled and unskilled work associated with operating and maintaining nuclear fuel cycle plants. However, to minimize the impact of unmeasured confounding, here we limited the sample to industrial radiation worker pairs, while we also limited the study sample to matched worker pairs for which the controls had uncensored occupational histories (n = 715 pairs): radiation workers were identified as being monitored for exposure to external radiation and an identifier variable in the original dataset enabled exclusion of controls with censored occupational histories. The latter was done because inclusion of controls who were not monitored for external radiation exposure up to the death of the corresponding case but were monitored afterwards (information we do not have) would bias results (*22*). Employment duration was similar to the full case-control population (median, 8 years; range, 1 month to 42 years).

Potential factors that were previously suggested as possibly confounding factors in the observed associations between external radiation dose and IHD mortality (*11*) were included in these analyses, and were: systolic and diastolic blood pressure, BMI and tobacco smoking data (collected in pre-employment medical examinations); shift-work (ascertained from personnel records, records in the dosimetry department, and occupational health department records, and classified as ''ever or never engaged in shift-work for at least one month''); occupational exposure to noise [estimated using a job-exposure matrix derived from independent coding by occupational hygienists of noise levels above 85 dB(A)]; occupation (ascertained from employment records with longest-held occupation classified as either ''process workers'' or ''other workers''); and socioeconomic status based on longest held occupation (*22*).

Exposure Assessment

Estimates of annual equivalent doses from sources of external and internal (uranium and plutonium) radiation were provided by Public Health England using the latest dosimetric models. Estimates of external doses were the same as those used in a previously published study of cancer (*30*) and non-cancer (*11*) mortality in workers at BNFL sites but differed slightly from those used in the UK NRRW analyses, which included other dose corrections and dosimeter threshold adjustments, and may have treated notional doses differently (*31, 32*). The underlying data, dose assessment methodologies, and discussion of uncertainties are described in detail elsewhere (*33, 34*). Annual doses were summed to obtain career cumulative doses. Additional detail is provided in our recently published work (*22*). The current bias analyses are based on 15-year-lagged cumulative exposures, as this was considered to be the most important exposure metric in the analyses of the full cohort (*11*).

Quantitative Bias Analysis

Lash *et al*. (*25*) recommend that biases likely to have the greatest influence on study results should be prioritized. We assessed the impact of five specific factors identified *a priori* as possible important sources of bias on the observed dose-response associations we have previously described (*22*). We employ simple probabilistic bias analysis and examine the impact of each potential source of bias on risk estimates one at a time. Distributions of correct odds ratios and 95% confidence intervals are provided for all analytic results to summarize both the extent of the bias and the uncertainty of the bias parameters themselves (*3*).

Monitoring for Internal Dose

Cumulative internal equivalent doses to the liver from deposited plutonium (the main intake at Sellafield) and uranium (the dominant intake at Springfields) were based on urinalysis measurements, and samples were provided by workers with the potential for non-trivial exposures (*33, 35*). These were included as a confounding factor in models of cumulative external radiation, but because no association was observed with cumulative dose they were included as ''never/ever monitored for internal exposure''. In the case-control study (*22*) and in the cohort (*30*) from which these were derived, marked differences were observed between workers monitored for external radiation exposure only, for whom a clear dose-response association was observed, and workers monitored for both external and internal radiation exposure, where the external dose association is much less evident. An explanation for these findings remains unclear, but patterns of monitoring for internal exposure are complex and differ over time and possibly between sites. Moreover, risks may be associated with other factors, which may differ between the two sites located in different, albeit neighboring, counties. Here we conduct further stratified analyses to explore whether there is evidence for true confounding, which would have comparable patterns across strata, or alternatively whether observed associations are the result of some form of bias resulting from the inclusion of different nuclear sites and different population characteristics in the study. We hypothesize that when conducting analyses of more homogenous groups, such as for individual nuclear sites, for case and control workers with the same occupation only, and for workers with the same occupation and from the same site only, the confounding effect of ''internal monitoring'' would disappear within strata if the confounding effect resulted from some bias related to those strata.

Misspecification of Dose-Response Associations

Original analyses were conducted based on a log-linear dose-response model, and on comparison of quartiles in the distribution of cumulative external radiation dose in cases. An advantage of the latter is that dose-response associations do not need to be linear. However, the choice of group cut-offs can impact on observed associations and measurement error can result in misclassification bias towards or away from the null (*36, 37*), even if the pattern of misclassification is nondifferential. Here, we re-analyze the study using the continuous cumulative dose based on generalized additive models (GAMs) to accommodate non-linearity. We did not do a matched analysis. For GAMs thin plate regression splines were used to model dose-response associations (*38*) and these were compared to the cohort results and original case-control analyses. Adequacy of basic dimensions of the smooths were assessed based on the k-index. Assessment of non-linearity for other covariates (age at start of employment, age at exit, year of start of employment) did not indicate deviation from linear associations with IHD mortality (data not shown).

Bootstrapping

To evaluate the dependence of the observed associations on specific pairs in the case-control set, we conducted Monte Carlo analysis on 1,000 samples in which 10% of worker pairs were randomly removed from each analysis.

Exposure Measurement Error

Although in most situations imperfectly measured exposure attenuates the relationship with health outcomes, its effect can be much more complex in multivariable settings or in situations where the error correlates with the true value (*39, 40*), and it is therefore important to carefully and realistically consider both magnitude and direction of possible biases when making judgments about the interpretation of results (*41*). The cumulative external radiation dose used in this study can be subject to both classical and/or Berkson error structures (*42*). Whereas classical error is independent of the true exposure and occurs when exposures are measured with random error, Berkson error arises under the assumption that the worker's true (unobserved) cumulative dose, conditional on the observed value, equals observed value (*43*), and may also contribute to bias in this dataset.

