Supplement S1. Details of database search

The search was conducted on October 6th 2022. Articles were searched in PubMed/MEDLINE, Embase, Scopus, and Web of Science: Core Collection with no limits applied (date, language). Omitted from the searches were animal studies and publication/articles types not of interest (e.g., reviews, systematic reviews, meta-analyses, conference abstracts/proceedings, letters, retractions, corrigenda, errata, commentaries, news, protocols, and editorials). The literature searches produced 15,098 articles, which were uploaded to Covidence on October 6 2022.

Search script

((cardiotoxic*[tiab] OR "cardiac toxic*"[tiab] OR "cardiovascular disease*"[tiab] OR "heart disease*"[tiab] OR "ischemic heart disease*"[tiab] OR "ischaemic heart disease*"[tiab] OR "coronary occlusive disease*"[tiab] OR "myocardial ischemia*"[tiab] OR "myocardial infarction*"[tiab] OR "cardiovascular stroke*"[tiab] OR "heart attack*"[tiab] OR "heart failure"[tiab] OR "heart infarction*"[tiab] OR "cardiac failure"[tiab] OR "myocardial failure"[tiab] OR "angina pectoris"[tiab] OR "myocardial ischemia"[tiab] OR "cardiac valve disease*"[tiab] OR "heart valve disease*"[tiab] OR "valvular heart disease*"[tiab] OR "rheumatic heart disease*"[tiab] OR "bouillaud disease"[tiab] OR "rheumatic valve disease*"[tiab] OR "rheumatic valvular disease*"[tiab] OR "essential hypertension"[tiab] OR "essential arterial hypertension"[tiab] OR "idiopathic hypertension"[tiab] OR "hypertensive disease*"[tiab] OR "hypertensive heart disease*"[tiab] OR "hypertensive renal disease*"[tiab] OR "hypertensive nephropath*"[tiab] OR "renal hypertension"[tiab] OR "renovascular hypertension"[tiab] OR "hypertensive kidney disease*"[tiab] OR "hypertensive organ damage"[tiab] OR "secondary hypertension"[tiab] OR "pulmonary embolism*"[tiab] OR "lung embolism*"[tiab] OR "pulmonary thromboembolism*"[tiab] OR "pulmonary heart disease*"[tiab] OR "cor pulmonale"[tiab] OR pericarditis[tiab] OR pleuropericarditis[tiab] OR "pericardial inflammation"[tiab] OR endocarditis[tiab] OR endocarditides[tiab] OR "endocardial inflammation"[tiab] OR myocarditis[tiab] OR myocarditides[tiab] OR "myocardial inflammation"[tiab] OR cardiomyopath*[tiab] OR myocardiopath*[tiab] OR "myocardial disease*"[tiab] OR "cardiac conduction disorder*"[tiab] OR "cardiac conduction defect*"[tiab] OR "heart conduction disorder*"[tiab] OR "cardiac arrest"[tiab] OR "heart arrest"[tiab] OR "cardiac arrhythmia*"[tiab] OR "heart arrhythmia*"[tiab] OR arrhythmia*[tiab] OR "paroxysmal tachycardia*"[tiab] OR "paroxysmal reciprocal tachycardia*"[tiab] OR tachycardia*[tiab] OR "atrial fibrillation*"[tiab] OR "arterial disease*"[tiab] OR "artery disease*"[tiab] OR arteriopathy[tiab] OR "cerebrovascular disease*"[tiab] OR "cerebrovascular disorder*"[tiab] OR "cerebrovascular occlusion*"[tiab] OR stroke*[tiab] OR "cerebrovascular accident*"[tiab] OR "brain infarction*"[tiab] OR "brain vascular accident*"[tiab] OR "subarachnoid hemorrhage*"[tiab] OR "subarachnoid haemorrhage*"[tiab] OR "cerebrovascular haemorrhage*"[tiab] OR "cerebrovascular hemorrhage*"[tiab] OR "brain hemorrhage*"[tiab] OR "brain haemorrhage*"[tiab] OR "cerebral hemorrhage*"[tiab] OR "cerebral haemorrhage*"[tiab]

OR "intracerebral hemorrhage*"[tiab] OR "intracerebral haemorrhage*"[tiab] OR "cerebral infarction*"[tiab] OR "cerebral infarct*"[tiab] OR "subcortical infarct*"[tiab] OR "cerebral arterial occlusion*"[tiab] OR "cerebral arterial thrombosis"[tiab] OR "occlusive cerebrovascular disease*"[tiab] OR "cerebral artery occlusion*"[tiab] OR "cerebral arterial stenos*"[tiab] OR "cerebral artery stenos*"[tiab] OR arterioscleros*[tiab] OR atheroscleros*[tiab] OR "aortic aneurysm*"[tiab] OR "carotid artery aneurysm*"[tiab] OR "carotid aneurysm*"[tiab] OR aneurysm*[tiab] OR embolism*[tiab] OR "arterial embolism"[tiab] OR "artery embolism"[tiab] OR "arterial disease*"[tiab] OR "artery disease*"[tiab] OR "diseases of the arteries"[tiab] OR "peripheral arterial disease*"[tiab] OR "capillary leak*"[tiab] OR "capillary disease*"[tiab] OR microangiopath*[tiab] OR "microvascular disease*"[tiab] OR "microcirculatory disease*"[tiab] OR "circulatory system disease*"[tiab] OR "circulatory disease"[tiab] OR "circulatory diseases"[tiab] OR "vein disease*"[tiab] OR "venous disease*"[tiab] OR "venous disorder*"[tiab] OR "diseases of the veins"[tiab] OR "varicose vein*"[tiab] OR varicosis[tiab] OR thrombophlebitis[tiab] OR "peripheral vascular disease*"[tiab] OR "peripheral angiopath*"[tiab] OR "peripheral arteriopathy*"[tiab] OR "peripheral vascular disorder*"[tiab] OR "vein embolism"[tiab] OR "venous embolism"[tiab] OR phlebitis[tiab] OR "portal vein thrombos*"[tiab] OR phlebothrombos*[tiab] OR "venous thrombos*"[tiab] OR "deep vein thrombos*"[tiab] OR haemorrhoid*[tiab] OR hemorrhoid*[tiab] OR "esophageal varices"[tiab] OR "esophageal varix"[tiab] OR "esophagus varices"[tiab] OR "esophagus varix"[tiab] OR hypotension[tiab] OR "low blood pressure"[tiab] OR "bundle branch block*"[tiab] OR "fascicular block*"[tiab] OR "atrioventricular block*"[tiab] OR "Cardiovascular Diseases"[Mesh:NoExp] OR "Cardiomyopathies"[Mesh] OR "Myocarditis"[Mesh] OR "Endocarditis"[Mesh] OR "Pericarditis"[Mesh] OR "Myocardial Ischemia"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Heart Failure"[Mesh] OR "Angina Pectoris"[Mesh] OR "Myocardial Ischemia"[Mesh] OR "Heart Valve Diseases"[Mesh] OR "Rheumatic Heart Disease"[Mesh] OR "Essential Hypertension"[Mesh] OR "Hypertension"[Mesh:NoExp] OR "Hypertensive Nephropathy" [Supplementary Concept] OR "Hypertension, Renal"[Mesh] OR "Hypertension, Renovascular"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Pulmonary Heart Disease"[Mesh] OR "Cardiomyopathies"[Mesh:NoExp] OR "Cardiac Conduction System Disease"[Mesh] OR "Heart Arrest"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR "Tachycardia, Paroxysmal"[Mesh] OR "Tachycardia"[Mesh:NoExp] OR "Atrial Fibrillation"[Mesh] OR "Cerebrovascular Disorders"[Mesh:NoExp] OR "Stroke"[Mesh] OR "Subarachnoid Hemorrhage"[Mesh] OR "Cerebral Hemorrhage"[Mesh] OR "Cerebral Infarction"[Mesh] OR "Arteriosclerosis"[Mesh] OR "Atherosclerosis"[Mesh] OR "Aortic Aneurysm"[Mesh] OR "Carotid Artery Injuries"[Mesh] OR "Aneurysm"[Mesh] OR "Embolism"[Mesh] OR "Arterial Occlusive Diseases"[Mesh] OR "Peripheral Arterial Disease"[Mesh] OR "Capillary Leak Syndrome"[Mesh] OR "Varicose Veins"[Mesh] OR "Thrombophlebitis"[Mesh] OR "Peripheral Vascular Diseases"[Mesh] OR "Phlebitis"[Mesh] OR "Venous Thrombosis"[Mesh] OR "Hemorrhoids"[Mesh] OR "Esophageal and Gastric Varices"[Mesh] OR "Hypotension"[Mesh] OR "Cardiotoxicity"[Mesh] OR "Bundle-Branch Block"[Mesh]) AND (radiation[tiab] OR radiotherapy[tiab] OR radiotherapies[tiab] OR radionuclide*[tiab] OR radioisotope*[tiab] OR "radioactive nuclide*"[tiab] OR "radioactive isotope*"[tiab] OR "roentgen therapy"[tiab] OR "roentgen treatment"[tiab] OR "nuclear fuel"[tiab] OR uranium[tiab] OR "atomic bomb"[tiab] OR Hiroshima[tiab] OR Nagasaki[tiab] OR Goiânia[tiab] OR Chernobyl[tiab] OR Chornobyl[tiab] OR Fukushima[tiab] OR "nuclear accident*"[tiab] OR "nuclear reactor*"[tiab] OR "nuclear worker*"[tiab] OR "nuclear power"[tiab] OR "Radiation Exposure"[Mesh] OR "Radiotherapy"[Mesh] OR

"Radioisotopes"[Mesh] OR "Radiation, Ionizing"[Mesh] OR "Radiation Injuries"[Mesh] OR "Radiation"[Mesh:NoExp] OR "Radiation Effects"[Mesh] OR "Radiation Dosage"[Mesh] OR "Nuclear Power Plants"[mesh] OR "Chernobyl Nuclear Accident"[Mesh] OR "Radioactive Hazard Release"[Mesh] OR "Fukushima Nuclear Accident"[Mesh]) AND (radioepidemiological[tiab] OR "radio epidemiological"[tiab] OR "epidemiological study"[tiab] OR "epidemiological studies"[tiab] OR cohort*[tiab] OR "concurrent study"[tiab] OR "concurrent studies"[tiab] OR "incidence study"[tiab] OR "incidence studies"[tiab] OR "cross sectional study"[tiab] OR "cross sectional studies"[tiab] OR "cross sectional survey*"[tiab] OR "prevalence study"[tiab] OR "prevalence studies"[tiab] OR "case control"[tiab] OR "case controls"[tiab] OR "followup study"[tiab] OR "followup studies"[tiab] OR "follow up study"[tiab] OR "follow up studies"[tiab] OR "followed up"[tiab] OR followedup[tiab] OR longitudinal[tiab] OR prospective[tiab] OR retrospective[tiab] OR registry[tiab] OR registries[tiab] OR “controlled before-after studies”[tiab] OR Registries[mesh] OR "Epidemiologic Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR "Cohort Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Controlled Before-After Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh]) AND medline[sb]) NOT (letter[ptyp] OR editorial[ptyp] OR comment[ptyp] OR news[ptyp] OR "Congress"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR editorial[tiab] OR commentary[tiab] OR “conference abstract*”[tiab] OR “conference proceeding*”[tiab] OR “systematic review*”[ti] OR “meta-analysis”[ptyp] OR “meta-analysis”[ti] OR “meta-analyses”[ti] OR "Review"[Publication Type] OR "Systematic Review"[Publication Type] OR “retracted publication”[ptyp] OR “retraction of publication”[ptyp] OR “retraction of publication”[tiab] OR “retraction notice”[ti] OR “retracted publication”[tiab] OR "Published Erratum"[Publication Type] OR Corrigenda[tiab] OR corrigendum[tiab] OR errata[tiab] OR erratum[tiab] OR protocol[ti] OR protocols[ti]) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[tiab] OR mouse[tiab] OR rat[tiab] OR rats[tiab] OR dog[tiab] OR dogs[tiab] OR pig[tiab] OR pigs[tiab] OR swine[tiab] OR porcine*[tiab] OR rodent*[tiab] OR animal*[tiab])

Further restrictions imposed in selecting papers

1) A study had to have a quantitative estimate of risk for some clinically detectable endpoint in relation to some measure of administered dose to some relevant organ (heart, carotid artery, aorta, liver, kidney), which must be predominantly low LET. Dose to the thyroid or salivary glands was deemed an adequate surrogate for dose to the carotid artery. However, if a whole body dose was all that was available that would be acceptable, if the dose was largely uniform (so e.g. predominantly radiation with >100 keV energy). So for example this would rule out studies only in relation to radon exposure, or of ^{125}I or ^{131}I where there was no obvious way to converting the given exposures (e.g. in GBq) to low LET organ

dose (with organs as above). So any endpoints listed in ICD10 390-459, or in ICD10 I00-I99 are included.

2) No small case series (e.g. < 10 people)
3) No studies that appear to be only abstracts, correspondence, or relating to conference proceedings, or reviews (these should have been screened out by the above search, but it appears not all have been).

