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

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Table S1. Nested matched case-control study population characteristics

Variable		Controls	Cases
N		715	715
Site	Springfield	330	330
	Sellafield	385	385
Socio-economic status (longest-held occupation)	1-2 (highest)	13	10
	3	304	282
	4	360	384
	5 (lowest)	14	17
	missing	24	22
Start of employment at either site	< 1950	20	30
	1950-1959	507	494
	1960-1969	153	155
	1970 +	35	36
Age at start of employment	Mean (SD)	35.7 (8.4)	35.8 (8.4)
Age of death (or censoring) (years)	<40	136	132
	40-49	139	141
	50-59	212	216
	60-69	228	226
Main occupation (longest-held occupation)	Other	363	345
	Process worker	328	349
	unknown	24	21
Pre-employment smoking status	Non/ex-smoker	151	129
	Current smoker	305	407
	Unknown	259	179
Pre-employment Body Mass Index (BMI)	<18.5	479	454
	18.5-24.9	16	20
	25.0-29.9	180	201
	30+	26	24
	missing	14	16
Pre-employment diastolic blood pressure (mmHg)	<70	13	19
	70-85	352	298
	86-99	233	256
	100+	78	111
	missing	39	31
Pre-employment systolic blood pressure (mmHg)	<120	52	41
	120-138	317	285
	138-159	231	247
	160+	76	111
	missing	39	31
Shiftwork (ever)	Never	242	228
	Ever	414	442
	Missing	59	45
Cumulative NIL_{85} exposure (dB(A)-years)	<85.0	279	213
	85.0-94.8	168	168
	94.9-99.7	126	164
	99.8+	138	167
	missing	4	3

Monitored for internal exposure	No	323	315
	Yes	392	400
Cumulative external radiation dose	(median (mSv), (IQR))	26.62 (6.05-95.15)	34.15 (8.87-144.84)
15 year lagged Cumulative external radiation dose	(median (mSv), (IQR))	37.20 (9.97-117.06)	44.43 (10.60-155.83)

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

Variables		N (controls/cases)	Matched logistic regression [20]		GAM	
			Odds Ratio	95% Confidence Interval	Odds Ratio	Approximate 95% CI
15-yr lagged Cumulative external radiation dose (mSv)[1]	0-10.6	188/180	1		1	
	10.6-44.4	199/178	0.99	0.71-1.38	0.96	0.71-1.30
	44.4-155.8	183/178	1.10	0.78-1.55	1.08	0.77-1.50
	155.8-1,290.7	145/179	1.54	1.01-2.35	1.49	1.00-2.22
Site	Springfields	330/330	Not included		1	
	Sellafield	385/385			0.87	0.66-1.16
Monitored for internal dose	no	323/315	1		1	
	yes	392/400	0.94	0.75-1.19	0.97	0.77-1.23
Age of death (or censoring) (years)	<40	136/132	1		1	
	40-49	139/141	3.13	0.33-29.59	1.01	0.71-1.43
	50-59	212/216	3.13	0.27-36.08	0.97	0.68-1.36
	60-69	228/226	1.81	0.11-29.39	0.92	0.64-1.32
Start of employment at either site	<1950	20/30	1		1	
	1950-1960	507/494	0.26	0.10-0.70	0.64	0.35-1.17
	1960-1970	153/155	0.27	0.05-1.34	0.69	0.36-1.33
	1970+	35/36	0.26	0.01-6.40	0.68	0.31-1.50
Age at start of employment	year		1.19	1.01-1.40	1.00	0.99-1.02
Main occupation	Other	363/345	1		1	
	Process worker	328/349	0.99	0.59-1.67	0.94	0.56-1.59
	unknown	24/21	0.00		0.00	
Socio-economic Status	1-2 (highest)	13/10	1		1	
	3	304/282	1.18	0.51-2.77	1.23	0.52-2.91
	4	360/384	1.37	0.53-3.57	1.47	0.55-3.94
	5 (lowest)	14/17	1.41	0.46-4.26	1.59	0.51-4.89
	missing	24/22	>100		>100	

15-year lagged cumulative exposure	Per 100 mSv		1.05	0.97-1.14	1.03	0.34-3.13

Table S3. Comparison parameters fully adjusted and unadjusted Generalized Additive Model (GAM)

full model splines parameters			unadjusted splines parameters		
estimate	95% lower limit	95% upper limit	estimate	95% lower limit	95% upper limit
0.929	0.782	1.104	0.953	0.824	1.103
1.103	0.419	2.900	1.079	0.484	2.403
0.972	0.845	1.117	0.979	0.872	1.098
0.869	0.45	1.679	0.897	0.519	1.550
0.972	0.875	1.080	0.979	0.897	1.068
1.157	0.62	2.162	1.12	0.666	1.884
0.927	0.683	1.258	0.943	0.731	1.217
2.072	0.173	24.832	1.76	0.219	14.12
1.028	0.682	1.550	0.995	0.705	1.403

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.