To assess the potential impact of exposure measurement error, probabilistic modeling was conducted for four plausible scenarios. Scenarios A and B describe unconditional exposure measurement error scenarios in which the error was, arbitrarily, set to the first (30%) and third (60%) tertiles of the standard deviation of the exposure metric. For scenario A, a random error term was added to the 15-year-lagged cumulative external radiation dose to incorporate random measurement error from a Gaussian distribution with mean zero and standard deviation of 0.3× standard deviation of the exposure metric [$\sim N(0,0.3*\text{sd}(\text{15-year-lagged cumulative external radiation dose}))$]. For scenario B, measurement error was assumed to be positively correlated with lagged cumulative dose and ranged 0–60% of the standard deviation of the exposure metric. Scenarios C and D describe exposure measurement error scenarios conditional on the exposure metric. For scenario C, measurement error ranged 0–60% of the

standard deviation of the exposure metric but was negatively correlated. For scenario D, measurement error was ranged 0–60% of the standard deviation of the exposure metric and negatively correlated with the first year of employment of each worker. Scenario A describes standard nondifferential measurement error, scenario B describes the situation in which higher concentrations are measured with more error, scenario C describes a situation where lower exposures, possibly close to the limit of detection, are measured with relatively more error, and scenario D describes a situation where older measurements have resulted in higher error. Where incorporation of measurement error resulted in cumulative exposure values below 0, these were replaced with 0 mSv.

Missing Data on Tobacco Consumption

Tobacco smoking at the pre-employment medical examination was included in the case-control study as ''current smoker'' or ''non/ex-smoker'' (*22*). However, 29.3% of this self-reported information was missing: 28.4% and 30.2% among cases and controls, respectively. For the radiation worker sample in this study, 30.6% of the smoking information was missing, slightly less in cases (25.0%). Missing smoking information was negative correlated with 15-year-lagged cumulative external radiation dose in the case-control data [$r_{Pearson}$ = –0.14 (–0.17, –0.10)] and radiation worker sample [$r_{Pearson}$ = –0.16 (–0.21, –0.11)].

Missing smoking data were imputed based on five scenarios. As a basis, missing smoking data were imputed conditional on disease status, 15-year-lagged cumulative dose, covariates in the model (site, monitored for internal exposure, year of exit, decade of start of employment, age at start of employment, main occupation and socioeconomic status), and additional relevant factors (body mass index, systolic and diastolic blood pressure and employment duration). Additionally, four theoretical plausible scenarios were modeled to assess the impact of plausible boundary conditions; scenarios a and b describe unconditional missingness; for scenario a, missing data were mostly smokers (60%, or twice as high as reported) and for scenario b, missing data were mostly ex/non-smokers (15% smokers, or half of reported). Scenarios c and d describe missingness conditional on disease status; for scenario c, percentage of smokers with missing data was higher for cases (80%) than controls (20%) and for scenario d, percentage of smokers with missing data was lower for cases (20%) than controls (80%). Tobacco consumption data were imputed using a probabilistic process: 1,000 samples were generated for each analysis.

In an additional evaluation, based on conversations with the occupational physician from one of the sites who indicated that over the duration of employment, the vast majority of workers had taken up smoking, an additional Monte Carlo sampling analysis was run in which the smoking status of all non/ex-smokers or workers with missing smoking information was imputed with 80% or 60% probability of being a smoker for cases and controls, respectively. This analysis was also based on 1,000 samples.

Uncontrolled Confounding

As we discussed elsewhere previously (*22*), only pre-employment physiological traits, anthropometric measurements and tobacco smoking information were available; information on the temporal nature of these measures across workers' careers was not available. Plausibly, the absence of the inclusion of these factors may have confounded the observed associations to a lesser or greater extent. In addition, confounding effects from other, mainly non-occupational factors such as nutrition could also not be excluded. To evaluate the possible impact of uncontrolled confounding, probabilistic analyses were conducted in which an additional simulated factor was included which confounded the association between cumulative external radiation dose and IHD mortality. Different scenarios of positive correlations with cumulative external radiation dose were simulated, set to Pearson correlations of 0.10, 0.30, 0.60 and 0.90, and negative correlations of –0.10, –0.30, –0.60 and –0.90. Correlations with IHD mortality were determined post hoc; 1,000 samples were generated for each analysis. All analyses were conducted in R statistical software, version 4.0.2.

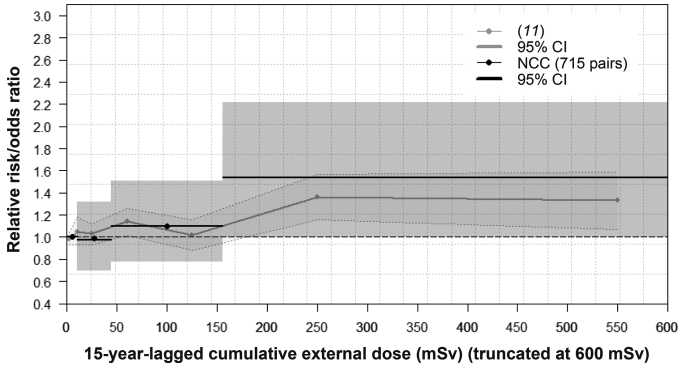

FIG. 1. Comparison results of the original cohort study (*11*) and those for radiation worker pairs (n = 715 pairs) in the matched case-control study nested in the cohort. Associations of nested case-control study are adjusted for monitoring for internal exposure, age of exit, decade of start of first job, age at first job, socioeconomic status and main job.

RESULTS

An overview of the study population and distributions of variables is provided in Supplementary Table S1 (https://doi.org/10.1667/RADE-21-00078.1.S1). As described in Materials and Methods, we did not use the complete nested case-control population in these analyses, but only those monitored for exposure to external radiation, i.e., ''radiation workers''. This has reduced the sample size from 1,220 pairs to 715 pairs. For comparison with the cohort from which the cases and controls were drawn, Fig. 1 shows the original analyses, and indicates that results are comparable with some indication of increased excess risk in this subgroup of cases and controls.

Monitoring for Internal Exposure

Table 1 shows the results of the same model for the complete case-control population [similar to (*22*)] and for a more homogenously exposed subpopulation of radiation workers, shown in Fig. 2. In addition, to further increase the homogeneity of the sample, analyses stratified by nuclear site are also presented. Effect estimates that are unadjusted or adjusted for internal monitoring exposure among radiation worker pairs are more homogenous than those for all case-control pairs, while analyses by site further reduces differences between unadjusted and adjusted results.