A first pass by NH and MPL looking only at title and abstracts found a total of 369 agreed articles to be screened, and 1239 articles where the votes had still to be reconciled. A second stage screening looking at the 414 articles agreed from the first stage screening, and in which the papers themselves were then examined in some detail, but considering only each paper by itself. For Russian and Chinese articles MPL and NH screened articles based on translations provided by NIH library translation services. Of these 194 articles were agreed to be potentially informative, but a number of additional checks were then conducted. In a final stage of the review both reviewers (MPL, NH) determined the most current study of each cohort, and excluded studies of cohorts included in otherwise larger cohorts and where there was minimal extra follow-up, as detailed below, also for certain other specific reasons, again as detailed below. This resulted in a final group of 93 papers being used.

In general, higher dose medical (radiotherapy) studies were excluded if there was not reliable estimation of organ (heart, brain, carotid artery) dose; in occupational studies, dose is generally assumed to be administered uniformly, so that whole-body dose (effective dose) should approximate that to the heart. For the Japanese atomic bomb survivors and Russian Mayak worker cohort and a few other groups where both incidence and mortality data were available, both endpoints were analysed, as they are likely to be to some extent disjoint. Nevertheless, in

sensitivity analyses we assessed the effect of excluding either the Mayak mortality or the Mayak incidence data (Supplement S3 Table S3.7), as the overlap in endpoints in this dataset was judged to be most likely. In a number of studies where risk was evaluated over restricted dose range, in particular the studies of Tran *et al* [1] and Zhang *et al* [2] in both of which information on risk was available relating to the dose range ≤0.5 Gy, which prior biological data suggest may differ from the full dose range [3 4], data for the restricted dose range was employed. We performed a similar exclusion in the Mayak worker data, using where available risk evaluated over the range ≤4 Gy [5 6]. We employed the then most recent follow-up of each cohort.

Medical therapeutic studies in which only administered treatment dose was used, rather than organ dose, were deemed quantitatively uninformative and were removed. In a number of studies the endpoints were not obviously relevant to CVD, or the measurements of dose did not allow assessment of risk.

If any study had an underlying study population that was largely contained in another study, and did not contribute more than 5 extra years of follow-up it was removed. So for example, the Sellafield part of the study of Azizova *et al* [7], with follow-up 1947-2005, is less than 5 years different from the INWORKS study [8] which otherwise subsumes it, and the UK part of which has follow-up ending in 2001; the Mayak worker follow-up is very similar to that of Azizova *et al* [5 6 9], but suffers from the disadvantage of use of a 10 year lag, and also does not, unlike the study of Azizova *et al* [6], furnish information on mortality risk under 4 Gy so neither part of Azizova *et al* [7] was used in the meta-analysis, although listed in Supplement S3 Table S3.5. For similar reasons we did not use the analyses of Azizova *et al* [10 11], which used only a 10 year lag and did not assess information on risk under 4 Gy; the dose metric used in both newer studies, external gamma dose to the liver, we also judged to be less relevant to the endpoints considered. However, the UK NRRW studies of Zhang *et*

al [2] and Hinksman *et al*[12] have follow-up ending 2011, 10 years greater than that of the INWORKS study [8] and so were included. In a similar way, the IARC 15-Country analysis of Vrijheid *et al* [13] includes many radiation workers not included in the later INWORKS study [8] and so was included in the meta-analysis along with INWORKS. However, in various sensitivity analyses we assessed the effect of excluding this earlier study. The Canadian National Dose Registry data of Zielinski *et al* [14] overlaps slightly with the IARC study [13]. However, this study has been much criticised [15], and it appears quite likely that there is substantial bias in the reported risks. Nevertheless we list it in Supplement S3 Table S3.5, and include it in most meta-analysis, although we test the effect of excluding it in sensitivity analysis (Supplement S3 Table S3.7).

Two reviewers (MPL, KA) independently coded the information from the final 93 papers and prepared a database that was used for the meta-analysis. In a few cases where the information in a published report was ambiguous, the first reviewer (MPL) contacted study authors to resolve discrepancies. In coding the maximum dose in each study we take account of the fact that for some data we do not have a precise estimate of maximum dose, but for example only know that the maximum dose is $<X$ Gy or $>X$ Gy. For those studies where the maximum dose is known to be $<X$ Gy or as $=X$ with the value of $X \leq 0.5$ we can confidently put these in the ≤0.5 Gy group, likewise those studies for which maximum dose is known to be $>X$ Gy or $=X$ with the value of $X > 5$, which we can confidently put in the >5 Gy group; all other studies the maximum dose level had to be given exactly (in other words it was known that there was an individual with dose = X) in order to assign them to a dose group, otherwise this dose group was coded as missing.

Wherever possible the ERR was taken directly from the relevant publication, which are reproduced in Supplement S3 Tables S3.4, S3.5 and S3.6. The studies of Cutter *et al*[16], van Nimwegen *et al*[17], Liao *et al*[18], Mueller *et al*[19], Fullerton *et al*[20], Mulrooney *et al*[21], Mulrooney *et*

al[22], Shrestha *et al*[23], Markabayeva *et al*[24], Boice *et al*[25], Moseeva *et al*[26], Wang *et al*[27], Cho *et al*[28], Kim *et al*[29], Ni *et al*[30], Martin and Ségala[31], Gillies and Haylock[32], Semenova *et al*[33] and Tatarenko [34] did not directly give such estimates, so subsidiary analysis was performed to derive useful risk estimates for these papers, as described in Supplement S2.

There were a number of exclusions where the disease endpoint did not obviously relate to standard clinical endpoints, or in which the measure of dose used was not useful (*n*=15), and agreed by consensus. For example, the Seversk study of Karpov *et al* [35 36] is only minimally informative, comprising simply standardised relative risks by dose group; as radiation dose appears to be highly correlated with both smoking and prevalence of shift work, which are both substantial risk factors for CVD [37 38], the possibility of substantial bias due to confounding appears likely. Therefore, this study was not used in the meta-analysis.

There were three studies which although they largely overlapped with other studies, we provide details of in Supplement S3 Tables S3.4 and S3.5, specifically the Mayak worker stroke subtype analysis of Moseeva *et al*[26], which uses almost the same underlying cohort as Azizova *et al*[9], the case-control study of Drubay *et al*[39], nested within the French uranium miner cohort of Rage *et al*[40], and the study of breast cancer patients of Kim *et al*[29], a substudy of the slightly earlier study of Chung *et al*[41]. None of these three substudies were employed in the meta-analysis. The study of Hahn *et al*[42] was not found by our database search, although it was identified by a PubMed literature search that was used as the basis for a previous review[3]. It is listed in Supplement S3 Table S3.4, and is used in the meta-analysis. Studies of the Los Alamos workers[43] and of the Rochester thymus cohort[44] were also not found in our database review, being discovered more adventitiously. We list the results of these two accidentally discovered articles in Supplement S3 Tables S3.4 and S3.5, but

do not include them in the meta-analysis. However, we performed sensitivity analysis in which they were added to the sample (Supplement S3 Table S3.7).

We classified the studies in relation to the maximum dose, and also the maximum dose rate. In accordance with standard terminology studies in which the maximum dose rate was <5 mGy/hour were deemed low dose rate [45], and all others moderate/high dose rate.

The ROBINS-I framework for assessing risk of bias was used [46], assessing bias due to:

(a) confounding;

(b) selection of participants into the study;

(c) classification of interventions;

(d) deviations from intended interventions;

(e) missing data;

(f) measurement of outcomes;

(g) selection of the reported result.

Numeric scores in a range 1-5 were assigned to each of these bias components, using the following scheme:

5 - definitely no risk of material bias (>50%);

4 - probably no risk of material bias (>50%);

3 - possibly risk of material bias (>50%);

2 - probably risk of material bias (>50%);

1 - definitely risk of material bias (>50%).

A similar, and more objectively defined multipart score for study-quality related meta-variables was constructed as follows:

(a) Dosimetry (out of 5)

Starting with a score of 5 points: subtract 1 point if dosimetry is not based on concurrent registry-derived records, or possibility of evaluation not blind to outcome, or if method of evaluation is unclear; subtract 1 point if some substantial component of dose is not assessed (e.g., neutrons) or substantial (>5%) part of cohort lacks individual dose data; subtract 2 points if dosimetry is based on area-based assessment of exposure; subtract 1 point if no attempt is made to correct for dose error; subtract 1 point if dose is not calculated to relevant organ (heart for IHD or all cardiovascular, brain/carotid for CeVD).

(b) Endpoint ascertainment (out of 5)

Starting with a score of 5 points: subtract 1 point if the follow-up is substantially incomplete (>5% of deaths/cases in cohort are lost to follow-up); subtract 1 point if follow-up is not based on local (regional), national or cohort-based registers, or details of follow-up unclear; subtract 1 point if date of ascertainment of disease incidence/mortality may be substantially in error (> 1 year); subtract 1 point if there is no clinical review of pathology data to verify diagnosis of mortality/incidence; subtract 1 point if diagnosis may not be blind to exposure status, or be subject to other types of bias; subtract 1 point if endpoints are a small subset (<50%) of available CVD, unless the endpoint is part of a focused study (e.g. case-control study) (implying selection of endpoint prior to analysis).

(c) Selection criteria (out of 5)

Starting with a score of 5 points: subtract 1 point if the selection criteria are not clear (e.g. clinical case series over unspecified period, unspecified nature of recruitment criteria); subtract 1 point if the selection may result in omission of potentially highly exposed persons; subtract 2 points if the selection does not stringently exclude persons with missing dose records; subtract 2 points if the selection does not exclude workers working for a short time (< 6 months).

(d) Lifestyle/cardiovascular disease risk factors assessed (out of 5)

Starting with a score of 5 points: subtract 1 point if there is no information on (and adjustment for) total serum cholesterol status (or LDL/HDL); subtract 1 point if there is no information on (and adjustment for) cigarette smoking; subtract 1 point if there is no information on (and adjustment for) obesity; subtract 1 point if there is no information on (and adjustment for) diabetes; subtract 1 point if there is no information on (and adjustment for) blood pressure;

add 1 point if there is adjustment for socioeconomic status.

(e) Statistical analysis (out of 5)

Starting with a score of 5 points: subtract 1 point if there is no attempt to assess interactions of dose response with age at exposure, attained age or time since exposure; subtract 1 point if the method of analysis is unclear; subtract 1 point if an inappropriate lag period is used (outside the range 5-10 years), or if lag period is not mentioned; subtract 1 point if log-linear rather than linear model used; subtract 1 point if no trend (or CI) reported - so trend (or CI) had to be reconstructed (e.g. from point estimates).

For all components of the quality score the codes were constrained to lie between 0 and 5. This study quality scores are slight expansions of the scoring scheme implemented in a previous meta-analysis [4]. Averages of these two sets of scores were used to limit the meta-analysis to consider only higher quality studies in certain subsidiary analyses (Tables 4, 5, Supplement S3 Figs. S3.1, S3.2).

Supplement S2. Details of preliminary analyses performed to derive risk estimates in certain studies

In the Netherlands Hodgkin lymphoma (HL) studies of Cutter *et al* [16], van Nimwegen *et al* [17] and in the thymoma study of Liao *et al* [18] ERR was estimated from tabulations of numbers of cases and controls in the associated paper. To make such estimations a simple linear odds ratio (OR) model was fitted, in which the OR in dose group i with average organ dose D_i, relative to group 0, with organ dose $D_0 = 0$, is assumed to be given by:

$$OR_i = 1 + \alpha D_i \qquad \text{(S1)}$$

where α is the excess OR per Gy. Assuming binomially-distributed numbers of $n_{1,i}$ cases and $n_{0,i}$ controls in each dose group i for $i = 0,1,...,N$, the prospective likelihood (known to be equivalent to the retrospective likelihood [47]) is given by:

$$\prod_{i=0}^{N} \binom{n_{1,i} + n_{0,i}}{n_{1,i}} \frac{\left[\lambda_0[1+\alpha D_i]\right]^{n_{1,i}}}{\left[1+\lambda_0[1+\alpha D_i]\right]^{n_{1,i}+n_{0,i}}} \qquad \text{(S2)}$$

where the parameter λ_0 is the baseline odds. Fitting of this model is performed by maximum likelihood [48] using Epicure [49]. Central (maximum likelihood) estimates and 95% profile likelihood confidence intervals (CI) [48] are given in Supplement S3 Table S3.4. As is well known, when disease rates are low the OR is approximately equal to the RR [50], so that the parameter α that we estimate in this way is approximately equal to the ERR per Gy.

For the Childhood Cancer Survivor Study (CCSS) analyses of Mueller *et al* [19], Fullerton *et al* [20], Mulrooney *et al* [21] and Shrestha *et al*[23], in the St Jude Lifetime Cohort analysis of Mulrooney *et al*[22], the Semipalatinsk analysis of Markabayeva *et al*[24], the Mound worker

analysis of Boice *et al* [25], the Mayak worker analysis of Moseeva *et al*[26] and the Semipalatinsk data of Semenova *et al*[33] the most useful information given are estimates of the (adjusted) relative risk, RR_i (and associated 95% CI $(\mathrm{CI}_{li}, \mathrm{CI}_{ui})$) in each dose group i; estimates of α and associated CI are obtained by weighted least squares, i.e., by minimising the inverse-variance-weighted sum of squares:

$$\sum_i w_i [RR_i - 1 - \alpha D_i]^2 \qquad \text{(S3)}$$

where w_i is the inverse-variance weight attached to dose group i, which is approximately given by:

$$w_i = \left[2 \frac{N_{0.975}}{(\mathrm{CI}_{ui} - \mathrm{CI}_{li})} \right]^2 \qquad \text{(S4)}$$

[$N_{0.975} \approx 1.96$ is the 97.5% percentile point of the standard normal distribution:

$0.975 = P[N(0,1) < N_{0.975}]$.]