Complete case-control population (1,220 matched pairs)			
	Non/ex-smokers (%)	Current smokers (%)	Missing (%)
Controls	285 (23.4)	567 (46.5)	368 (30.2)
Cases	207 (19.7)	667 (63.3)	179 (17.0)
Subset Radiation workers with complete career information (715 matched pairs)			
	Non/ex-smokers (%)	Current smokers (%)	Missing (%)
Controls	151 (21.1)	305 (42.7)	259 (36.2)
Cases	129 (18.0)	407 (56.9)	179 (25.0)

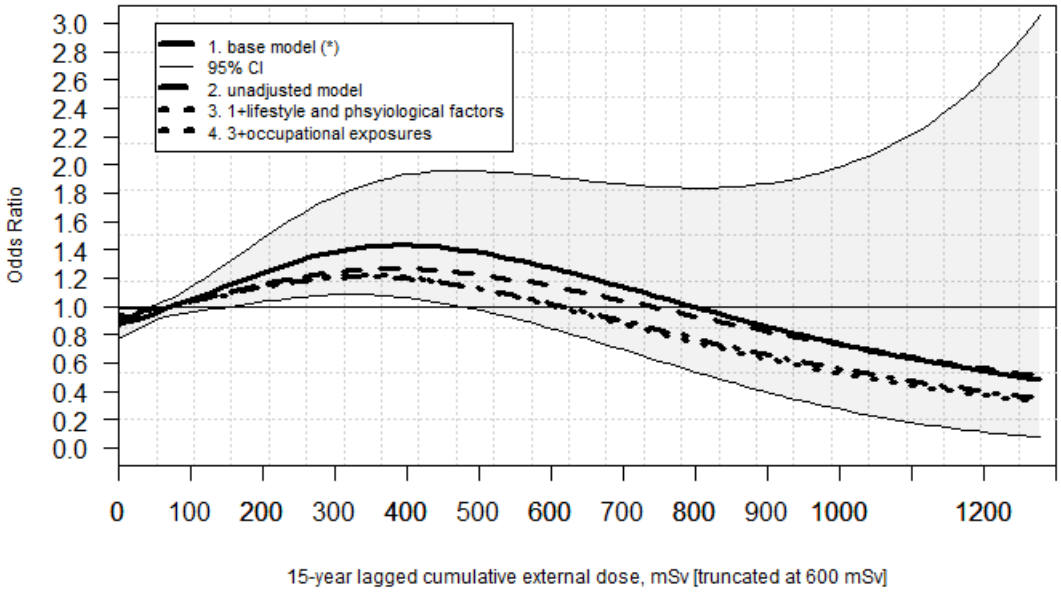

Figure S1. Dose-response association of GAM model for different sets of confounder adjustments. (*) base model adjusted for site, monitored for internal exposure, decade of exit, age at start of employment, main job and socio-economic status.

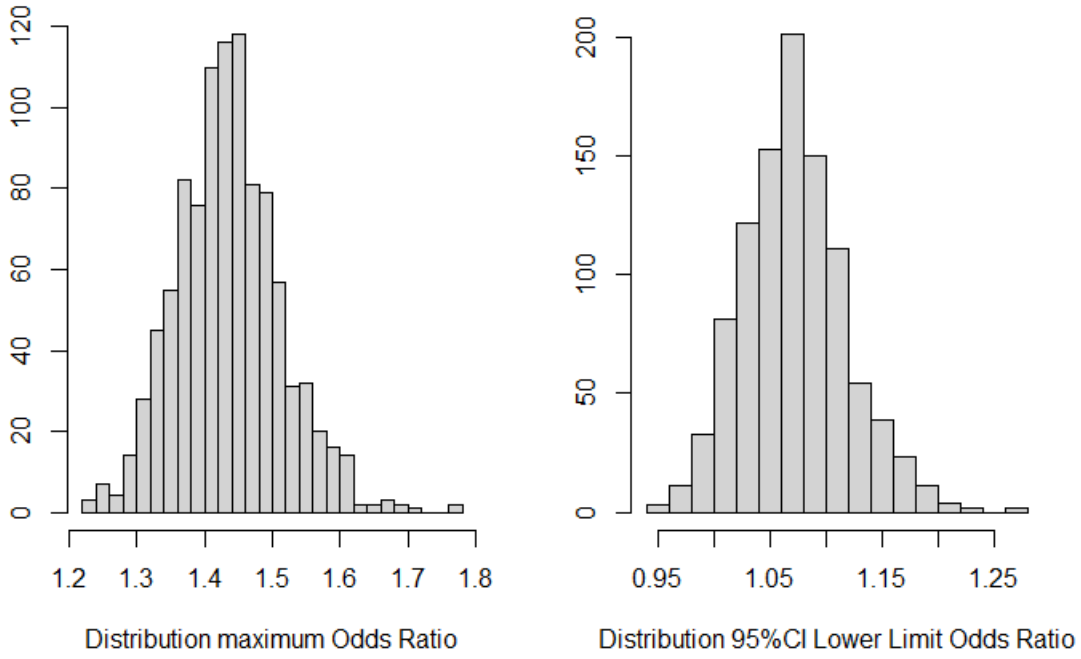

Figure S2. Distribution of maximum Odds Ratio (left) and 95% lower limit (right) for association between cumulative external radiation dose and ischaemic heart disease for 1,000 MCMC bootstrap samples.