Evaluation of Non-linearity in Dose-Response Associations

A direct comparison of GAM models (using dose quartiles) with the matched logistic analysis results in our previously reported analysis (*22*) is presented in Supple-

TABLE 1
Adjusted and Unadjusted Analyses of the Association between 15-Year-Lagged Cumulative External Radiation Dose and IHD Mortality for the Complete Matched Case-Control Population (which Includes Censored Controls) and for the Subgroup of Radiation Workers with Uncensored Controls Only

15-year-lagged cumulative external radiation dose[a]	Odds ratio		Odds ratio		Odds ratio	
	Adjusted[b]	Unadjusted[c]	Adjusted[b]	Unadjusted[c]	Adjusted[b]	Unadjusted[c]
	Complete case-control population (censored controls included)					
	Both sites (1,220 pairs)		Sellafield (651 pairs)		Springfields (569 pairs)	
0–1.94 mSv	1.00	1.00	1.00	1.00	1.00	1.00
1.94–25.11 mSv	0.97 (0.76–1.26)	0.83 (0.65–1.06)	0.98 (0.64–1.50)	0.94 (0.61–1.44)	1.03 (0.72–1.45)	0.73 (0.53–1.00)
25.11–108.77 mSv	1.03 (0.79–1.34)	0.80 (0.62–1.02)	0.88 (0.60–1.27)	0.80 (0.55–1.15)	1.28 (0.85–1.94)	0.75 (0.53–1.07)
>108.77 mSv	1.35 (0.99–1.84	0.94 (0.71–1.24)	1.23 (0.85–1.78)	1.00 (0.72–1.41)	1.10 (0.45–2.69)	0.59 (0.25–1.36)
	Radiation worker pairs (uncensored controls only)					
	Both sites (715 pairs)		Sellafield (385 pairs)		Springfields (330 pairs)	
0.01–10.60 mSv	1.00	1.00	1.00	1.00	1.00	1.00
10.60–44.43 mSv	1.08 (0.78–1.51)	0.97 (0.71–1.34)	0.81 (0.45–1.46)	0.82 (0.45–1.47)	1.11 (0.73–1.68)	0.98 (0.66–1.45)
44.43–155.83 mSv	1.21 (0.85–1.71)	1.08 (0.77–1.51)	0.89 (0.51–1.57)	0.91 (0.52–1.59)	1.30 (0.81–2.08)	1.15 (0.73–1.80)
>155.83 mSv	1.80 (1.17–2.77)	1.49 (1.00–2.22)	1.33 (0.74–2.36)	1.38 (0.79–2.42)	0.86 (0.19–3.89)	0.72 (0.16–3.20)

[a] Cumulative exposure category cut-offs based on quartiles of its distribution in IHD cases.
[b] Adjusted for age at exit, monitored for internal dose (lagged 15 years), decade of start of first job, age at start of first job, socioeconomic status, and main job.
[c] Same as *a*, but without ''monitored for internal dose (lagged 15 years)''.

mentary Tables S2 and S3 (https://doi.org/10.1667/RADE-21-00078.1.S1), and indicates comparable results for most variables with the exception of groups with small numbers of observations for which the GAM provides more stable results; dose-response associations are similar.

Figure 2 shows the comparison of the non-linear dose-response associations with the results from the case-control study (Fig. 2A) and cohort study (Fig. 2B). Good comparability is shown with both sets of results, but these show a nearly perfect overlay of point estimates of the cohort dose-response associations. A maximum excess risk of OR = 1.43 (1.07–1.92) was observed at 387 mSv, with little evidence of increased risk at higher cumulative external radiation dose.

Supplementary Fig. S1 (https://doi.org/10.1667/RADE-21-00078.1.S1) shows models with different sets of confounding structures. These have little impact on the shape of the dose response, but full adjustment results in attenuation of the dose-response curve to a maximum excess risk of 21% (a reduction of 51%); however, this overparametrized model does not include statistically significant factors.

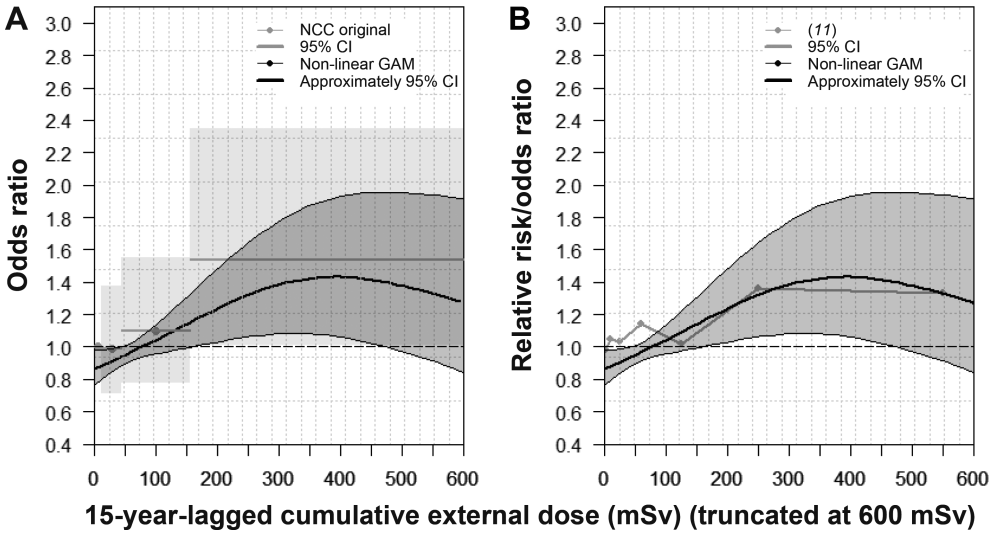

FIG. 2. Comparison non-linear generalized additive (GAM) model (adjusted for site monitored for internal dose, age of exit, decade of first job in industry, age at start of first job, socioeconomic status and main job) with: (panel A) model used in original analysis case-control study (similarly adjusted except for ''site'', which could not be included because of matching) (*22*) and (panel B) results from analysis of the cohort from (*11*).