In the study of Wang *et al*[27] only the ERR/Sv and a 2-sided *p*-value were given. From this was derived the standard deviation (SD) of the estimate and hence the 95% CI using percentiles of the normal distribution.

In the studies of Kim *et al*[29], Cho *et al*[28], Ni *et al* [30] and Tatarenko *et al*[34] the excess odds ratio (EOR)/Gy was derived from the given ln[OR] for dose above and below a given mean heart dose cutpoint, and using given values of the minimum and maximum mean heart dose, D_{min} and D_{max}, and using midpoint estimates for $[D_{min} + D_{cut}]/2$ and $[D_{max} + D_{cut}]/2$ Gy to scale the ln[odds ratios].

In the study of Gillies and Haylock[32] a Poisson linear ERR model was fitted via maximum likelihood[48] using Epicure[49] to data in which the expected number of deaths in group i was:

$$E_i[1+\alpha D_i]$$

(S5)

where the offset E_i is the given expected number of deaths in that group. In the dataset of Martin and Ségala[31] a similar Poisson linear ERR model was fitted in the same way, in which the offset E_i was computed by [observed number of deaths]/[relative risk] in that group.

Supplement S3. Supplementary Tables and Figures used for (Table S3.1) and used by meta-regression analysis (Tables 2-5, Figure 2).

Table S3.1. Studies used in analysis of four main endpoints (ischaemic heart disease, other heart disease, cerebrovascular disease, all other cardiovascular diseases). Unless otherwise stated all endpoints are of mortality.

Reference	Study/endpoint description	Endpoint group	Mean bias score / minimum bias score	Mean quality score / minimum quality score
Anderson *et al* [51]	US uranium enrichment worker ischaemic heart disease	Ischaemic heart disease	4.29 / 2	3.20 / 1
Anderson *et al* [51]	US uranium enrichment worker cerebrovascular disease	Cerebrovascular disease	4.29 / 2	3.20 / 1
Azizova *et al*[9]	Mayak worker cerebrovascular disease incidence, 5 year lag	Cerebrovascular disease	4.14 / 3	4.00 / 3
Azizova *et al*[9]	Mayak worker cerebrovascular disease, 5 year lag	Cerebrovascular disease	3.71 / 2	3.60 / 2
Azizova *et al* [5]	Mayak worker ischaemic heart disease incidence (ICD9 410-414), 5 year latency, < 4 Gy	Ischaemic heart disease	4.14 / 3	4.00 / 3
Azizova *et al* [5]	Mayak worker ischaemic heart disease (ICD9 410-414), 5 year latency, < 4 Gy	Ischaemic heart disease	3.71 / 2	3.60 / 2
Azizova *et al*[52]	Mayak worker lower extremity arterial disease (ICD9 440.2) incidence [external gamma 5-yr lag]	All other cardiovascular disease (than heart disease, cerebrovascular disease)	4.00 / 2	4.20 / 3
Azizova *et al*[53]	Mayak worker hypertension incidence	All other cardiovascular disease (than heart disease, cerebrovascular disease)	3.71 / 2	3.80 / 2
Boekel *et al* [54]	Netherlands-NKI-Rotterdam breast cancer case-control study heart failure incidence (CTCAE grade ≥2) - all data	Other heart disease	4.00 / 3	3.80 / 2
Boice *et al* [55]	US nuclear power industry workers - ischaemic heart disease (ICD9 410-414)	Ischaemic heart disease	3.43 / 2	2.60 / 1
Boice *et al* [56]	US 8 series nuclear test veterans - ischaemic heart disease	Ischaemic heart disease	3.00 / 1	2.20 / 0
Boice *et al* [57]	US medical workers - ischaemic heart disease (ICD9 410-414)	Ischaemic heart disease	3.71 / 2	3.40 / 1
Boice *et al* [57]	US medical workers - cerebrovascular disease (ICD9 430-438)	Cerebrovascular disease	3.71 / 2	3.40 / 1
Borkenhagen *et al* [58]	Medical College of Wisconsin lung cancer study cardiotoxicity morbidity (arrhythmia, pericardial disease, valvular disease) - mean dose to pericardium	Other heart disease	3.29 / 1	2.60 / 0
Bouet *et al* [59]	French nuclear fuel workers - ischaemic heart disease	Ischaemic heart disease	4.71 / 3	4.20 / 3
Bouet *et al* [59]	French nuclear fuel workers - cerebrovascular disease	Cerebrovascular disease	4.71 / 3	4.20 / 3
Cha *et al* [60]	Korean diagnostic medical workers – hypertension	All other cardiovascular disease (than heart disease, cerebrovascular disease)	4.43 / 3	4.40 / 3
Cha *et al* [60]	Korean diagnostic medical workers - ischaemic heart disease	Ischaemic heart disease	4.43 / 3	4.40 / 3
Cha *et al* [60]	Korean diagnostic medical workers - cerebrovascular disease	Cerebrovascular disease	4.43 / 3	4.40 / 3
Cutter *et al* [16]	Netherlands Hodgkin lymphoma valvular disease case-control study - valvular heart disease incidence CTCAE 4.0 grades ≥2	Other heart disease	4.14 / 3	3.80 / 2
Darby *et al* [61]	Nordic breast cancer case–control study, ischaemic heart disease incidence (ICD10 I20-I25), cumulative heart dose	Ischaemic heart disease	4.14 / 3	4.00 / 3
Dorth *et al* [62]	Duke Cancer Institute head and neck cancer study - carotid stenosis incidence	Cerebrovascular disease	3.43 / 2	2.80 / 1
El-Fayech *et al* [63]	French (Institut Gustave Roussy) childhood cancer stroke study - all stroke incidence	Cerebrovascular disease	3.43 / 2	3.00 / 2
Elgart *et al* [64]	NASA astronauts, adjusted for age at exit+entrance, medical diagnostic dose - ischaemic heart disease	Ischaemic heart disease	3.86 / 2	3.40 / 2

Elgart *et al* [64]	NASA astronauts, adjusted for age at exit+entrance, medical diagnostic dose - cerebrovascular disease	Cerebrovascular disease	3.86 / 2	3.00 / 0
Errahmani *et al*[65]	French MEDIRAD-BRACE breast cancer arrhythmia incidence case-control study after left sided breast cancer	Other heart disease	4.29 / 3	3.40 / 2
Errahmani *et al*[65]	French MEDIRAD-BRACE breast cancer arrhythmia incidence case-control study after right sided breast cancer	Other heart disease	4.29 / 3	3.40 / 2
Fullerton *et al* [20]	Childhood Cancer Survivor Study of second stroke incidence in relation to maximum (4-segment) brain dose	Cerebrovascular disease	3.86 / 2	3.40 / 2
Gillies *et al* [8]	International Nuclear Workers Study (INWORKS) - ischaemic heart disease	Ischaemic heart disease	4.29 / 2	3.60 / 1
Gillies *et al* [8]	International Nuclear Workers Study (INWORKS) - cerebrovascular disease	Cerebrovascular disease	4.29 / 2	3.60 / 1
Gillies & Haylock[32]	UK nuclear test veterans ischaemic heart disease (ICD10 I20-I25)	Ischaemic heart disease	3.86 / 2	2.80 / 1
Gillies & Haylock[32]	UK nuclear test veterans cerebrovascular disease (ICD10 I60-I69)	Cerebrovascular disease	3.86 / 2	2.80 / 1
Golde *et al* [66]	Mallinckrodt workers - ischaemic heart disease (ICD9 410-414)	Ischaemic heart disease	3.71 / 2	2.80 / 1
Green *et al* [67]	National Wilms' Tumor Study Group - congestive heart failure incidence (requiring treatment with digoxin & diuretics) - analysis using lung dose	Other heart disease	3.43 / 2	2.40 / 1
Grosche *et al* [68]	Kazakhstan nuclear weapons test study, 10 year lag, stroke (ICD9 430-438): exposed settlements only	Cerebrovascular disease	3.43 / 1	2.80 / 0
Haddy *et al* [69]	France-UK cohort - cerebrovascular disease (ICD9 430-439, ICD10 I60-I69)	Cerebrovascular disease	3.71 / 2	3.40 / 1
Hinksman *et al*[12]	UK NRRW cerebrovascular disease (ICD10 I60-I69) <0.5 Gy	Cerebrovascular disease	3.71 / 2	3.40 / 1
Ivanov *et al*[70]	Russian Chernobyl liquidators ischaemic heart disease (ICD10 I20-I25) incidence	Ischaemic heart disease	3.43 / 1	2.20 / 0
Ivanov *et al*[70]	Russian Chernobyl liquidators other heart disease (ICD10 I30-I52) incidence	Other heart disease	3.43 / 1	2.20 / 0
Ivanov *et al*[70]	Russian Chernobyl liquidators diseases of arteries, arterioles and capillaries (ICD10 I70-I79) incidence	All other cardiovascular disease (than heart disease, cerebrovascular disease)	3.43 / 1	2.20 / 0
Ivanov *et al*[70]	Russian Chernobyl liquidators disease of veins, lymphatic vessels and lymph nodes (ICD10 I80-I89) incidence	All other cardiovascular disease (than heart disease, cerebrovascular disease)	3.43 / 1	2.20 / 0
Jacobse *et al* [71]	Netherlands-NKI-Rotterdam breast cancer case-control study myocardial infarction incidence	Ischaemic heart disease	3.71 / 2	3.60 / 3
Kashcheev *et al*[72]	Russian Chernobyl liquidators cerebrovascular disease (ICD10 I60-I69) morbidty	Cerebrovascular disease	3.00 / 1	2.20 / 0
Krasnikova *et al* [73]	Ukrainian Chernobyl cleanup workers 1+ Gy vs unexposed - chronic cerebrovascular disease (ICD10 I67, I69)	Cerebrovascular disease	3.00 / 2	1.60 / 0
Krestinina *et al* [74]	Techa River cohort - ischaemic heart disease latency 5 years	Ischaemic heart disease	3.71 / 1	2.80 / 0
Krestinina *et al* [74]	Techa River cohort - cerebrovascular disease latency 5 years	Cerebrovascular disease	3.71 / 1	2.80 / 0
Kreuzer *et al* [75]	German uranium miner study ischaemic heart disease	Ischaemic heart disease	4.29 / 3	3.80 / 3
Kreuzer *et al* [75]	German uranium miner study cerebrovascular disease	Cerebrovascular disease	4.29 / 3	3.80 / 3
Lane *et al* [76]	Eldorado uranium miners ischaemic heart disease	Ischaemic heart disease	4.00 / 1	2.60 / 0
Lane *et al* [76]	Eldorado uranium miners stroke	Cerebrovascular disease	4.00 / 1	2.60 / 0
Lee *et al* [77]	Singapore non-small cell lung cancer study - acute myocardial infarction incidence (ICD9 410, ICD10 I21, I22)	Ischaemic heart disease	3.57 / 1	2.60 / 0
Little *et al* [78]	US peptic ulcer study ischaemic heart disease, heart dose	Ischaemic heart disease	4.14 / 2	3.60 / 1
Little *et al* [78]	US peptic ulcer study cerebrovascular, thyroid dose	Cerebrovascular disease	4.14 / 2	3.60 / 1
Lorenzen *et al* [79]	Danish breast cancer case-control study - ischaemic heart disease incidence (ICD10 I21-I25)	Ischaemic heart disease	3.86 / 3	3.80 / 3