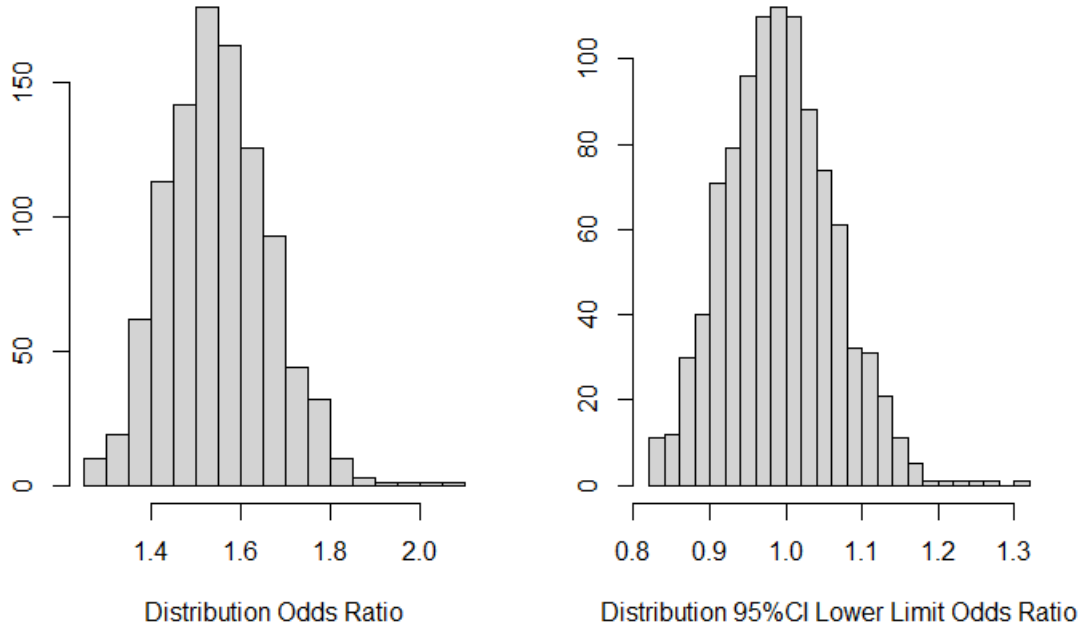

Figure S3. Histogram of Odds Ratios in highest quartile of cumulative external radiation dose from 1,000 bootstrap samples (left panel) and corresponding distribution of 95% lower limits (right panel).

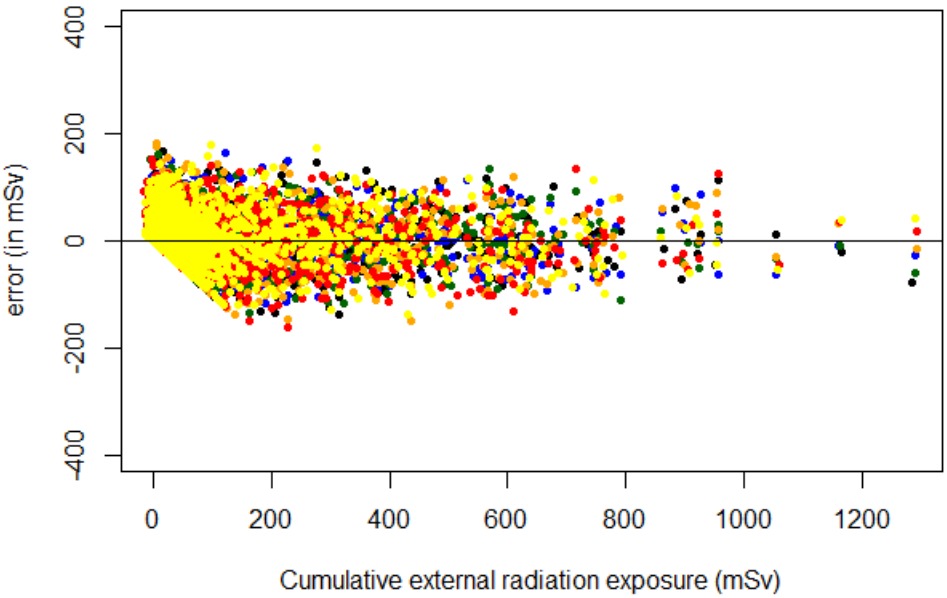

Figure S4. Illustration of measurement error for scenario (a) for 5 randomly selected MCMC samples (colours indicate different samples)

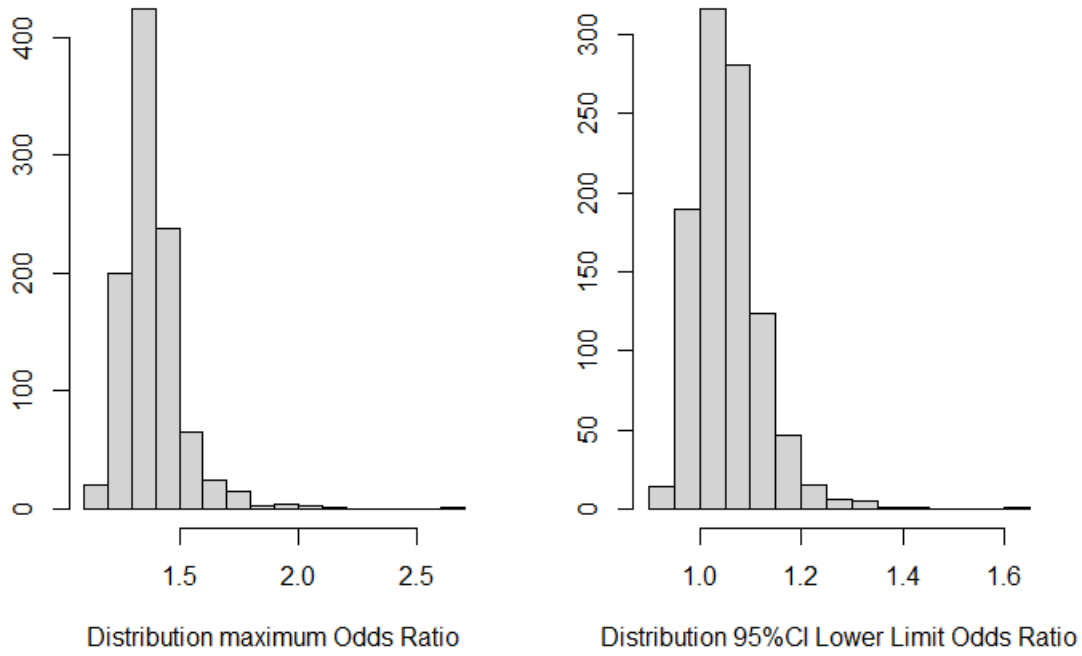

Figure S5. Distribution of maximum Odds Ratio (left) and 95% lower limit for 1,000 MCMC samples for scenario (a)