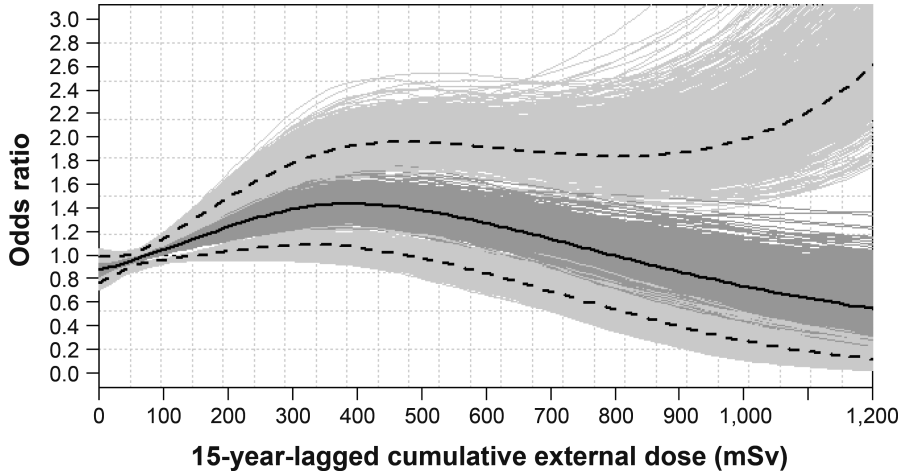

FIG. 3. Results of bootstrapped models, based on generalized additive (GAM) modeling. There were 1,000 samples with random removal of 10% of worker pairs from the dataset. Dose-response associations are indicated in dark gray and 95% confidence limits are indicated in light gray. Dose-response association complete sample and corresponding 95% confidence limits (dotted line) are indicated in black.

Bootstrapping

Figure 3 shows the results of 1,000 bootstrap samples in which 10% of the case-control pairs were randomly removed prior to analyses. These analyses indicate that the observed association between cumulative external radiation dose and IHD mortality is relatively stable and does not depend on the inclusion of specific worker pairs. Mean maximum observed ORs in these bootstrap samples is 1.44 (range 1.22–1.77), with 95.3% of samples having a lower 95% confidence limit >1 (histograms provided in Supplementary Fig. S2; https://doi.org/10.1667/RADE-21-00078.1.S1).

For a direct comparison with the original results based on quartiles of cumulative dose, the analyses were also conducted using the original matched analyses. The results for the highest quartile of cumulative dose are shown in Supplementary Fig. S3 [(left-side panel) (https://doi.org/10.1667/RADE-21-00078.1.S1)] and similarly suggest the results are relatively insensitive to specific worker pairs with a mean OR of 1.55 (range 1.28–2.08). Although partly explained by a smaller sample size, mean 95% lower limit OR was 0.99 (range 0.82–1.31) with 43.9% of samples indicated in a statistically significant excess risk in the highest quartile.

Exposure Measurement Error

Figure 4 shows the results of 1,000 samples in which measurement error is incorporated according to four different scenarios, a–d, compared to the main analyses. Illustrations of modeled measurement error patterns and histograms of Monte Carlo results for all scenarios are provided in Supplementary Figs. S4–11. The analyses suggest that four plausible scenarios of measurement error mostly resulted in bias towards the null. The mean maximum odds ratio (OR) in scenario a was 1.39 (range of ORs 1.12–2.75), with 80.3% of samples having a lower limit of the 95% confidence interval over 1, indicating effect estimates in line with excess risk. In scenario b, the mean OR was 1.43 (1.36–1.53) with all samples having a lower limit of the 95% confidence interval above 1. In scenario c, measurement error was negatively correlated with cumulative external exposure, with a mean OR of 1.27 (1.00–2.68) with only 46.2% of samples having a lower limit of the 95% confidence interval above 1. Scenario d, in which measurements error is negatively correlated with workers' first year of employment at one of the sites, shows a mean OR of 1.32 (range 1.00–3.42) with 51.8% of samples having a lower limit of the 95% confidence interval above 1.

Figure 5 further shows that in some cases measurement errors can lead to maximum excess risks up to twice those observed in the standard analysis.

Missing Smoking Data

A comparison of the pattern of missing information on smoking status of the original case-control dataset and the subset in this study is provided in Supplementary Table S4 (https://doi.org/10.1667/RADE-21-00078.1.S1). Whereas inclusion of pre-occupation smoking status, including missing data, had little impact on excess risks in categorical analyses, it did reduce excess risks using GAMs and continuous cumulative dose data from a maximum OR point estimate of 1.43 to 1.21 (Supplementary Fig. S1; https://doi.org/10.1667/RADE-21-00078.1.S1).

The results for the full conditional imputation are shown in Fig. 5. This scenario results in a smoking prevalence of 73.9% (range 71.9%, 75.5%) in the subgroup with missing data. The adjusted OR for smoking in this simulation is 1.53 (range 1.31–1.86), and little evidence of an association between smoking status and 15-year-lagged cumulative exposure in this group ($r_{Pearson} = -0.07$, $P = 0.12$). Full conditional imputation of smoking status suggests that the