Mansouri *et al* [80]	French Childhood Cancer Study (case-control study) - heart failure incidence (CTCAE 4.03 grade ≥1) - exposed to anthracyclines	Other heart disease	3.43 / 2	3.00 / 1
Mansouri *et al* [80]	French Childhood Cancer Study (case-control study) - heart failure incidence (CTCAE 4.03 grade ≥1) - unexposed to anthracyclines	Other heart disease	3.43 / 2	3.00 / 1
Markabayeva *et al* [24]	Semipalatinsk test site exposure - essential hypertension incidence	All other cardiovascular disease (than heart disease, cerebrovascular disease)	3.57 / 2	3.20 / 2
Moignier *et al* [81]	Institut Gustave Roussy Hodgkin lymphoma case-control study - coronary artery stenosis incidence in relation to dose to damaged segments of coronary artery	Ischaemic heart disease	3.57 / 1	2.40 / 0
Mueller *et al* [19]	Childhood Cancer Survivors Study - stroke incidence in relation to maximum (4-segment) brain dose	Cerebrovascular disease	3.71 / 2	2.40 / 1
Mulrooney *et al* [22]	St Jude's Lifetime cohort - cardiomyopathy incidence	Other heart disease	3.71 / 2	3.00 / 1
Mulrooney *et al* [21]	Childhood Cancer Survivor Study - heart failure CTCAE 4.03 ≥3 incidence	Other heart disease	3.71 / 2	3.00 / 1
Mulrooney *et al* [21]	Childhood Cancer Survivor Study - coronary artery disease CTCAE 4.03 ≥3 incidence	Ischaemic heart disease	3.71 / 2	3.00 / 1
Mulrooney *et al* [21]	Childhood Cancer Survivor Study - valvular heart disease CTCAE 4.03 ≥3 incidence	Other heart disease	3.71 / 2	3.00 / 1
Mulrooney *et al* [21]	Childhood Cancer Survivor Study - pericardial disease CTCAE 4.03 ≥3 incidence	Other heart disease	3.71 / 2	3.00 / 1
Mulrooney *et al* [21]	Childhood Cancer Survivor Study - arrhythmia CTCAE 4.03 ≥3 incidence	Other heart disease	3.71 / 2	3.00 / 1
Nakashima *et al* [82]	Japanese atomic bomb survivors in utero exposed followed up to age 9-19 - hypertension incidence	All other cardiovascular disease (than heart disease, cerebrovascular disease)	4.00 / 2	3.60 / 1
Rage *et al* [40]	Netherlands-Groningen breast cancer study - acute coronary event incidence (myocardial infarction (ICD10 I21-I24), coronary revascularisation, death from ischaemic heart disease (ICD10 I20-I25))	Ischaemic heart disease	4.14 / 1	3.20 / 0
Rage *et al* [40]	French uranium miner cohort study in relation to external gamma rays - cardiovascular disease	Cerebrovascular disease	4.14 / 1	3.20 / 0
Roos *et al* [83]	Netherlands-Groningen breast cancer study - acute coronary event morbidity (myocardial infarction (ICD10 I21-I24), coronary revascularisation, death from ischaemic heart disease (ICD10 I20-I25))	Ischaemic heart disease	3.71 / 2	3.00 / 1
Sadetzki *et al*[84]	Israeli tinea capitis patients ischaemic heart disease incidence (breast dose)	Ischaemic heart disease	4.00 / 3	3.80 / 3
Sadetzki *et al*[84]	Israeli tinea capitis patients cerebrovascular disease incidence (brain dose)	Cerebrovascular disease	4.00 / 3	3.80 / 3
Semenova *et al*[33]	Semipalatinsk cross sectional study ischaemic stroke incidence	Cerebrovascular disease	3.43 / 3	3.20 / 2
Semenova *et al*[33]	Semipalatinsk cross sectional study haemorrhagic stroke incidence	Cerebrovascular disease	3.43 / 3	3.20 / 2
Shafransky *et al* [85]	Russian Chernobyl liquidators - ischaemic heart disease (Chernobyl NPP + occupational dose)	Ischaemic heart disease	2.86 / 1	2.20 / 0
Shimizu *et al* [86]	Japanese atomic bomb survivors stroke (underlying or contributed cause of death)(ICD9 430-438)	Cerebrovascular disease	4.86 / 4	4.60 / 4
Shimizu *et al* [86]	Japanese atomic bomb survivors cardiovascular disease other than heart disease or stroke (underlying or contributed cause of death)	All other cardiovascular disease (than heart disease, cerebrovascular disease)	4.86 / 4	4.60 / 4
Tagami *et al*[87]	William Beaumont Hospital breast cancer study LAD stenosis incidence (via cardiovascular computed tomography grade ≥3) (LAD dose)	Ischaemic heart disease	3.71 / 2	3.20 / 1
Takahashi *et al* [88]	Japanese atomic bomb survivors ischaemic heart disease (ICD9 410-414)	Ischaemic heart disease	4.00 / 2	3.60 / 0
Takahashi *et al* [88]	Japanese atomic bomb survivors valvular heart disease (ICD9 394-397, 424)	Other heart disease	4.00 / 2	3.60 / 0
Takahashi *et al* [88]	Japanese atomic bomb survivors heart failure (ICD9 428 exc 428.8)	Other heart disease	4.00 / 2	3.60 / 0
Takahashi *et al* [89]	Japanese atomic bomb survivors AHS incidence - peripheral artery disease, multivariable adjusted	All other cardiovascular disease (than heart disease, cerebrovascular disease)	4.43 / 2	4.40 / 3

Tatarenko[34]	Ukraine Chernobyl liquidators - myocardial infarction incidence	Ischaemic heart disease	2.71 / 1	1.40 / 0
Tatsukawa *et al* [90]	Japanese atomic bomb survivors hypertension incidence in utero exposure	All other cardiovascular disease (than heart disease, cerebrovascular disease)	4.14 / 2	3.80 / 2
Tran *et al* [1]	Massachusetts and Canadian TB fluoroscopy ischaemic heart disease < 0.5 Gy	Ischaemic heart disease	4.14 / 2	3.60 / 1
Tran *et al* [1]	Massachusetts and Canadian TB fluoroscopy cerebrovascular disease < 0.5 Gy	Cerebrovascular disease	4.14 / 2	3.60 / 1
Tran *et al* [1]	Massachusetts and Canadian TB fluoroscopy hypertensive heart disease < 0.5 Gy	Other heart disease	4.14 / 2	3.60 / 1
Tran *et al* [1]	Massachusetts and Canadian TB fluoroscopy heart disease excluding IHD+hypertensive < 0.5 Gy	Other heart disease	4.14 / 2	3.60 / 1
van Aken *et al*[91]	Groningen ischaemic cerebrovascular event incidence after head and neck cancers (carotid dose)	Cerebrovascular disease	3.57 / 2	2.80 / 1
van Nimwegen *et al* [92]	Netherlands Hodgkin lymphoma - coronary heart disease incidence (myocardial infarction, angina pectoris requiring intervention) CTCAE 4.0 grades ≥2	Ischaemic heart disease	3.57 / 2	3.80 / 1
van Nimwegen *et al* [17]	Netherlands Hodgkin lymphoma patients case-control study - heart failure incidence CTCAE 3.0, 4.0 grades ≥2	Other heart disease	3.71 / 2	4.00 / 2
Vrijheid *et al* [13]	IARC 15-Country nuclear worker study ischaemic heart disease	Ischaemic heart disease	4.14 / 2	3.80 / 1
Vrijheid *et al* [13]	IARC 15-Country nuclear worker study heart failure	Other heart disease	4.14 / 2	3.80 / 1
Vrijheid *et al* [13]	IARC 15-Country nuclear worker study stroke	Cerebrovascular disease	4.14 / 2	3.80 / 1
Wang *et al*[27]	University of North Carolina non-small cell lung cancer study - pericardial event incidence	Other heart disease	3.14 / 1	2.40 / 0
Wang *et al*[27]	University of North Carolina non-small cell lung cancer study - ischaemic event incidence	Ischaemic heart disease	3.14 / 1	2.40 / 0
Wang *et al*[27]	University of North Carolina non-small cell lung cancer study - arrhythmic event incidence	Other heart disease	3.14 / 1	2.40 / 0
Xue *et al* [93]	University of Michigan non small cell lung cancer study - pericardial effusion incidence using mean pericardial dose	Other heart disease	3.29 / 2	2.60 / 1
Yamada *et al* [94]	Japanese atomic bomb survivors hypertension incidence linear model (ICD9 401)	All other cardiovascular disease (than heart disease, cerebrovascular disease)	4.14 / 3	3.80 / 1
Yamada *et al* [94]	Japanese atomic bomb survivors ischaemic heart disease incidence (ICD9 410-414)	Ischaemic heart disease	4.14 / 3	3.80 / 1
Yamada *et al* [94]	Japanese atomic bomb survivors stroke incidence (ICD9 430, 431, 433, 434, 436)	Cerebrovascular disease	4.14 / 3	3.80 / 1
Yamada *et al* [94]	Japanese atomic bomb survivors aortic aneurysm incidence (ICD9 441-442)	All other cardiovascular disease (than heart disease, cerebrovascular disease)	4.14 / 3	3.80 / 1
Zablotska *et al* [95]	Port Hope and Wismut uranium workers - ischaemic heart disease (ICD10 I20-I25, I51.6)	Ischaemic heart disease	3.71 / 1	2.80 / 0
Zablotska *et al* [95]	Port Hope and Wismut uranium workers - stroke (ICD10 I60-I69)	Cerebrovascular disease	3.71 / 1	2.80 / 0
Zhang *et al* [2]	UK NRRW - ischaemic heart disease (ICD9 410-414) < 0.4 Sv	Ischaemic heart disease	4.14 / 2	3.40 / 1
Zhang *et al* [2]	UK NRRW - rheumatic heart disease (ICD9 393-398) < 0.4 Sv	Other heart disease	4.14 / 2	3.40 / 1
Zhang *et al* [2]	UK NRRW - heart failure (ICD9 428) < 0.4 Sv	Other heart disease	4.14 / 2	3.40 / 1
Zhang *et al* [2]	UK NRRW - hypertensive heart disease (ICD9 402, 404) < 0.4 Sv	Other heart disease	4.14 / 2	3.40 / 1
Zhang *et al* [2]	UK NRRW - other heart disease (415-427, 429) < 0.4 Sv	Other heart disease	4.14 / 2	3.40 / 1
Zureick *et al*[96]	William Beaumont hospital major cardiac event incidence after breast cancer	Ischaemic heart disease	4.00 / 3	3.60 / 2

Table S3.2. Studies used in analysis of the all cardiovascular diseases endpoint, using maximal endpoints within each study. Unless otherwise stated all endpoints are of mortality.

Reference	Abbreviated study description	Mean bias score / minimum bias score	Mean quality score /minimum quality score
Abraham *et al*[97]	Alberta breast cancer cardiac incidence CTCAE grade ≥2	3.14 / 1	2.60 / 0
Anderson *et al* [51]	US uranium enrichment worker ischaemic heart disease	4.29 / 2	3.20 / 1
Anderson *et al* [51]	US uranium enrichment worker cerebrovascular disease	4.29 / 2	3.20 / 1
Atkins *et al*[98]	Dana Farber/Brigham Women's Hospital lung cancer study - major adverse cardiac event incidence (cardiac death, unstable angina, myocardial infarction, heart failure hospitalization or urgent visit, coronary revascularization) in relation to mean heart dose	4.14 / 3	3.40 / 2
Azizova *et al*[9]	Mayak worker cerebrovascular disease incidence, 5 year lag	4.14 / 3	4.00 / 3
Azizova *et al*[5]	Mayak worker ischaemic heart disease incidence (ICD9 410-414), 5 year latency, < 4 Gy	4.14 / 3	4.00 / 3
Azizova *et al*[6]	Mayak worker all cardiovascular disease (ICD9 390-459) 5 year lag, dose < 4 Gy	4.14 / 3	3.80 / 3
Azizova *et al*[52]	Mayak worker lower extremity arterial disease (ICD9 440.2) incidence [external gamma 5-yr lag]	4.00 / 2	4.20 / 3
Azizova *et al*[53]	Mayak worker hypertension incidence	3.71 / 2	3.80 / 2
Baaken *et al* [99]	Cardiac events (incidence or mortality) after breast cancer in German case-control study nested within ESCaRa cohort	3.57 / 2	2.60 / 1
Boekel *et al* [54]	Netherlands-NKI-Rotterdam breast cancer case-control study heart failure incidence (CTCAE grade ≥2) - all data	4.00 / 3	3.80 / 2
Boice *et al* [25]	Mound workers heart disease (ICD9 390-398, 404, 410-429)	3.71 / 2	2.80 / 1
Boice *et al* [55]	US nuclear power industry workers - ischaemic heart disease (ICD9 410-414)	3.43 / 2	2.60 / 1
Boice *et al* [56]	US 8 series nuclear test veterans - ischaemic heart disease	3.00 / 1	2.20 / 0
Boice *et al* [57]	US medical workers - ischaemic heart disease (ICD9 410-414)	3.71 / 2	3.40 / 1
Boice *et al* [57]	US medical workers - cerebrovascular disease (ICD9 430-438)	3.71 / 2	3.40 / 1
Borkenhagen *et al* [58]	Medical College of Wisconsin lung cancer study cardiotoxicity morbidity (arrhythmia, pericardial disease, valvular disease) - mean dose to pericardium	3.29 / 1	2.60 / 0
Bouet *et al* [59]	French nuclear fuel workers - cardiovascular disease (adjusted for SES, blood pressure, BMI, smoking status, glycemic level)	4.71 / 3	4.20 / 3
Cai *et al* [100]	Shandong hospital patients treated for esophageal cancer - CTCAE 4.03 Grade ≥2 cardiac event incidence (excluding pericardial effusions) among patients without pre-existing ischaemic heart disease, using mean heart dose	3.71 / 3	2.80 / 2
Cha *et al* [60]	Korean diagnostic medical workers - all cardiovascular disease	4.43 / 3	4.40 / 3
Chekin *et al*[101]	Russian Chernobyl liquidators all cardiovascular disease	3.71 / 1	2.60 / 0
Chen *et al* [102]	Shanghai non-small cell lung cancer study from major adverse cardiac morbidity after non small cell lung cancer - CTCAE 4 grade ≥ 3	4.00 / 3	3.40 / 2
Cho *et al*[28]	Korean non small cell lung cancer cardiac incidence (CTCAE v5.0 ≥2)	3.86 / 2	3.20 / 1
Chung *et al*[41]	Severance Hospital breast cancer cardiac event incidence	4.00 / 2	3.20 / 2
Cutter *et al* [16]	Netherlands Hodgkin lymphoma valvular disease case-control study - valvular heart disease incidence CTCAE 4.0 grades ≥2	4.14 / 3	3.80 / 2
Darby *et al* [61]	Nordic breast cancer case–control study, ischaemic heart disease incidence (ICD10 I20-I25), cumulative heart dose	4.14 / 3	4.00 / 3
Dess *et al*[103]	University of Michigan non-small cell lung cancer study, CTCAE v4.03 ≥ 3 - cardiac event incidence	3.86 / 3	3.40 / 2
Dorth *et al* [62]	Duke Cancer Institute head and neck cancer study - carotid stenosis incidence	3.43 / 2	2.80 / 1
El-Fayech *et al* [63]	French (Institut Gustave Roussy) childhood cancer stroke study - all stroke incidence	3.43 / 2	3.00 / 2