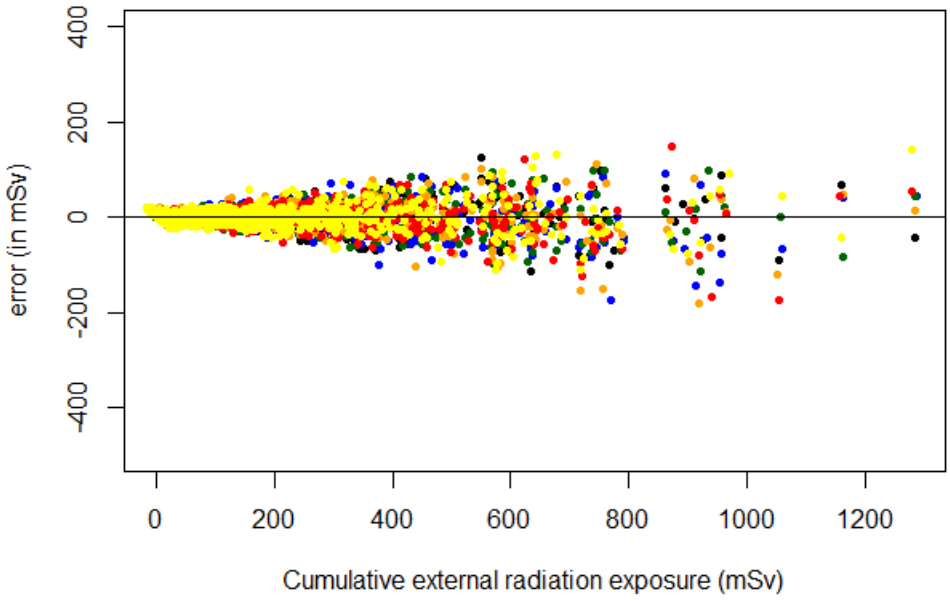

Figure S6. Illustration of measurement error for scenario (b) for 5 randomly selected MCMC samples (colours indicate different samples)

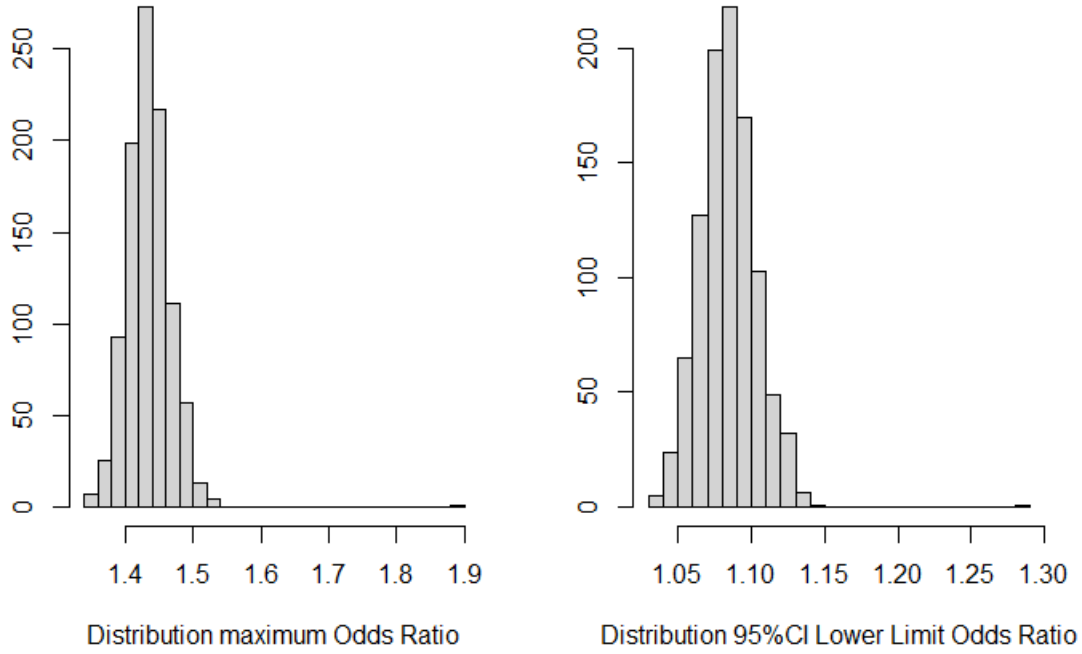

Figure S7. Distribution of maximum Odds Ratio (left) and 95% lower limit for 1,000 MCMC samples for scenario (b)