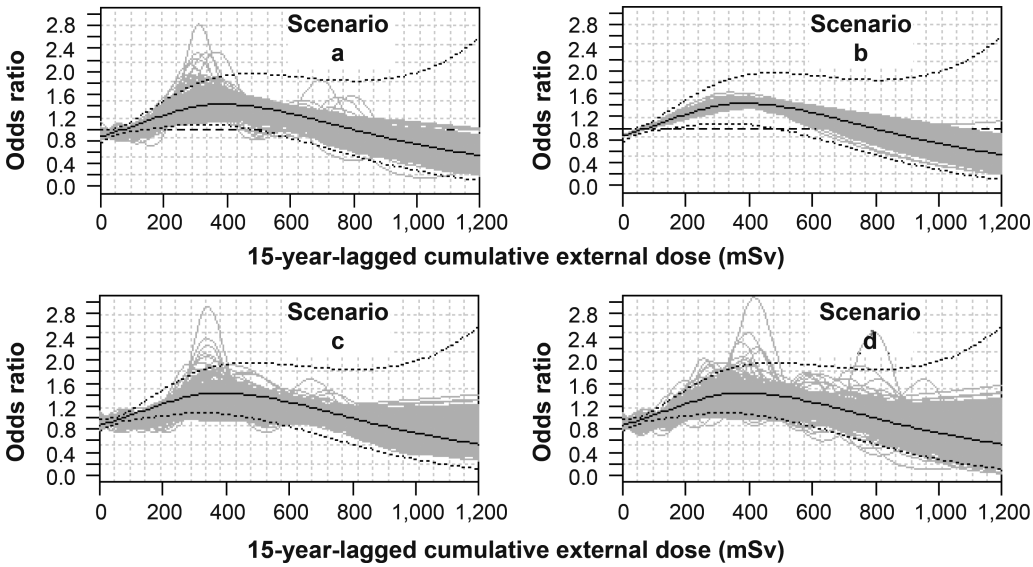

FIG. 4. Results of 1,000 Monte Carlo GAM models incorporating exposure measurement error for four scenarios. Two are unconditional exposure measurement error scenarios: Random measurement error [30% sd (cumulative external radiation exposure)] (scenario a) and random measurement error correlated with cumulative external radiation exposure (scenario b). And two are exposure measurement error scenarios conditional on the exposure: Random measurement error inversely correlated with cumulative external radiation exposure (scenario c) and random measurement error correlated with year of first employment (scenario d).

original analyses were biased towards the null, with the distribution of maximum ORs for IHD mortality from cumulative external radiation dose being 1.49 (1.45–1.54).

In all four theoretical scenarios only missing smoking data were replaced, which equates to 179 cases (25.0%) and 259 controls (36.2%), respectively (Supplementary Tables). Results of the 1,000 GAM analyses for the four plausible scenarios of missing tobacco smoking information are shown in Fig. 6. When included, current smoking was associated with an OR of 1.56 in the GAM model with continuous cumulative dose data and missing info with OR = 0.78. For scenario a with a mean percentage of smokers of 68.2% (range 65.8–70.1) the mean OR of ''current smoker'' was 1.41 (range 1.09–1.81), for scenario b with mean 54.4% (range 52.9–56.1) of current smokers the OR was 1.65 (1.39–1.88), for scenario c with mean 56.7% (55.7–57.6) current smokers the OR was 3.38 (2.77–4.00), and for scenario d with 58.39% (range 57.3–59.3) current smokers the OR for current smoking at start of employment was 0.63 (0.53–0.78), respectively, indicating that the models are sensitive to the distribution of smokers in the population. These analyses indicate that missing smoking data biased associations between cumulative external radiation dose and IHD mortality in the GAM analyses towards the null, and imputation of missing data for the four plausible scenarios goes some way to re-addressing the bias (Fig. 6). Specifically, for scenario a, the largest observed risk from 1,000 samples had a mean OR of 1.44 (range 1.40–1.49), for scenario b compared to the other scenarios, however, a lower maximum mean OR of 1.33 (1.29–1.37), for scenario c this was 1.35 (1.25–1.49), and for scenario d this was 1.43 (1.39–1.48). Post hoc based on the OR for ''current smoker at start of employment'', which was highest for scenario c, this may indicate that missing smoking data were related to subsequent case-control status.

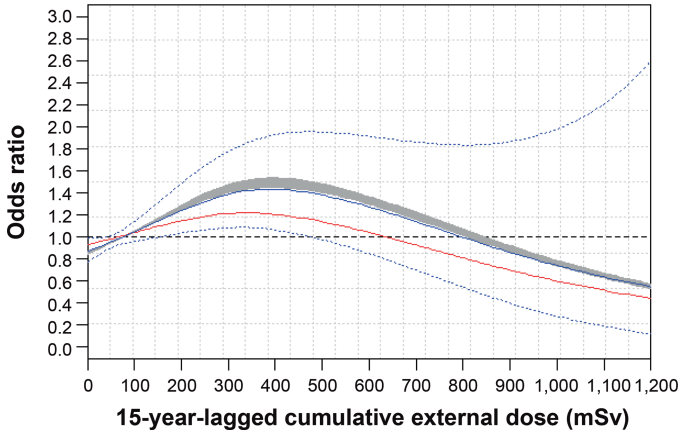

FIG. 5. Results of 1,000 Monte Carlo GAM models with imputed missing smoking information conditional on disease status, 15-year-lagged cumulative dose, covariates in the model (site, monitored for internal exposure, year of exit, decade of start of employment, age at start of employment, main occupation and socioeconomic status), and additional factors considered to be important (body mass index, systolic and diastolic blood pressure, and employment duration) in gray. Dose-response association of main case-control model plus 95% confidence limits is shown in blue and point estimates of main case-control model additionally adjusted for original, non-imputed, smoking status are shown in red.

The additional scenario in which 80% of cases and 60% of controls who were non/ex-smokers or had missing smoking information at start of employment smoked by the end of employment resulted in a mean prevalence of smokers of 67.1% (range 65.8–68.6) and a maximum OR