Elgart *et al* [64]	NASA astronauts, adjusted for age at exit+entrance, medical diagnostic dose - all cardiovascular disease (IHD+CeVD)	3.86 / 2	3.00 / 0
Errahmani *et al*[65]	French MEDIRAD-BRACE breast cancer arrhythmia incidence case-control study after left sided breast cancer	4.29 / 3	3.40 / 2
Errahmani *et al*[65]	French MEDIRAD-BRACE breast cancer arrhythmia incidence case-control study after right sided breast cancer	4.29 / 3	3.40 / 2
Fullerton *et al* [20]	Childhood Cancer Survivor Study of second stroke incidence in relation to maximum (4-segment) brain dose	3.86 / 2	3.40 / 2
Gillies *et al* [8]	International Nuclear Workers Study (INWORKS) - all cardiovascular disease	4.29 / 2	3.60 / 1
Gillies & Haylock [32]	UK nuclear test veterans all cardiovascular disease (ICD10 I00-I99)	3.86 / 2	2.80 / 1
Golden *et al* [66]	Mallinckrodt workers - ischaemic heart disease (ICD9 410-414)	3.71 / 2	2.80 / 1
Green *et al* [67]	National Wilms' Tumor Study Group - congestive heart failure incidence (requiring treatment with digoxin & diuretics) - analysis using lung dose	3.43 / 2	2.40 / 1
Grosche *et al* [68]	Kazakhstan nuclear weapons test study, 10 year lag, all cardiovascular disease (ICD9 390-459): exposed settlements only	3.43 / 1	2.80 / 0
Haddy *et al* [69]	France-UK cohort - cerebrovascular disease (ICD9 430-439, ICD10 I60-I69)	3.71 / 2	3.40 / 1
Haddy *et al* [104]	French (Institut Gustave Roussy) childhood cancer - cardiac disease incidence without anthracyclines	3.71 / 2	3.40 / 2
Haddy *et al* [104]	French (Institut Gustave Roussy) childhood cancer - cardiac disease incidence with anthracyclines	3.71 / 2	3.40 / 2
Hahn *et al* [42]	Toronto Hodgkin lymphoma study all cardiovascular disease after Hodgkin disease - adverse cardiac outcome incidence (ischaemic heart disease, pericardial disease, conduction disorders, valvular disease, ventricular function abnormalities, and cardiac surgeries and procedures such as coronary artery bypass and implantation of a cardiac device)	3.86 / 2	3.40 / 2
Hinksman *et al*[12]	UK NRRW cerebrovascular disease (ICD10 I60-I69) <0.5 Gy	3.71 / 2	3.40 / 1
Jacobse *et al* [71]	Netherlands-NKI-Rotterdam breast cancer case-control study myocardial infarction incidence	3.71 / 2	3.60 / 3
Kashcheev *et al*[105]	Russian Chernobyl liquidators - all cardiovascular disease incidence	3.43 / 1	2.40 / 0
Killander *et al* [106]	Swedish breast cancer study - cardiac disease (ICD10 I05-I07, I11, I13, I20-I22, I25, I33-I38, I40, I42, I44-I51)	3.86 / 2	2.80 / 0
Killander *et al* [106]	Swedish breast cancer study - cardiac disease incidence (ICD10 I05-I07, I11, I13, I20-I22, I25, I33-I38, I40, I42, I44-I51)	3.86 / 2	2.80 / 0
Krasnikova *et al* [73]	Ukrainian Chernobyl cleanup workers 1+ Gy vs unexposed - chronic cerebrovascular disease (ICD10 I67, I69)	3.00 / 2	1.60 / 0
Krestinina *et al* [74]	Techa River cohort - cardiovascular disease latency 5 years	3.71 / 1	2.80 / 0
Kreuzer *et al* [75]	German uranium miner study all cardiovascular disease	4.29 / 3	3.80 / 3
Lane *et al* [76]	Eldorado uranium miners ischaemic heart disease	4.00 / 1	2.60 / 0
Lane *et al* [76]	Eldorado uranium miners stroke	4.00 / 1	2.60 / 0
Lane *et al* [76]	Eldorado uranium miners other cardiovascular disease	4.00 / 1	2.60 / 0
Lee *et al* [77]	Singapore non-small cell lung cancer study - acute myocardial infarction incidence (ICD9 410, ICD10 I21, I22)	3.57 / 1	2.60 / 0
Liao *et al* [18]	Chenyang thymoma study - CTCAE 4.0 grade ≥2 cardiovascular disease incidence	4.14 / 2	3.00 / 1
Little *et al* [78]	US peptic ulcer study ischaemic heart disease, heart dose	4.14 / 2	3.60 / 1
Little *et al* [78]	US peptic ulcer study cerebrovascular, thyroid dose	4.14 / 2	3.60 / 1
Little *et al* [78]	US peptic ulcer data study all other cardiovascular disease, heart dose	4.14 / 2	3.60 / 1
Lorenzen *et al* [79]	Danish breast cancer case-control study - ischaemic heart disease incidence (ICD10 I21-I25)	3.86 / 3	3.80 / 3
Mansouri *et al* [80]	French Childhood Cancer Study (case-control study) - heart failure incidence (CTCAE 4.03 grade ≥1) - exposed to anthracyclines	3.43 / 2	3.00 / 1
Mansouri *et al* [80]	French Childhood Cancer Study (case-control study) - heart failure incidence (CTCAE 4.03 grade ≥1) - unexposed to anthracyclines	3.43 / 2	3.00 / 1
Maraldo *et al* [107]	EORTC cardiovascular disease after Hodgkin lymphoma - all cardiovascular incidence	3.86 / 1	2.80 / 0

Markabayeva *et al* [24]	Semipalatinsk test site exposure - essential hypertension incidence	3.57 / 2	3.20 / 2
Martin & Ségala[31]	CEA tritium workers all cardiovascular disease (ICD10 I00-I99)	4.43 / 2	3.60 / 2
Moignier *et al* [81]	Institut Gustave Roussy Hodgkin lymphoma case-control study - coronary artery stenosis incidence in relation to dose to damaged segments of coronary artery	3.57 / 1	2.40 / 0
Mueller *et al* [19]	Childhood Cancer Survivors Study - stroke incidence in relation to maximum (4-segment) brain dose	3.71 / 2	2.40 / 1
Nakashima *et al* [82]	Japanese atomic bomb survivors in utero exposed followed up to age 9-19 - hypertension incidence	4.00 / 2	3.60 / 1
Ni *et al* [30]	University of Chicago lung cancer study - CTCAE 4.03 grade ≥3 cardiac event incidence (new arrhythmia, structural disease/valvulopathy, myocardial infarction, new or recurrent congestive heart failure, pericarditis or pericardial effusion requiring intervention)	3.14 / 2	2.20 / 1
Park *et al*[108]	French uranium miner cohort study in relation to external gamma rays - cerebrovascular disease	3.57 / 2	2.20 / 2
Rage *et al* [40]	French uranium miner cohort study in relation to external gamma rays - ischaemic heart disease	4.14 / 1	3.20 / 0
Roos *et al* [83]	Netherlands-Groningen breast cancer study - acute coronary event morbidity (myocardial infarction (ICD10 I21-I24), coronary revascularisation, death from ischaemic heart disease (ICD10 I20-I25))	3.71 / 2	3.00 / 1
Sadetzki *et al*[84]	Israeli tinea capitis patients ischaemic heart disease incidence (breast dose)	4.00 / 3	3.80 / 3
Sadetzki *et al*[84]	Israeli tinea capitis patients cerebrovascular disease incidence (brain dose)	4.00 / 3	3.80 / 3
Semenova *et al*[33]	Semipalatinsk cross sectional study ischaemic stroke incidence	3.43 / 3	3.20 / 2
Semenova *et al*[33]	Semipalatinsk cross sectional study haemorrhagic stroke incidence	3.43 / 3	3.20 / 2
Shafransky *et al* [85]	Russian Chernobyl liquidators - ischaemic heart disease (Chernobyl NPP + occupational dose)	2.86 / 1	2.20 / 0
Shimizu *et al* [86]	Japanese atomic bomb survivors stroke (underlying or contributed cause of death)(ICD9 430-438)	4.86 / 4	4.60 / 4
Shimizu *et al* [86]	Japanese atomic bomb survivors cardiovascular disease other than heart disease or stroke (underlying or contributed cause of death)	4.86 / 4	4.60 / 3
Shrestha *et al*[23]	CCSS study - any cardiac disease incidence CTCAE 4.03 ≥3	3.43 / 2	2.40 / 1
Tagami *et al*[87]	William Beaumont Hospital breast cancer study LAD stenosis incidence (via cardiovascular computed tomography grade ≥3) (LAD dose)	3.71 / 2	3.20 / 1
Takahashi *et al* [88]	Japanese atomic bomb survivors heart disease (ICD9 394-397, 402, 404, 410-414, 424, 428 (excl 428.8))	4.00 / 2	3.60 / 0
Takahashi *et al* [89]	Japanese atomic bomb survivors AHS incidence - peripheral artery disease, multivariable adjusted	4.43 / 2	4.40 / 3
Tatarenko[34]	Ukraine Chernobyl liquidators - myocardial infarction incidence	2.71 / 1	1.40 / 0
Tatsukawa *et al* [90]	Japanese atomic bomb survivors hypertension incidence in utero exposure	4.14 / 2	3.80 / 2
Tatsukawa *et al* [90]	Japanese atomic bomb survivors nonfatal CVD (stroke or myocardial infarction) incidence in utero exposure	4.14 / 2	3.80 / 2
Tran *et al* [1]	Massachusetts and Canadian TB fluoroscopy all cardiovascular disease < 0.5 Gy	4.14 / 2	3.60 / 1
Tukenova *et al* [109]	French–UK childhood cancer study cardiac disease	4.14 / 1	3.40 / 0
van Aken *et al*[91]	Groningen ischaemic cerebrovascular event incidence after head and neck cancers (carotid dose)	3.57 / 2	2.80 / 1
van Nimwegen *et al* [92]	Netherlands Hodgkin lymphoma - coronary heart disease incidence (myocardial infarction, angina pectoris requiring intervention) CTCAE 4.0 grades ≥2	3.57 / 2	3.80 / 1
van Nimwegen *et al* [17]	Netherlands Hodgkin lymphoma patients case-control study - heart failure incidence CTCAE 3.0, 4.0 grades ≥2	3.71 / 2	4.00 / 2
Vrijheid *et al* [13]	IARC 15-Country nuclear worker study all cardiovascular	4.14 / 2	3.80 / 1
Wang *et al*[27]	University of North Carolina non-small cell lung cancer study symptomatic cardiac event incidence - symptomatic pericardial effusion, myocardial infarction, unstable angina, pericarditis, significant arrhythmia, heart failure	3.43 / 2	2.80 / 1
Wang *et al* [110]	MD Anderson esophageal cancer patients - CTCAE v5.0 grade ≥3 adverse cardiac event incidence (acute coronary event, arrhythmia, heart failure, cardiac arrest, pericardial effusion, pericarditis)	3.43 / 2	2.80 / 1
Xue *et al* [93]	University of Michigan non small cell lung cancer study - pericardial effusion incidence using mean pericardial dose	3.29 / 2	2.60 / 1

Yamada *et al* [94]	Japanese atomic bomb survivors hypertension incidence linear model (ICD9 401)	4.14 / 3	3.80 / 1
Yamada *et al* [94]	Japanese atomic bomb survivors hypertensive heart disease incidence (ICD9 402-404)	4.14 / 3	3.80 / 1
Yamada *et al* [94]	Japanese atomic bomb survivors ischaemic heart disease incidence (ICD9 410-414)	4.14 / 3	3.80 / 1
Yamada *et al* [94]	Japanese atomic bomb survivors stroke incidence (ICD9 430, 431, 433, 434, 436)	4.14 / 3	3.80 / 1
Yamada *et al* [94]	Japanese atomic bomb survivors aortic aneurysm incidence (ICD9 441-442)	4.14 / 3	3.80 / 1
Yegya-Raman *et al* [111]	Rutgers Cancer Institute non small cell lung cancer study of persons without prior thoracic radiotherapy - first symptomatic cardiac event incidence (myocardial infarction, unstable angina, significant arrythmia, symptomatic pericardial effusion, pericarditis, congestive heart failure)	3.43 / 2	3.00 / 2
Zablotska *et al* [95]	Port Hope and Wismut uranium workers - all cardiovascular disease (ICD10 I00-I99)	3.71 / 1	2.80 / 0
Zhang *et al* [2]	UK NRRW - all heart disease (ICD9 393-398, 402, 404, 410-429) <0.4 Sv	4.14 / 2	3.40 / 1
Zielinski *et al* [14]	Canadian NDR study - cardiovascular disease - males	4.00 / 2	3.20 / 1
Zielinski *et al* [14]	Canadian NDR study - cardiovascular disease - females	4.00 / 2	3.20 / 1
Zureick *et al*[96]	William Beaumont hospital cardiac event incidence after breast cancer	4.00 / 3	3.60 / 2

Table S3.3. Comparison of meta excess relative risk / Gy (mERR/Gy) (+95% CI) using maximum likelihood, restricted maximum likelihood (REML) and DerSimonian-Laird fitting methods.