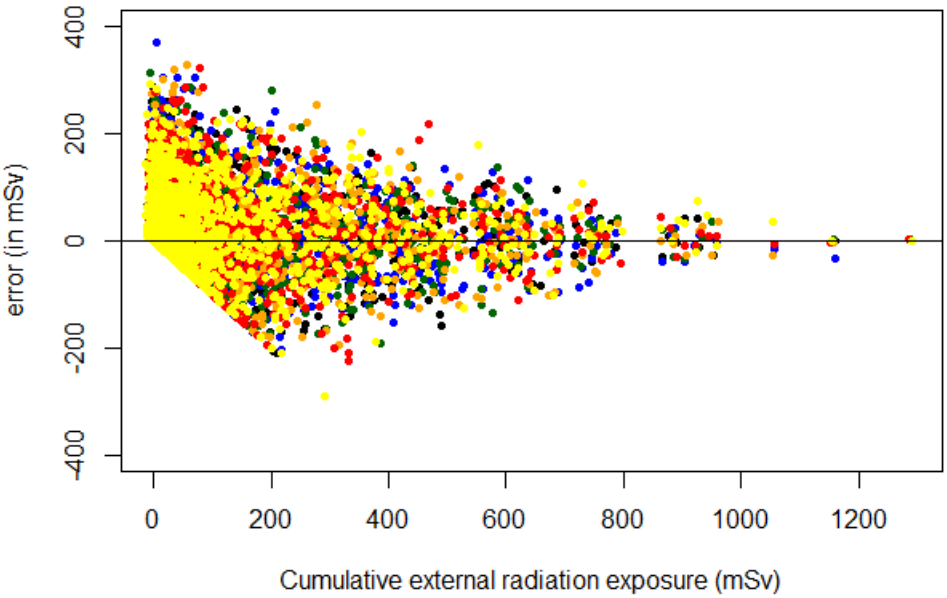

Figure S8. Illustration of measurement error for scenario (c) for 5 randomly selected MCMC samples (colours indicate different samples)

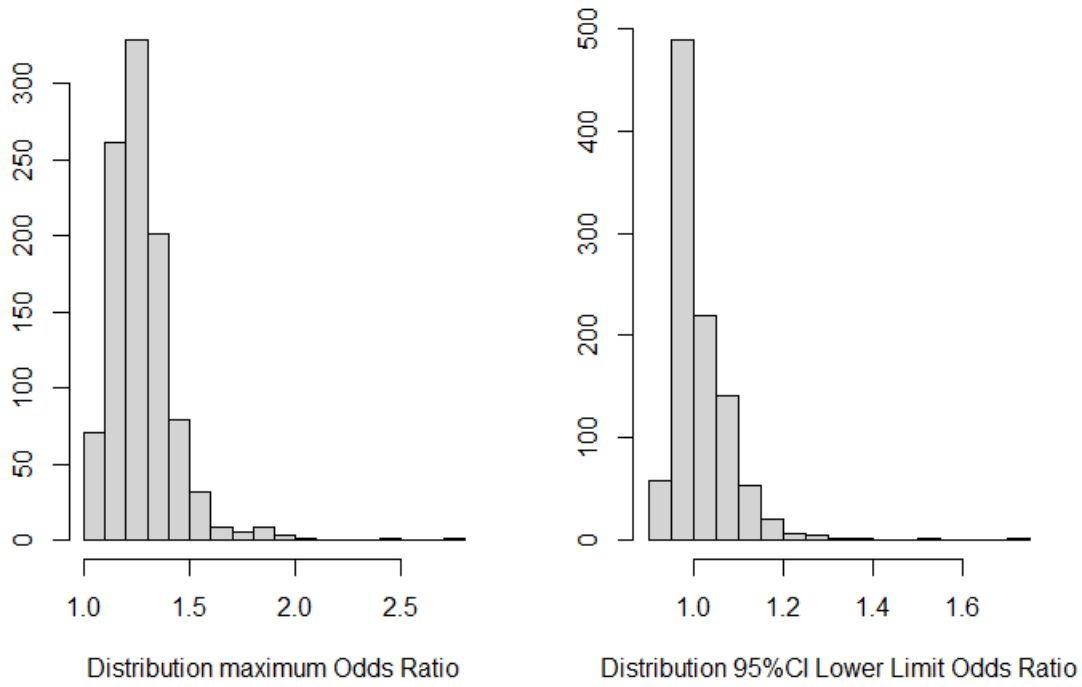

Figure S9. Distribution of maximum Odds Ratio (left) and 95% lower limit for 1,000 MCMC samples for scenario (c)