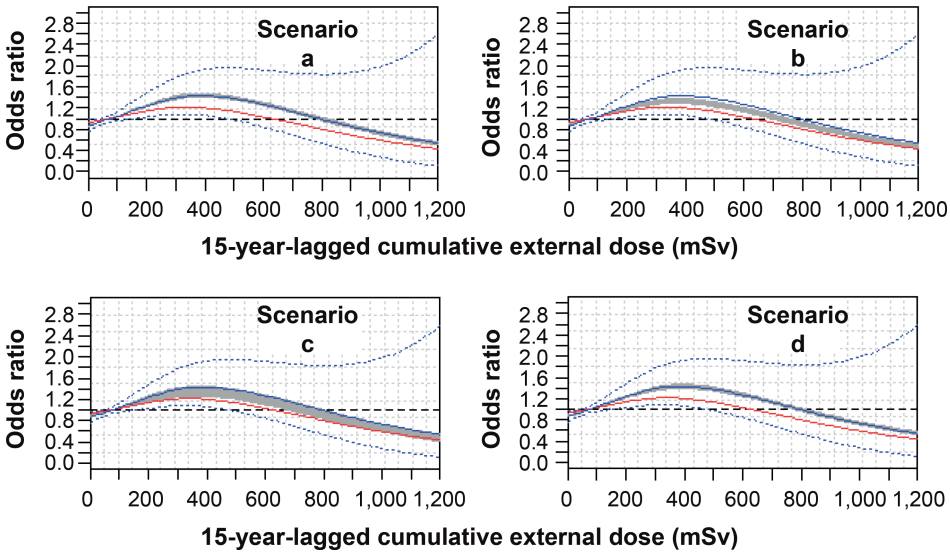

FIG. 6. Results of 1,000 Monte Carlo GAM models with imputed missing smoking information for four scenarios (in gray). Scenario a: Missing data 60% smokers. Scenario b: Missing data 15% smokers. Scenario c: Missing data positively correlated with IHD mortality (80% smokers/20% non-smokers). Scenario d: Missing data negatively correlated with IHD mortality (20% smokers/80% non-smokers). Dose-response association of main case-control model plus 95% confidence limits is shown in blue and point estimates of main case-control model additionally adjusted for original, non-imputed, smoking status are shown in red.

point estimate of 1.34 (range 1.22–1.44). The corresponding OR for smoking was 3.14 (range 2.08–4.92).

The magnitude of the impact of missing smoking data did not indicate this could have explained the observed association between cumulative external radiation dose and IHD mortality.

Residual Confounding

For illustration, correlations between cumulative external radiation exposure and the modeled confounding factor are shown in Supplementary Figs. S12–S15 (https://doi.org/10.1667/RADE-21-00078.1.S1).

Figure 7 shows the results for 1,000 samples for the four scenarios in which an unmeasured confounder is positively correlated with cumulative dose and modeled as a linear continuous variable. The confounding variable has a mean OR ranging from 0.99 to 1.10 for correlations with cumulative exposure (r_p) of 0.10 to 0.90, respectively. Mean maximum ORs for cumulative exposure are 1.43 (range 1.38–1.49) for $r_p = 0.10$, 1.43 (1.32–1.58) for $r_p =$

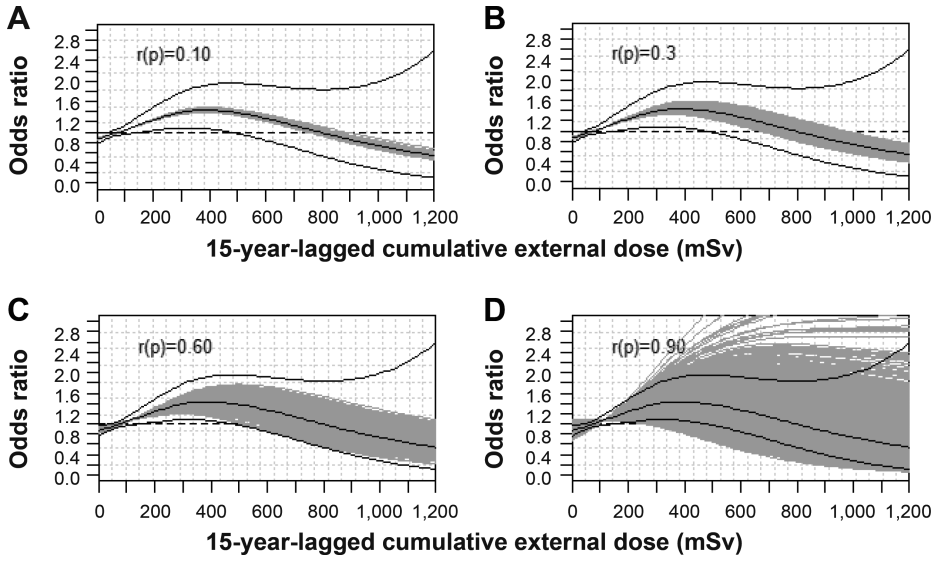

FIG. 7. Results of 1,000 Monte Carlo GAM models incorporating additional adjustment for uncontrolled confounding: correlated with cumulative external radiation r(p) ~ 0.10 (panel A), r(p) ~ 0.30 (panel B), r(p) ~ 0.60 (panel C) and r(p) ~ 0.90 (panel D).

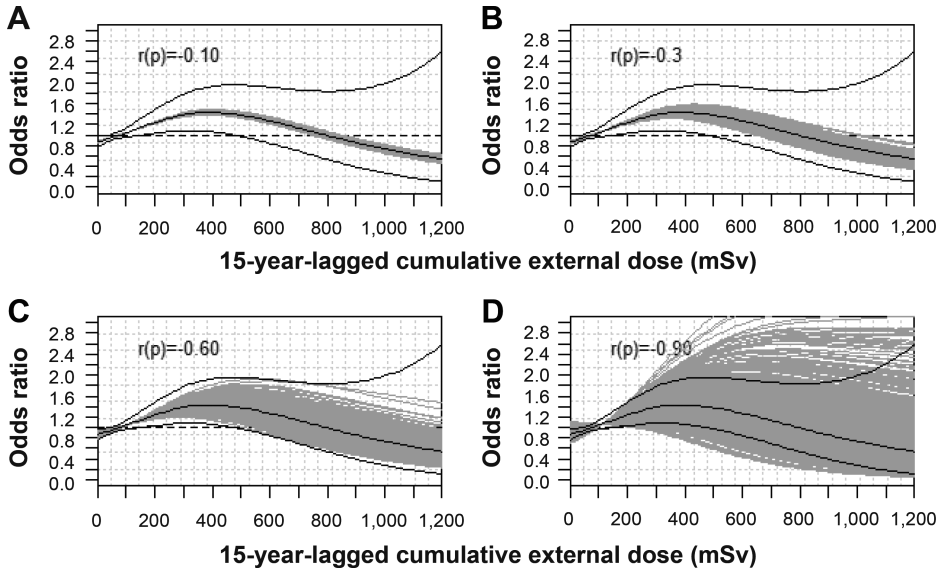

FIG. 8. Results of 1,000 Monte Carlo GAM models incorporating additional adjustment for uncontrolled confounding: correlated with cumulative external radiation r(p)~ –0.10 (panel A), r(p) ~ –0.30 (panel B), r(p) ~ 0.60 (panel C) and r(p) ~ –0.90 (panel D).