	Maximum likelihood mERR/Gy (95% CI)	REML mERR/Gy (95% CI)	DerSimonian Laird mERR/Gy (95% CI)
Full data			
Ischaemic heart disease	0.0725 (0.0471 to 0.0980)	0.0730 (0.0473 to 0.0988)	0.0814 (0.0499 to 0.1129)
Other heart disease[a]	0.0344 (0.0202 to 0.0486)	0.0344 (0.0202 to 0.0486)	0.0344 (0.0202 to 0.0486)
Cerebrovascular disease	0.1869 (0.0934 to 0.2803)	0.1879 (0.0927 to 0.2831)	0.1839 (0.0947 to 0.2731)
Other cardiovascular disease [b]	0.1721 (-0.0244 to 0.3687)	0.1720 (-0.0288 to 0.3729)	0.1746 (-0.0120 to 0.3612)
All cardiovascular disease (using maximal cardiovascular disease data per study)	0.1055 (0.0761 to 0.1349)	0.1057 (0.0763 to 0.1352)	0.0925 (0.0684 to 0.1166)
Maximum dose ≤0.5 Gy			
Ischaemic heart disease	0.3908 (0.0197 to 0.7620)	0.4380 (-0.1306 to 1.0067)	0.4463 (-0.2308 to 1.1235)
Other heart disease[a]	-0.1077 (-0.5281 to 0.3126)	-0.1077 (-0.5281 to 0.3126)	-0.1077 (-0.5281 to 0.3126)
Cerebrovascular disease	0.5423 (-0.2814 to 1.3661)	0.5423 (-0.2814 to 1.3661)	0.9242 (-1.0043 to 2.8528)
Other cardiovascular disease [b]	-1.8000 (-11.9500 to 8.3500)	-1.8000 (-11.9500 to 8.3500)	-1.8000 (-11.9500 to 8.3500)
All cardiovascular disease (using maximal cardiovascular disease data per study)	0.3749 (0.1094 to 0.6403)	0.4523 (0.0642 to 0.8404)	0.4173 (0.0903 to 0.7444)
Low dose rate data only			
Ischaemic heart disease	0.1397 (0.0804 to 0.1989)	0.2021 (0.0849 to 0.3194)	0.1824 (0.0806 to 0.2842)
Other heart disease[a]	-0.2070 (-0.4564 to 0.0423)	-0.2070 (-0.4564 to 0.0423)	-0.2070 (-0.4564 to 0.0423)
Cerebrovascular disease	0.3005 (0.1116 to 0.4894)	0.2980 (0.1005 to 0.4954)	0.2933 (0.0750 to 0.5115)
Other cardiovascular disease [b]	0.1478 (0.0622 to 0.2335)	0.1659 (-0.0691 to 0.4009)	0.1663 (-0.0582 to 0.3909)
All cardiovascular disease (using maximal cardiovascular disease data per study)	0.2283 (0.1370 to 0.3197)	0.2286 (0.1357 to 0.3216)	0.2277 (0.1397 to 0.3156)
Maximum dose ≤0.5 Gy or low dose rate			
Ischaemic heart disease	0.1930 (0.0892 to 0.2969)	0.2049 (0.0916 to 0.3182)	0.1969 (0.0901 to 0.3037)
Other heart disease[a]	-0.1675 (-0.4294 to 0.0943)	-0.1675 (-0.4294 to 0.0943)	-0.1675 (-0.4294 to 0.0943)
Cerebrovascular disease	0.3081 (0.1357 to 0.4805)	0.3064 (0.1274 to 0.4854)	0.3027 (0.1045 to 0.5009)
Other cardiovascular disease [b]	0.1478 (0.0622 to 0.2335)	0.1659 (-0.0691 to 0.4009)	0.1663 (-0.0582 to 0.3909)
All cardiovascular disease (using maximal cardiovascular disease data per study)	0.2304 (0.1424 to 0.3184)	0.2307 (0.1412 to 0.3203)	0.2299 (0.1438 to 0.3161)

[a]heart disease other than ischaemic heart disease.
[b]cardiovascular disease other than heart disease and cerebrovascular disease.

Table S3.4. Estimated excess relative risk of cardiovascular diseases in various therapeutically and diagnostically treated groups, exposed at moderate or high doses and high dose rates. All data are in relation to underlying cause of death, unless otherwise indicated.

Study	Reference	Average Organ Dose (Gy) mean/median (range)	Organ used	Variables (other than age, sex, year) available to assess possible confounding	Persons (person years of follow-up)	Deaths/ cases	Endpoint (mortality unless otherwise indicated, mean heart dose unless otherwise indicated)	Excess relative risk Gy^{-1} (95% CI)
Therapeutically treated groups								
Childhood Cancer Survivor Study	Mueller *et al* [19]	14.5[a] (0 to >50)	Brain	Smoking, diabetes, hypertension, use of oral contraceptives, NF1 history, racial/ethnic group	18,381 (~260,200[b])	292	Cerebrovascular disease incidence, using maximum (4-segment) brain dose	0.097 (-0.052 to 0.246)[a]
Childhood Cancer Survivor Study	Fullerton *et al* [20]	28.1[c] (0 to >50)	Brain	Smoking, diabetes, hypertension, chemotherapy, NF1 diagnosis	271 (NA)	70	Second cerebrovascular disease incidence, using maximum (4-segment) brain dose	0.050 (-0.007 to 0.107)[c]
Childhood Cancer Survivor Study	Mulrooney *et al* and Shrestha *et al* [21 23]	~7.8 (0 to >35)	Heart	Smoking, BMI, diabetes, hypertension, dyslipidaemia, racial/ethnic group, education, chemotherapy	23,462 (NA)	658	All cardiac disease incidence CTCAE v4.03 ≥3	0.063 (-0.067 to 0.193)[d]
						272	Heart failure incidence CTCAE v4.03 ≥3	0.022 (-0.093 to 0.138)[d]
						190	Coronary artery disease incidence CTCAE v4.03 ≥3	0.066 (-0.020 to 0.152)[d]
						40	Valvular disease incidence CTCAE v4.03 ≥3	0.064 (-0.178 to 0.306)[d]
						22	Pericardial disease incidence CTCAE v4.03 ≥3	-0.005 (-0.082 to 0.072)[d]
						72	Arrhythmia incidence CTCAE v4.03 ≥3	0.005 (-0.049 to 0.058)[d]
St Jude Lifetime childhood cancer cohort	Mulrooney *et al* [22]	~7.1[e] (0 to >15)	Heart	Smoking, BMI, diabetes, hypertension, alcohol consumption, dyslipidaemia, physical activity+fitness, anthracyclines	1853 (NA)	118	Cardiomyopathy incidence	0.032 (-0.077 to 0.141)[e]
French–UK childhood cancer study	Tukenova *et al* [109]	11.1[f] (<1 to >15)	Heart	Epipodophyllotoxins, anthracyclines, alkylating agents, vinca alkaloids, antimetabolites, antibiotics	4122 (86,453)	32	All cardiac disease	0.6 (0.2 to 2.5)
French–UK childhood cancer	Haddy *et al* [69]	7.8 (1.9 to 49.2)	Prepontine	Alkylating agents,	4227	23	Cerebrovascular disease (ICD9 430-	0.22 (0.01 to 0.44)

study			cistern	vinca alkaloids, anthracyclines, antimetabolites	(~120,000[b])		439, ICD10 I60-I69), using dose to prepontine cistern	
French (Institut Gustave Roussy) childhood cancer cardiac study	Haddy *et al* [104]	7.5 (<1 to >30)	Heart	Smoking, BMI, anthracyclines, alkylating agents, vinca alkaloids, epipodophyllotoxins, antimetabolites	3162 (~82,200[b])	106	Cardiac disease (ICD9 391, 393-397, 410-413, 420, 423-424, 426–428; ICD10 I05–I09, I20–I25, I30–I32, I44–I50) incidence: without anthracyclines	0.49 (0.26 to 1.3)
						128	Cardiac disease incidence: with anthracyclines	0.07 (0.03 to 0.13)
French (Institut Gustave Roussy) childhood cancer stroke study	El-Fayech *et al* [63]	7.7[g] (<1 to >40)	Willis Circle arteries	Smoking, BMI, anthracyclines, alkylating agents, vinca alkaloids, epipodophyllotoxins, antimetabolites, brain surgery	3172 (~82,500[b])	54	All stroke (ICD9 430-439) incidence	0.24 (0.11 to 0.53)
						39	Ischemic stroke incidence	0.42 (0.16 to 1.20)
French Childhood Cancer Study case-control study	Mansouri *et al* [80]	2.1[h] (0.004 to 49.1)	Heart	Smoking, BMI, physical activity, anthracyclines, alkylating agents, vinca alkaloids	NA	239 cases, 1042 controls	Heart failure incidence (CTCAE v4.03 grade ≥1) with concomitant anthracyclines	0.09 (0.02 to 0.22)
							Heart failure incidence (CTCAE v4.03 grade ≥1) without concomitant anthracyclines	0.44 (0.18 to 1.12)
National Wilms' Tumor Study Group case-control study	Green *et al* [67]	6.7 (0 to >81.5)[i]	Lung	Doxorubicin	2710 (NA)	35	Congestive heart failure incidence (requiring treatment with digoxin & diuretics)	0.06 (0.00 to 0.14)[i]
EORTC 9-cohort Hodgkin lymphoma study	Maraldo *et al* [107]	23.3 (<2.2 to >32.5)	Heart	Anthracyclines, vinca alkaloids. country	6039 (~54,000[b])	1238	All cardiovascular event incidence	0.015 (0.006 to 0.024)
						639	Major cardiovascular event incidence	0.019 (0.009 to 0.028)
Netherlands Hodgkin lymphoma valvular disease case-control study	Cutter *et al* [16]	30.7[h] (0 to >42.2)	EQD2 affected valve	Smoking, BMI, diabetes, hypertension, hyper-cholesterolaemia, anthracyclines, vincristine, procarbazine, splenectomy	NA	89 cases, 200 controls	Valvular heart disease incidence CTCAE v4.0 grades ≥2	0.141 (0.024 to 1.013)[j]
Netherlands Hodgkin lymphoma coronary heart disease case-control study	van Nimwegen *et al* [92]	20.4[h] (0 to >35)	Heart EQD2	Smoking, BMI, diabetes, hypertension, hyper-cholesterolaemia, physical activity, alkylating agents, procarbazine,	NA	325 cases, 1204 controls	Coronary heart disease incidence (myocardial infarction, angina pectoris requiring intervention) CTCAE v4.0 grades ≥2	0.074 (0.033 to 0.148)

				vincristine, anthracyclines, splenectomy				
Netherlands Hodgkin lymphoma heart failure case-control study	van Nimwegen *et al* [17]	20.1[h] (0 to >33)	Heart EQD2	Smoking, BMI, diabetes, hypertension, hyper-cholesterolaemia, physical activity, anthracyclines, splenectomy	NA	91 cases, 278 controls	Heart failure incidence CTCAE v3.0, v4.0 grades ≥2	0.038 (-0.001 to 0.146)[k]
Toronto Hodgkin lymphoma study	Hahn *et al* [42]	24.93 (3.61 to 32.74)	Heart	Smoking, hypertension, dyslipidaemia, diabetes, doxorubicin	125 (~1300[b])	44	Adverse cardiac outcome (ischaemic heart disease, pericardial disease, conduction disorders, valvular disease, ventricular function abnormalities, and cardiac surgeries and procedures such as coronary artery bypass and implantation of a cardiac device) incidence	0.086 (0.022 to 0.150)
Institut Gustave Roussy Hodgkin lymphoma case-control study	Moignier *et al* [81]	36 (20 to 60)[l]	Coronary artery	Hypertension, hyper-cholesterolaemia, chemotherapy	NA	12 cases, 21 controls	Coronary artery stenosis incidence in relation to segmented dose to coronary artery	0.049 (0.004 to 0.095)[l]
Nordic breast cancer case–control study	Darby *et al* [61]	4.9 (0.03 to 27.72)	Heart	Smoking, BMI, diabetes, hypertension, analgesic medication, thyroid medication, surgery, HRT, chemotherapy, ovarian ablation, history of IHD or COPD	NA	963 cases, 1205 controls	IHD incidence (ICD10 I20-I25)	0.074 (0.029 to 0.145)
Sweden breast cancer study	Killander *et al* [106]	2.0 (0.5 to 8.1)	Heart	Endocrine treatment, chemotherapy (tamoxifen, cyclophosphamide, methotrexate, 5-fluorouracil),	1187 (~24,400[b])	137 ≥347	Cardiac disease (ICD10 I05-I07, I11, I13, I20-I22, I25, I33-I38, I40, I42, I44-I51) Cardiac disease incidence (ICD10 I05-I07, I11, I13, I20-I22, I25, I33-I38, I40, I42, I44-I51)	-0.073 (-0.352 to 0.326) -0.061 (-0.252 to 0.179)
Danish breast cancer case-control study	Lorenzen *et al* [79]	2.03[h] (0.4 to 10.3)	Heart	Smoking, BMI, diabetes, hypertension, COPD, HRT, chemotherapy (anthracyclines, other), endocrine	NA	531 cases, 1069 controls	IHD incidence (ICD10 I21-I25)	0.09 (-0.01 to 0.24)