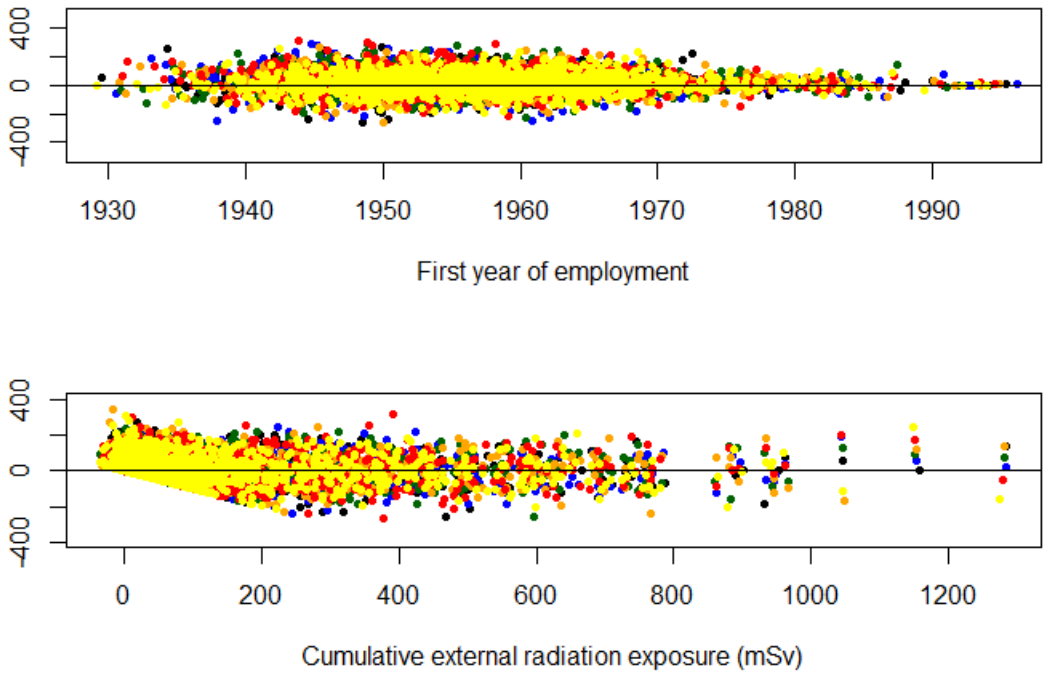

Figure S10. Illustration of measurement error for scenario (d) for 5 randomly selected MCMC samples (colours indicate different samples)

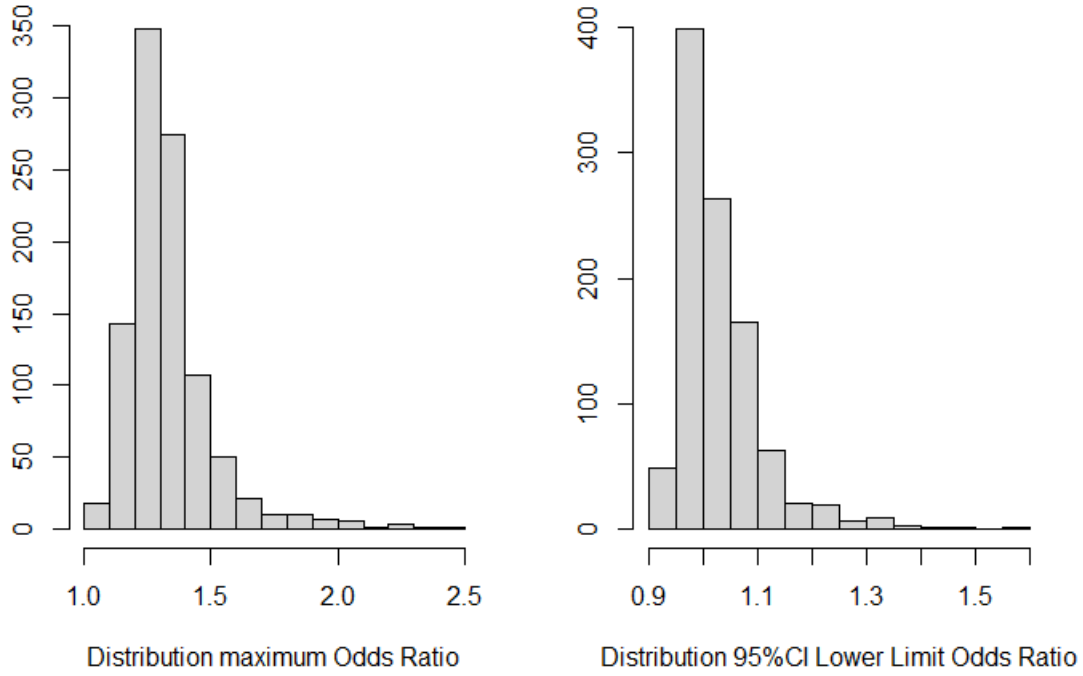

Figure S11. Distribution of maximum Odds Ratio (left) and 95% lower limit for 1,000 MCMC samples for scenario (d)

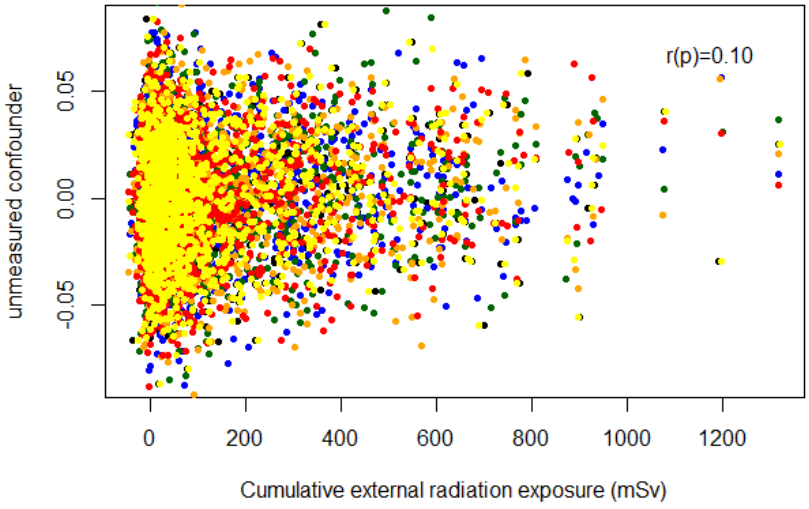

Figure S12. Illustration of patterns of cumulative external radiation dose and random 'unmeasured confounder', correlated with Pearson correlation (r(p)) of 0.10, for 5 randomly selected MCMC samples (colours indicate different samples)