0.30, 1.44 (1.21–1.85) for $r_p = 0.60$ and 1.52 (1.07–9.21) for $r_p = 0.90$, with corresponding 95% lower limits above OR = 1 for 100%, 100%, 94.3% and 46.5%, respectively.

Results for negative correlations with cumulative external radiation dose are comparable (Fig. 8) with ORs for the confounding variable ranging 0.98–1.06, mean ORs for cumulative exposure of 1.43 (1.38–1.49), 1.43 (1.31–1.61), 1.44 (1.20–1.89), 1.52 (1.07–5.48), and corresponding 95% lower limits above OR = 1 for 100%, 100%, 94.2% and 48.7%, respectively, for $r_p = –0.10$, –0.30, –0.60 and –0.90.

Complementary analyses in which the unmeasured confounder was modeled using a spline function instead of a linear function are shown in Supplementary Figs. S16 and S17 (https://doi.org/10.1667/RADE-21-00078.1.S1), and similarly show relatively little impact for an unmeasured confounder with low to moderate correlations with cumulative exposure ($–0.60 \geq r_p \leq 0.6$). However, high correlations of 0.90 or –0.90 have a larger impact with mean maximum ORs of 3.23 (range 1.00–100) and 3.28 (1.02–61.4), respectively.

DISCUSSION

The scientific question of whether protracted low-dose or low-dose-rate exposure to external sources of radiation is causally related to the risk of circulatory disease continues to be an important issue for radiation protection. Observational epidemiological studies in radiation worker populations in different countries provide strong suggestive evidence but remain susceptible to bias. We previously conducted a matched case-control study nested in a large cohort of UK nuclear fuel cycle workers with the specific aim of assessing whether observed associations between external radiation dose and IHD mortality risk could, to some extent, be explained by confounding from other occupational exposures or baseline lifestyle factors or physiological traits. The current quantitative bias analyses were performed to further explore this issue by investigating the possible impact of several identified important possible biases using probabilistic methods for plausible scenarios. Importantly, these analyses indicate that missing information on tobacco smoking at start of employment in this study population was unlikely to have significantly impacted on observed associations. The difference between the full conditional imputation of missing smoking information and the simulated scenarios where imputation is unconditional or conditional only on 15-year-lagged cumulative exposure indicate that missingness was unrelated to exposure but was related to other factors. They also indicate that tobacco smoking at the start of employment was a more important confounding factor when dose-response associations were modeled using a continuous measure than when cumulative external radiation dose was categorized in four quartiles. Moreover, some unmeasured confounder, which could have been smoking during employment, would have had to have been highly correlated with cumulative external radiation dose [correlation coefficient (r_p) over 0.60], which is unlikely in practice. Secondly, these analyses indicated that the confounding effect of ''having been monitored for internal dose'' was unlikely to have been a true confounder in a biological sense, but instead may be correlated with some selection effect specific to this population and which, although unknown, may be a form of collider bias resulting from specifics of decisions on which workers were monitored for internal dose and when (*17*). These patterns are complex and differ between sites and over time (*22*), and differences between workers monitored and unmonitored for internal exposure

have also been observed in this population for cancer outcomes, particularly for digestive cancers (*30*). Collider bias as a possible explanation is further supported by the observation that having been monitored for internal exposure, as well as being associated with higher levels of cumulative internal exposure, was also associated with reduced IHD mortality risk in these and in the original case-control analyses (*22*), which can be illustrative of such bias (*44*).

Additionally, incorporation of exposure measurement error negatively biased associations regardless of the modeled scenario but did not importantly change the shape of the observed dose-response associations. And finally, these analyses provided further evidence that the dose-response association between cumulative external radiation exposure and IHD mortality may be non-linear in that it mimics LNT until approximately 400 mSv with little evidence of further increasing excess risks thereafter. This is consistent with the broader evidence base, which describes anti-inflammatory effects up to about 0.5 Gy, with the balance shifting to upregulation of inflammatory markers measurable at higher doses of 0.5–5 Gy (*3*). In other settings, data from medical X-ray exposures and from LSS mortality data similarly suggest steeper dose-response slopes for circulatory diseases at low doses compared to high doses (*45, 46*).

Although these bias analyses provide a good insight into the possible impacts of different factors which may have biased results in the original case-control analyses, and plausibly extend to the cohort in which it was nested and possibly to other cohorts of nuclear fuel cycle workers as well, there are several considerations that need to be taken into account. We identified plausible scenarios for each identified possible source of bias, but it is not inconceivable that other scenarios may also be plausible which have resulted in larger biases. Similarly, we may not have included possible sources of bias that are important as well, but we did not recognize as such. For example, assessment of exposure measurement error was limited to Berkson error because of our interest in the impact of Berkson error arising from the group effect of cumulative radiation dose calculated from repeated exposure measurements (*47*). Although Berkson error can also produce biased associations away from the null in logistic regression, classical error is generally thought to have larger effects (*48*), and it may be worthwhile to specifically evaluate its impact in this setting. We assessed the impact of each bias independently. It is not unlikely however, that there are joint or simultaneous effects of different biases both in terms of direction and strength (*26*). We did not perform additional complex multiple bias modeling here because the aim of these analyses was to specifically assess the direction and strength of important individual threats to validity. However, we recommend that such an approach be incorporated in future analyses of complete worker cohorts. Finally, these analyses were performed to assess the impact of internal threats to validity only and not to assess the impact of threats to external validity. These analyses addressed main sources of information bias, measurement error and confounding, but did not address potential selection biases (*24*). Previously published analyses indicated that this matched case-control population resulted in risk estimates comparable to those for the full cohort (*22*), indicating that over-matching reported previously (*23*) was unlikely to be an important factor in this population. Current analyses show that GAM analyses incorporating non-linear dose-response associations resulted in even better similarity to the cohort results (*11*), indicating that threats to external validity with respect to the UK nuclear fuel cycle worker population were likely minimal. However, the complexities in the interpretation of the effect of monitoring for internal dose identified in these analyses suggest that there are some remaining threats to external validity to be further explored.