				therapy, ovarian ablation, history of CVD, breast surgery				
Netherlands-Groningen breast cancer study	Roos *et al* [83]	2.36 (0.51 to 15.25)	Heart	Smoking, BMI, diabetes, hypertension, hyper-cholesterolaemia, COPD, pulmonary embolism, chemotherapy, endocrine therapy, history of IHD	939 (~7040[b])	29	Acute coronary event incidence (myocardial infarction (ICD10 I21-I24), coronary revascularization, death from ischemic heart disease (ICD10 I20-I25))	0.18 (0.00 to 0.39)
Netherlands-Groningen breast cancer study	van den Bogaard *et al*[112]	2.73 (0.69 to 10.99)	Heart	Smoking, BMI, diabetes, hypertension, hyper-cholesterolaemia, chemotherapy, hormonal therapy, trastuzumab, other heart disease	910 (~8370[b])	19	Incidence of myocardial infarction (ICD10 I21-24), coronary revascularisation or death from IHD (CD10 I20-I25) among patients with atherosclerotic plaque in LAD	0.117 (-0.098 to 0.383)
		2.27 (0.51 to 15.25)				19	Incidence of myocardial infarction (ICD10 I21-24), coronary revascularisation or death from IHD (CD10 I20-I25) among patients without atherosclerotic plaque in LAD	0.161 (-0.034 to 0.395)
Netherlands-NKI-Rotterdam breast cancer case-control study	Jacobse *et al* [71]	8.5 (0 to >26)	Heart	Smoking, BMI, hypertension, diabetes, surgery, chemotherapy, endocrine therapy, prior CVD	NA	183 cases, 183 controls	Myocardial infarction incidence	0.064 (0.013 to 0.160)
Netherlands-NKI-Rotterdam breast cancer case-control study	Boekel *et al* [54]	5.55[m] (0 to >18.0)	Heart	Smoking, BMI, diabetes, hypertension, hyper-cholesterolaemia, menopausal status, chemotherapy, endocrine therapy, surgery	NA	102 cases, 306 controls	Heart failure (CTCAE v3.0, v4.0 grade ≥2) incidence – no treatment with anthracyclines	0.00 (-0.03 to 0.08)
							Heart failure (CTCAE v3.0, v4.0 grade ≥2) incidence – treatment with anthracyclines	0.08 (-0.03 to 0.43)
							Heart failure (CTCAE v3.0, v4.0 grade ≥2) incidence	0.01 (-0.02 to 0.10)
Case-control study nested within ESCaRa breast cancer cohort study	Baaken *et al*[99]	3.11[h] (0.44 to 13.56)	Heart	BMI, chemotherapy, endocrine therapy, previous CVD	9057 (NA)	494 cases, 988 controls	Incidence of myocardial infarction, angina pectoris, congestive heart failure, dysrhythmia, valvular heart disease, or mortality from cardiac infarction (ICD10 I21-I23), chronic IHD (ICD10 I25.0-I25.9), acute IHD (ICD10 I21.0-I24.9), congestive heart	-0.01 (-0.06 to 0.05)

							failure (ICD10 I50.0-I50.9), angina pectoris (ICD10 I20.0-I20.9), cardiac arrest (ICD10 I46), dysrhythmia/conduction disorder (ICD10 I44.0-I49.9), vitium cordis (ICD10 I34.0-I37.9)	
Alberta breast cancer study	Abraham *et al*[97]	2.46 (0.3 to 19.2)	Heart	Smoking, hypertension, diabetes, hyper-cholesterolaemia, chemotherapy, hormone therapy, previous CVD, hormone/HER2 status	181 (~1916[b])	20	Cardiac CTCAE v5 ≥2	0.067 (-0.067 to 0.220)
Severance Hospital breast cancer study	Chung *et al*[41]	3.35 (0 to 14.16)	Heart	Smoking, BMI, diabetes, hypertension, exercise, surgery, chemotherapy, endocrine treatment	1294 (~8540[b])	NA	Stable angina pectoris, unstable angina, myocardial infarction, IHD, heart failure, atrial fibrillation, coronary revascularisation, death from IHD	0.23 (0.15 to 0.32)
Severance Hospital breast cancer substudy	Kim *et al*[29]	3.4 (0 to 14.16)	Heart	Smoking, BMI, diabetes, hypertension, exercise, anthracycline and other chemotherapy, anti-HER2 treatment, surgery, previous CVD	1111 (~10,980[b])	7	Acute coronary events (ST-elevation/non-ST-elevation myocardial infarction and unstable angina pectoris)	0.22 (0.01 to 0.46)[n]
						44	Heart disease other than acute coronary events	0.13 (0.03 to 0.24)
French MEDIRAD-BRACE breast cancer cardiac arrhythmia case control study	Errahmani *et al*[65]	3.38 (0.79 to 11.47)	Heart	Smoking, diabetes, hypertension, hyper-cholesterolaemia, dyslipidaemia, chemotherapy, hormonal therapy, surgery	116 (~810[b])	21 cases, 95 controls	Conduction disorders or arrhythmia events after left sided breast cancer	0.28 (-0.17 to 0.98)
		0.59 (0.0021 to 1.48)					Conduction disorders or arrhythmia events after right sided breast cancer	0.00 (-0.19 to 0.25)
William Beaumont hospital breast cancer study	Zureick *et al*[96]	0.8 (<0.6 to >1.4)	Heart	Smoking, BMI, diabetes, hypertension, hyperlipidaemia, COPD, previous CVD or liver disease, paraplegia,	375 (~1500[b])	23	Major cardiac events (MCE) (cardiogenic death, myocardial infarction, coronary revascularisation, unstable angina, development of heart failure)	0.68 (0.24 to 2.77)
						36	MCE + valvular disease requiring surgical intervention, dysrhythmias,	0.86 (0.12 to 2.08)

				hemiplegia, dementia, chemotherapy, anti-HER2 immunotherapy, racial group			pericarditis	
William Beaumont Hospital breast cancer study	Tagami *et al*[87]	3.0 (0.5 to 12.8)	LAD	Smoking, BMI, diabetes, hypertension, hyperlipidaemia, chronic kidney disease, chemotherapy, statin use, aspirin use, beta blocker use, family history of premature CVD	94 (NA)	NA	Cardiovascular Computed Tomography grade ≥3 LAD stenosis	0.49 (0.03 to 1.17)
University of North Carolina non-small cell lung cancer study	Wang *et al*[27]	12.3 (<1.6 to >48.6)	Heart	Smoking, diabetes, hypertension, chemotherapy, previous CAD	112 (~990[b])	26	Symptomatic cardiac event (shortness of breath, myocardial infarction, unstable angina, pericarditis, significant arrhythmia, heart failure) incidence	0.04 (0.013 to 0.067)[o]
University of North Carolina non-small cell lung cancer study	Wang *et al*[113]	12.3 (<12.3 to >24.5)	Heart	Chemotherapy, baseline CAD	112 (~990[b])	9 7 12	Pericardial event incidence Ischemic event incidence Arrhythmic event incidence	0.04 (0.01 to 0.07) 0.04 (-0.004 to 0.08) 0.02 (0.00 to 0.05)
University of Michigan non-small cell lung cancer study	Dess *et al*[103]	11 (0.3 to 46)	Heart EQD2	Smoking, diabetes, systolic blood pressure, cholesterol, previous CVD, KPS	125 (~240[b])	19	CTCAE v4.03 grade ≥ 3 cardiac event incidence	0.07 (0.02 to 0.13)
University of Michigan non-small cell lung cancer study	Xue *et al* [93]	13.9 (0.2 to 46.9)	Pericardium	Smoking, hypertension, COPD, chemotherapy, previous CVD, KPS	94 (~450[b])	38	Pericardial effusion incidence	0.050 (0.009 to 0.093)
Dana Farber/Brigham Women's Hospital non-small cell lung cancer study	Atkins *et al* [98] [114]	12.1[p] (<5.8 to >19.1)	Heart	Smoking, BMI, diabetes, hypertension, cholesterol, hyperlipidaemia, previous CVD, chemotherapy, statins	748 (~1270[b])	77	Major adverse cardiac events (cardiac death, unstable angina, myocardial infarction, heart failure hospitalization or urgent visit, coronary revascularization)	0.03 (0.00 to 0.06)
Singapore non-small cell lung cancer study	Lee *et al* [77]	12.55 (<4.75 to >19.48)	Heart	Smoking, diabetes, COPD, previous IHD, chemotherapy, use of PET-CT, brain	120 (~180[b])	5	Acute myocardial infarction incidence (ICD9 410, ICD10 I21, I22)	0.03 (0.01 to 0.06)

				imaging				
Medical College of Wisconsin lung cancer study	Borkenhagen *et al* [58]	NA (>0 to >26.22[q])	Pericardium	Smoking, diabetes, previous cardiac or vascular disease, chemotherapy, surgery	76 (~90[b])	16	Pericardial disease, arrhythmia, valvular disease	0.052 (0.010 to 0.097)
Shanghai non-small cell lung cancer study	Chen *et al* [102]	13.2 (7.8 to 18.5)	Heart	Smoking, diabetes, systolic blood pressure, cholesterol, chemotherapy, pre-existing CAD	112 (~280[b])	14	CTCAE v4.0 grade ≥3 cardiac incidence (among patients without previous radiotherapy with fields including heart, persistent pericardial effusions or atrial fibrillation)	0.779 (0.151 to 1.750)
New Jersey non-small cell lung cancer study	Yegya-Raman *et al* [111]	15.8[r] (<4.5 to >53.2)	Heart	Smoking, blood pressure, diabetes, chemotherapy, pre-treatment CAD	140 (~550[b])	47	First symptomatic cardiac event (myocardial infarction, unstable angina, significant arrhythmia, symptomatic pericardial effusion, pericarditis, congestive heart failure) incidence	0.059 (0.032 to 0.086)
Chonnam National University Hwasun Hospital lung cancer study	Cho *et al*[28]	8.3 (0.4 to 44.1)	Heart	Smoking, BMI, diabetes, hypertension, pre-existing cardiac disease	133 (~500[b])	42	Cardiac CTCAE v5.0 grade ≥2	0.073 (0.041 to 0.105)[s]
University of Chicago lung cancer study	Ni *et al* [30]	13.1 (5.5 to 48.7)	Heart	Smoking, diabetes, Charlson index (and therefore possibly also hypertension, renal disease, liver disease), racial group	108 (~160[b])	12	CTCAE v4.03 grade ≥ 3 cardiac events (new arrhythmia, structural disease/valvulopathy, myocardial infarction, congestive heart failure, pericarditis or pericardial effusion requiring intervention)	0.059 (0.003 to 0.129)[t]
Chenyang thymoma study	Liao *et al* [18]	10.2 (0 to 30)	Heart	Smoking, BMI, diabetes, hypertension, hyperlipaemia, chemotherapy, myasthenia gravis, family history of CVD	130 (~760[b])	20	CTCAE v4.0 grade ≥2 cardiovascular disease incidence	0.518 (0.013 to 3.107)[u]
MD Anderson esophageal cancer study	Wang *et al* [110]	NA (<5 to >35)	Heart	Smoking, pre-existing cardiac disease, chemotherapy, surgery	479 (~3030[b])	88	CTCAE v5.0 grade ≥3 adverse cardiac event (acute coronary event, arrhythmia, heart failure, cardiac arrest, pericardial effusion, pericarditis) incidence	0.034 (0.006 to 0.062)
Shandong esophageal cancer study	Cai *et al* [100]	12.26 (<0.41 to >48.2)	Heart	Smoking, diabetes, alcohol consumption, chemotherapy,	346 (~870[b])	91	CTCAE v4.03 grade ≥2 cardiac event (excluding pericardial effusions) incidence among patients without	0.10 (0.02 to 0.19)