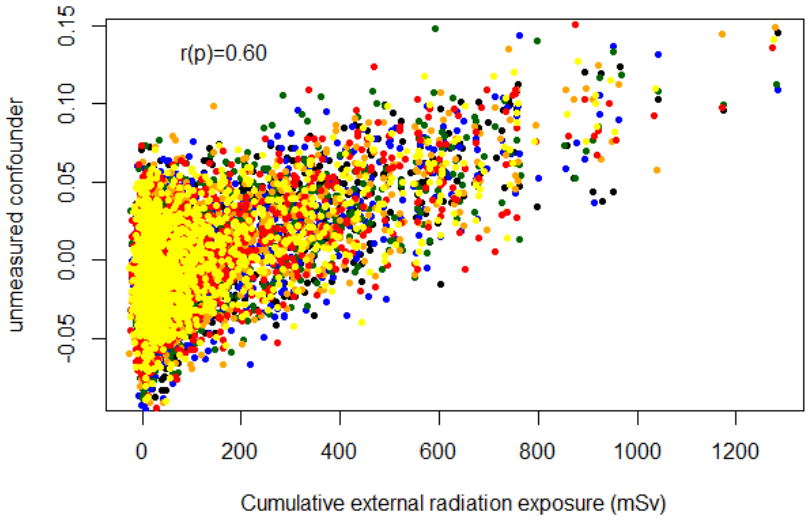

Figure S13. Illustration of patterns of cumulative external radiation dose and random 'unmeasured confounder', correlated with Pearson correlation (r(p)) of 0.30, for 5 randomly selected MCMC samples (colours indicate different samples)

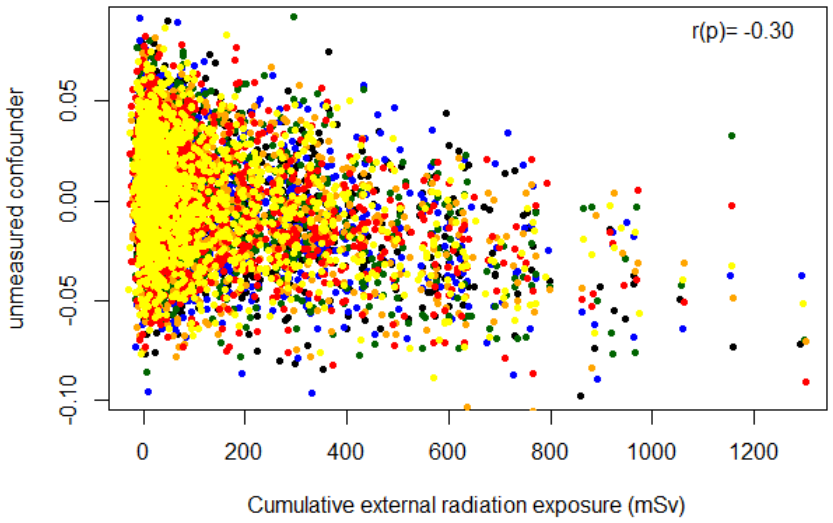

Figure S14. Illustration of patterns of cumulative external radiation dose and random 'unmeasured confounder', correlated with Pearson correlation (r(p)) of -0.30, for 5 randomly selected MCMC samples (colours indicate different samples)

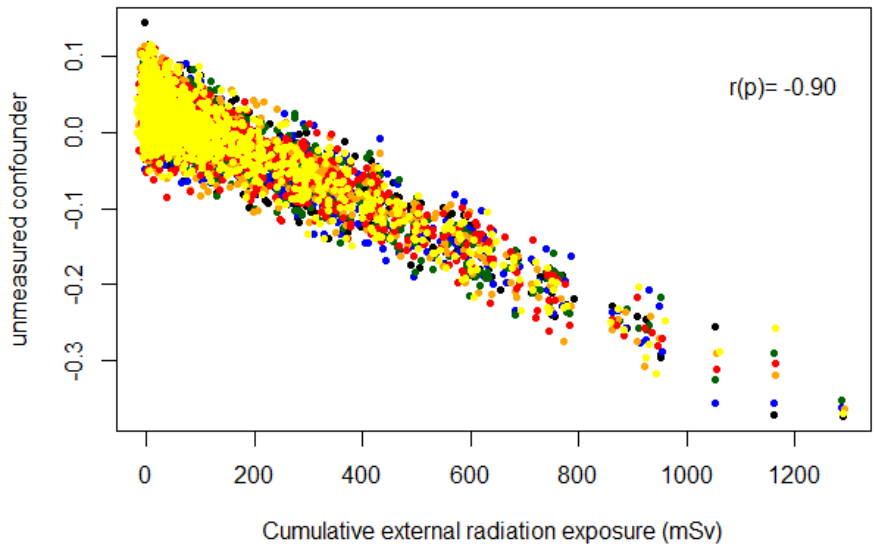

Figure S15. Illustration of patterns of cumulative external radiation dose and random 'unmeasured confounder', correlated with Pearson correlation (r(p)) of -0.90, for 5 randomly selected MCMC samples (colours indicate different samples)