The strength of this work lies in the implementation of probabilistic bias analysis for important threats to internal validity, which has the advantage over simple bias analysis of sampling from plausible distributions of bias parameters and gives a much better insight into the plausible impact a source of bias could have. Provided our choices of bias parameters and scenarios are valid, the analyses in this work provide additional support that the original findings (*22*) are sufficiently robust to issues of missing data, exposure measurement error and unmeasured confounding to supplement conclusions on the wider literature describing cardiovascular effects related to protracted low-dose or low-dose-rate external radiation exposures (*9*).

In conclusion, these analyses provide additional support for the hypothesis that the observed association between external radiation exposure and IHD mortality may be causal (*9*). Future analyses of larger populations with improved exposure assessment and occupational and non-occupational confounder information, as well as further triangulation (*49*) with mechanistic data, will be required to confirm this.

SUPPLEMENTARY INFORMATION

Table S1. Nested matched case-control study population characteristics.

Table S2. Comparison associations between cumulative radiation dose from external sources (15-year-lagged dose) and ischemic heart disease mortality using matched logistic regression and GAM estimation methods.

Table S3. Comparison parameters fully adjusted and unadjusted GAM.

Table S4. Comparison of distribution of non- and ex-smokers, current smokers and workers with missing information on tobacco smoking in cases and controls in the full study population and the subsample of the current study.

Fig. S1. Dose-response association of GAM model for different sets of confounder adjustments.

Fig. S2. Distribution of maximum odds ratio (left-side panel) and 95% lower limit (right-side panel) for association between cumulative external radiation dose and IHD for 1,000 MCMC bootstrap samples.

Fig. S3. Histogram of odds ratios in highest quartile of cumulative external radiation dose from 1,000 bootstrap samples (left-side panel) and corresponding distribution of 95% lower limits (right-side panel).

Fig. S4. Illustration of measurement error for scenario a for 5 randomly selected MCMC samples (colors indicate different samples).

Fig. S5. Distribution of maximum odds ratio (left-side panel) and 95% lower limit (right-side panel) for 1,000 MCMC samples for scenario a.

Fig. S6. Illustration of measurement error for scenario b for 5 randomly selected MCMC samples (colors indicate different samples).

Fig. S7. Distribution of maximum odds ratio (left-side panel) and 95% lower limit (right-side panel) for 1,000 MCMC samples for scenario b.

Fig. S8. Illustration of measurement error for scenario c for 5 randomly selected MCMC samples (colors indicate different samples).

Fig. S9. Distribution of maximum odds ratio (left-side panel) and 95% lower limit (right-side panel) for 1,000 MCMC samples for scenario c.

Fig. S10. Illustration of measurement error for scenario d for 5 randomly selected MCMC samples (colors indicate different samples).

Fig. S11. Distribution of maximum odds ratio (left-side panel) and 95% lower limit (right-side panel) for 1,000 MCMC samples for scenario d.

Fig. S12. Illustration of patterns of cumulative external radiation dose and random ''unmeasured confounder'', correlated using Pearson correlation [r(p)] of 0.10, for 5 randomly selected MCMC samples (colors indicate different samples).

Fig. S13. Illustration of patterns of cumulative external radiation dose and random ''unmeasured confounder'', correlated using Pearson correlation [r(p)] of 0.30, for 5 randomly selected MCMC samples (colors indicate different samples).

Fig. S14. Illustration of patterns of cumulative external radiation dose and random ''unmeasured confounder'', correlated using Pearson correlation [r(p)] of –0.30, for 5 randomly selected MCMC samples (colors indicate different samples).

Fig. S15. Illustration of patterns of cumulative external radiation dose and random ''unmeasured confounder'', correlated using Pearson correlation [r(p)] of –0.90, for 5 randomly selected MCMC samples (colors indicate different samples).

Fig. S16. Comparative results of associations between cumulative external radiation dose and IHD mortality with models including an ''unmeasured confounder'', modeled as a spline instead of a linear functional form, correlated using Pearson correlation coefficients r(p) ranging 0.10–0.90. Maximum odds ratios and range in 1,000 MCMC samples are 1.43 (1.38–1.49) for r(p) = 0.10, 1.44 (1.31–1.59) for r(p) = 0.30, 1.48 (1.21–6.41) for r(p) = 0.60, and 3.23 (1.00–100.1) for r(p) = 0.90. Corresponding percentages of samples with 95% lower limit >1 are 100%, 100%, 92.4% and 47.9%, respectively.

Fig. S17. Comparative results of associations between cumulative external radiation dose and IHD mortality with models including an ''unmeasured confounder'', modeled as a spline instead of a linear functional form, correlated with Pearson correlation coefficients r(p) ranging –0.10 to –0.90. Maximum odds ratios and range in 1,000 MCMC samples are 1.43 (1.37–1.51) for r(p) = –0.10, 1.44 (1.28–1.58) for r(p) = –0.30, 1.47 (1.21–3.40) for r(p) = –0.60, and 3.28 (1.02–61.4) for r(p) = –0.90. Corresponding percentages of samples with 95% lower limit >1 are 100%,100%,93.2% and 41.8%, respectively.

ACKNOWLEDGMENTS

This work was supported by the National Institute for Health Research (Policy Research Programme, Occupational Exposure to Ionising Radiation and Mortality from Ischaemic Heart Disease, PR-R14-0915-23004). The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service (NHS), the National Institute for Health Research or the Department of Health and Social Care. This study was approved by the University of Bristol Faculty of Health Sciences Research Ethics Committee (Application 40782) and by the NDA-PHE Research Governance Group, which includes representatives of employees, Sellafield Ltd, the Nuclear Decommission Authority (NDA) and Public Health England (PHE). We thank Less Scott [Public Health England, Centre for Radiation, Chemical and Environmental Hazards (CRCE)] for his help with exposure assessment and linkage of datasets, Will Atkinson (Nuvia) for his help with the SES-occupation coding scheme, Professor McNamee (University of Manchester) for her help with data identification, management and linkage, and Professor Agius (University of Manchester) for his medical and epidemiological contributions to the study on which the current work is based. RW is a member of the Technical Working Party of the UK Compensation Scheme for Radiation-Linked Diseases. Otherwise, the authors declare no actual or potential competing financial interests.

Received: April 25, 2021; accepted: July 25, 2021; published online: August 9, 2021

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