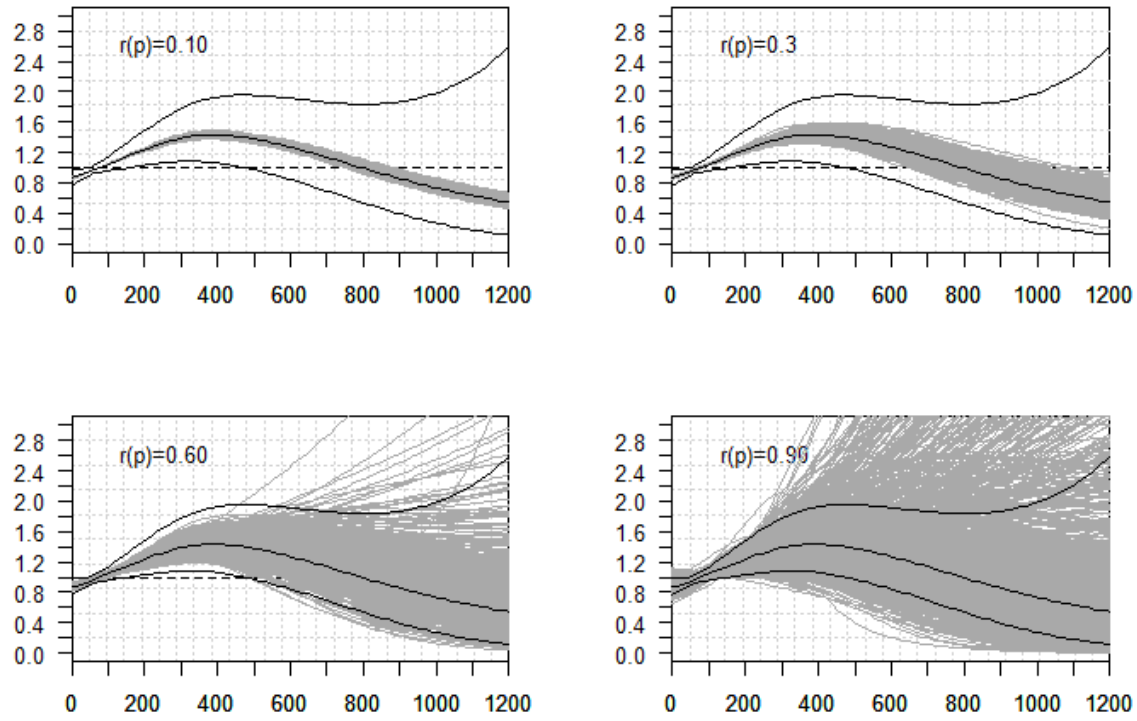

Figure S16. Comparative results of associations between cumulative external radiation dose and ischaemic heart disease mortality with models including an 'unmeasured confounder', modelled as a spline instead of a linear functional form, correlated with Pearson correlation coefficients r(p) ranging 0.10-0.90. 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 percentage of samples with 95% lower limit >1 are 100%,100%,92.4% and 47.9%, respectively.

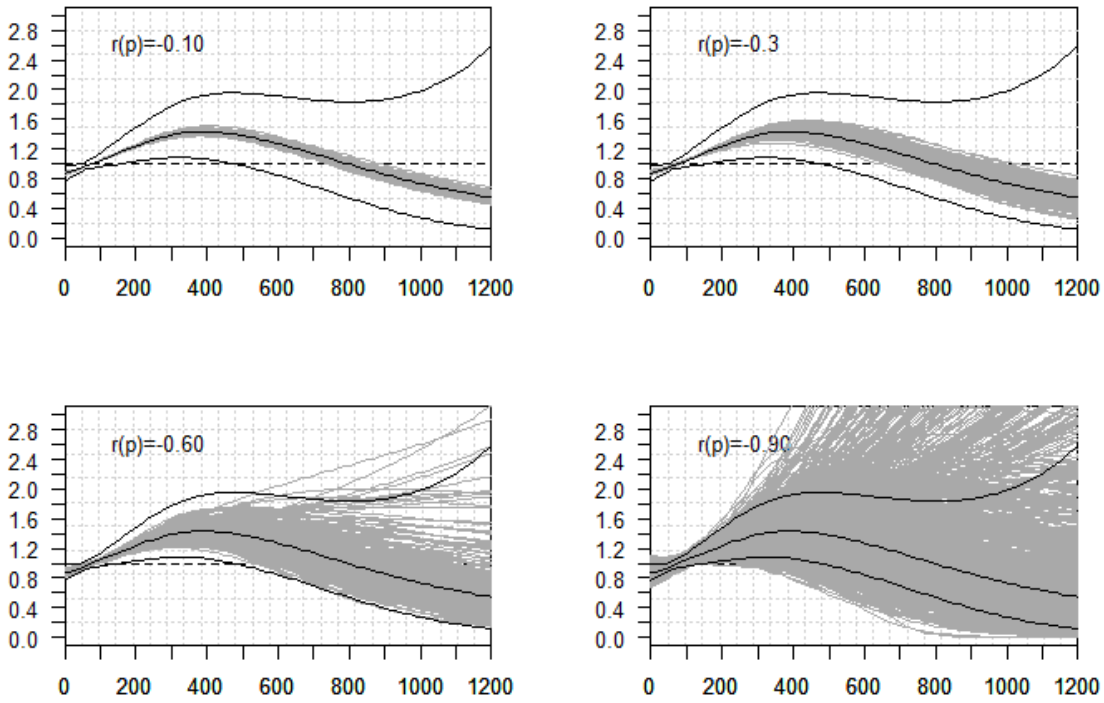

Figure S17. Comparative results of associations between cumulative external radiation dose and ischaemic heart disease mortality with models including an 'unmeasured confounder', modelled as a spline instead of a linear functional form, correlated with Pearson correlation coefficients r(p) ranging -0.10 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 percentage of samples with 95% lower limit >1 are 100%,100%,93.2% and 41.8%, respectively.