				COPD, pre-existing IHD		38	previous ischemic heart disease CTCAE v4.03 grade ≥3 cardiac event (excluding pericardial effusions) incidence among patients without previous ischemic heart disease	0.17 (0.07 to 0.28)
Duke Cancer Institute head and neck cancer study	Dorth *et al* [62]	50 (<50 to >50)	Carotid	Smoking, diabetes, hypertension, hyperlipidaemia, cardio/peripheral vascular disease, atrial fibrillation, chemotherapy	224 (810[b])	35	Carotid stenosis incidence	0.02 (-0.03 to 0.10)
Groningen head and neck cancer study	van Aken *et al*[91]	39.8 (<39.8 to >39.8)	Carotid	Smoking, diabetes, hypertension, alcohol consumption, chemotherapy, HPV status, angina, cardiac arrhythmia, prior ischaemic cerebrovascular event	750 (~2550[b])	27	Ischaemic cerebrovascular events (ischaemic cerebrovascular accident, transient ischaemic attack in the anterior circulation)	0.03 (0.00 to 0.07)
Peptic ulcer study	Little *et al* [78]	1.08 (0.0 to 6.20)	Heart	Smoking, alcohol consumption, marital status	3600 (76,571.7)	1003	IHD (ICD9 410-414)	0.102 (0.039 to 0.174)
		0.079 (0.0 to 0.46)	Thyroid			226	CeVD (ICD9 430-438)	0.422 (-1.455 to 3.039)
		1.08 (0.0 to 6.20)	Heart			240	All other CVD ICD9 390-409, 415-429, 439-459	0.050 (-0.053 to 0.194)
		1.08 (0.0 to 6.20)	Heart			1469	All CVD (ICD9 390-459)	0.082 (0.031 to 0.140)
Israeli tinea capitis prevalence study	Sadetzki *et al*[84]	0.0071 (0 to 0.074)	Breast	Smoking, BMI, diabetes, hypertension, SES	17,734 (NA)	1261	IHD incident prevalence	7 (1 to 14)[v]
		0.6266 (0 to 6)	Brain			1089	CeVD incident prevalence	0.20 (0.12 to 0.29)[v]
		0.3258 (0 to 2.8)	Salivary			321	Carotid artery stenosis incident prevalence	0.33 (0.04 to 0.71)[v]
Rochester thymus enlargement study	Adams *et al*[44]	0.62 (0 to 20.2)	Heart	Smoking, dyslipidaemia, diabetes, hypertension, family history of myocardial infarction	3071 (339,268)	350	Coronary heart disease incidence (ICD10 I21-I25, I46)	-0.03 (-0.07 to 0.10)
					3071 (339,924)	213	Myocardial infarction incidence (ICD10 I21-I24)	-0.06 (-0.16 to 0.06)
Diagnostically exposed groups								
Canadian and Massachusetts tuberculosis fluoroscopy cohorts	Tran *et al* [1]	0.18 (0 to 0.50) [<0.5 Gy] / 1.16	Lung	Smoking, diabetes, alcohol consumption,	77,275 (1,945,041)	12,983	All CVD ICD9 390-459	-0.024 (-0.042 to -0.005)[w]
						10,209	All CVD ICD9 390-459: <0.5 Gy	0.246 (0.036 to 0.469)[w]

	(0 to 27.77) [total][y]	antibiotic use, tuberculosis stage	8158	Ischemic heart disease ICD9 410-414	-0.037 (-0.060 to -0.013)[w]
			6410	Ischemic heart disease ICD9 410-414: < 0.5 Gy	0.268 (0.003 to 0.552)
			1953	Cerebrovascular disease ICD9 430-438	-0.014 (-0.067 to 0.044)[w]
			1561	Cerebrovascular disease ICD9 430-438: < 0.5 Gy	0.441 (-0.119 to 1.090)[w]
			323	Hypertensive heart disease ICD9 401-405	-0.035 (-0.152 to 0.153)[w]
			244	Hypertensive heart disease ICD9 401-405: < 0.5 Gy	1.121 (-0.351 to 3.228)[w]
			1679	Heart disease apart from hypertensive and IHD ICD9 390-400, 406-410	-0.010 (-0.064 to 0.043)[w]
			1309	Heart disease apart from hypertensive and IHD ICD9 390-400, 406-410: < 0.5 Gy	-0.226 (-0.679 to 0.307)[w]
			870	All CVD apart from heart and cerebrovascular ICD9 439-459	0.055 (-0.028 to 0.164)[w]
			685	All CVD apart from heart and cerebrovascular ICD9 439-459: < 0.5 Gy	0.507 (-0.322 to 1.541)[w]

CTCAE v, Common Terminology Criteria for Adverse Events version; CVD, cardiovascular disease; LAD, left anterior descending artery; MHD, mean heart dose; BMI, body mass index; HRT, hormone replacement therapy; COPD, chronic obstructive pulmonary disease; HER2, human epidermal growth factor receptor 2; KPS, Karnovsky performance score; CAD, coronary artery disease; NA, not available.

[a]estimate derived by fitting by (inverse variance) weighted least squares to excess hazard ratio, and assuming mean maximum brain doses of 15.25, 40 and 60 Gy for the 1.5-29, 30-49 and 50+ Gy maximum brain dose groups given by model I of Table 3 of Mueller *et al* [19]: see Supplements S1 and S2. The mean dose is obtained by weighting these mean doses by the case count in Table 1.

[b]estimate derived multiplying median/mean length of follow-up by number of persons.

[c]estimate derived by fitting a linear model by (inverse-variance) weighted least squares, applied to the aggregate data provided in Table 3 of Fullerton *et al* [20] using the maximum cranial doses of 0, 15, 40 and 60 Gy for the 0, 0.01-29.9, 30-49.9 and ≥50 Gy groups.

[d]estimate derived by fitting a linear model by (inverse-variance) weighted least squares, applied to the aggregate data provided in Table 3 of Mulrooney *et al* [21] and in Table 2 of Shrestha *et al*[23]. For the data of Mulrooney *et al* [21] (all endpoints except all cardiac disease) average cardiac doses of 0, 7.5, 25, and 45 Gy were assumed for the respective groups with the following specified ranges of cardiac doses: 0, 1-15, 15.1-34.99 Gy, ≥35 Gy. For the data of Shrestha *et al*[23] average cardiac doses of 0, 5, 15, 25 and 35 Gy were assumed for the respective groups with the following specified ranges of cardiac doses: 0, 0.1-9.9, 10-19.9, 20-29.9 Gy, ≥30 Gy, and the central estimates of ERR?Gy given in Figure 1 were used to correct the central estimates of trend.

[e]estimate derived by fitting a linear model by (inverse-variance) weighted least squares, applied to the aggregate data provided in Table 5 of Mulrooney *et al* [22]. Average cardiac doses of 0, 7.5 and 25 Gy were assumed for the respective groups with the following specified ranges of cardiac doses: 0, 1-15, ≥15 Gy.

[f]mean dose to heart in 21 persons who died of cardiovascular disease.

[g]estimate derived using number of cases by dose groups given in Table 2 of El-Fayech *et al*[63] and assuming mean doses of 0.5, 5.5, 25 and 50 Gy for the <1, 1-<10, 10-<40, 40+ Gy dose groups.

[h]using mean dose to controls.

[i]mean dose estimated from assuming mean doses 0, 15, and 25 Gy in dose groups 0, 10-19.9 and ≥20 Gy, weighted by numbers of controls, taken from Table 4 of Green *et al* [67].

[j]estimate derived by fitting a linear binomial odds model to aggregate numbers of cases and controls, and employing the median EQD2 heart-valve doses by dose group given in Table 4 of Cutter *et al* [16]: see Supplements S1 and S2.

[k]estimate derived by fitting a linear binomial odds model to aggregate numbers of cases and controls, and assuming mean heart doses of 0, 16, 23, 28, 33 Gy for the 0, 1-20, 21-25, 26-30, ≥31 Gy mean heart dose groups given in Table 2 of van Nimwegen *et al* [17]: see Supplements S1 and S2.

[l]mean of medians for controls.

[m]estimate derived using the aggregate data provided in Table 1 of Boekel *et al* [54] using the median heart doses by group given there weighted by number of controls.

[n]using midpoint estimates for [D_{min}+3]/2 and [D_{max}+3]/2 Gy (using given minimum and maximum heart doses, D_{min} and D_{max}) and ln[odds ratio] (and CI) for >3 Gy vs <3 Gy from Kim *et al*[29].

[o]CI derived by using the 2-sided *p*-value and central estimate of hazard ratio adjusted for baseline coronary artery disease given in Table 4 of Wang *et al* [27].

[p]based on mean of median MHD in statin and non-stain groups.

[q]dose to ventricles.

[r]median dose.

[s]using midpoint estimates for [D_{min}+11.1]/2 and [D_{max}+11.1]/2 Gy (using given minimum and maximum heart doses, D_{min} and D_{max}) and ln[odds ratio] (and CI) for >11.1 Gy vs <11.1 Gy from Cho *et al*[28].

[t]using midpoint estimates for [D_{min}+13.1]/2 and [D_{max}+13.1]/2 Gy (using given minimum and maximum heart doses, D_{min} and D_{max}) and ln[odds ratio] for >13.1 Gy vs < 13.1 Gy in Ni *et al* [30].

[u]estimate derived by fitting a linear binomial odds model to aggregate numbers of cases and controls, and assuming mean heart doses of 5, 15, 25 Gy for the 0-10, 10-20 and 20-30 Gy mean heart dose groups given in Table 4 of Liao *et al* [18]: see Supplements S1 and S2.
[v]prevalence excess odds ratio per Gy.
[w]based on 5-year lagged lung dose.

Table S3.5. Estimated excess relative risks of cardiovascular diseases in the Japanese atomic bomb survivors and in other groups with moderate- or low-dose radiation exposure, with mean dose generally < 0.5 Gy. All data are in relation to underlying cause of death, unless otherwise indicated.

Cohort/Study	Reference	Average Organ Dose (Gy/Sv) mean/ median (range)	Organ used	Variables (other than age, sex, year) available to assess possible confounding	Persons (person years of follow-up)	Deaths/ cases	Endpoint (mortality unless otherwise indicated)	Excess relative risk Gy^{-1} (95% CI)
Japanese atomic bomb survivors								
Japanese atomic bomb survivors	Shimizu *et al* [86]	0.1 (0 to 4)	Colon	Smoking, obesity (BMI), diabetes, alcohol intake, education, type of household occupation, city	86,611 (NA)	3252	IHD (ICD9 410-414)	0.02 (-0.10 to 0.15)
						1735	Myocardial infarction (ICD9 410)	0.00 (-0.15 to 0.18)
						922	Hypertensive heart disease (ICD9 402, 404)	0.37 (0.08 to 0.72)
						242	Rheumatic heart disease (ICD9 393-398)	0.86 (0.25 to 1.72)
						2983	Heart failure (ICD9 428)	0.22 (0.07 to 0.39)
						1064	Other heart disease (ICD9 390-392, 415-427, 429)	-0.01 (-0.21 to 0.24)
						411	Hypertensive disease without heart disease (ICD9 401, 403, 405)	0.07 (-0.22 to 0.55)
						14,018	Heart disease total (ICD9 390-398, 402, 404, 410-429)	0.18 (0.11 to 0.25)[a]
						2659	Cerebral infarction (ICD9 433,434)	0.04 (-0.10 to 0.20)
						4060	Cerebral haemorrhage (ICD9 431)	0.05 (-0.06 to 0.17)
						461	Subarachnoid haemorrhage (ICD9 430)	0.30 (-0.04 to 0.76)
						2442	Other or unspecified cerebrovascular disease	0.16 (0.01 to 0.34)
						12,139	Cerebrovascular disease total (ICD9 430-438)	0.12 (0.05 to 0.19)[a]
						5846	CVD apart from heart disease and stroke (ICD9 399-401, 403, 405-409, 439-459)	0.58 (0.45 to 0.72)[a]
						558	Other CVD (ICD9 399-400, 406-409, 439-459)	-0.01 (<-0.01 to 0.34)
						25,113	All CVD (ICD9 390-459)	0.15 (0.10 to 0.20)[a]
Japanese atomic bomb survivors	Yamada *et al* [94]	0.1 (0 to 4)[b]	Stomach	Smoking, alcohol consumption, city	10,339 (NA)	5035	Hypertension incidence, 1958-1998 (ICD9 401)	0.05 (-0.01 to 0.10)[b]
						1886	Hypertensive heart disease incidence, 1958-1998 (ICD9 402, 404)	-0.01 (-0.09 to 0.09)[b]
						1546	IHD incidence, 1958-1998 (ICD9 410-414)	0.05 (-0.05 to 0.16)[b]
						117	Myocardial infarction incidence, 1964-1998 (ICD9 410)	0.12 (-0.16 to 0.60)[b]
						440	Occlusion incidence, 1958-1998 (ICD9 433, 434)	0.06 (-0.11 to 0.30)[b]
						184	Aortic aneurysm incidence, 1958-1998 (ICD9 441, 442)	0.02 (-0.22 to 0.41)[b]
						729	Stroke incidence, 1958-1998 (ICD9 430, 431, 433, 434, 436)	0.07 (-0.08 to 0.24)[b]
Japanese atomic bomb survivors *in utero* followed to age 9-19	Nakashima *et al* [82]	0.116 (0 to 2.374)	Maternal uterus	BMI, city, trimester	1014 (NA)	118	Systolic hypertension incidence	1.23 (0.23 to 3.04)
					462 (6935)	155	Incidence *in utero*: hypertension	0.20 (-0.39 to 1.38)

Japanese atomic bomb survivors *in utero*	Tatsukawa *et al* [90]	0.001 (0 to 1.79)	Maternal uterus	Smoking, BMI, alcohol consumption, city, trimester	504 (9,265)	6	Incidence *in utero:* nonfatal stroke or myocardial infarction	-0.91 (-1.00 to 79.3)
Japanese atomic bomb survivors exposed in childhood (age < 10 y)	Tatsukawa *et al* [90]	0.13 (0 to 3.53)	Colon	Smoking, BMI, alcohol consumption, city	861 (13,180)	318	Incidence: hypertension	0.15 (-0.01 to 0.34)
					1,045 (20,216)	37	Incidence: stroke or myocardial infarction	0.72 (0.24 to 1.40)
Japanese atomic bomb survivors 1950-2008	Takahashi *et al* [88]	~0.1 (0 to 4)	Colon	City	86,600 (3,462,847)	9303	Heart disease (ICD10 I05–I08, I09.1, I11, I13, I20–25, I34–I39, I50) overall	0.140 (0.060 to 0.220)
						3556	IHD (ICD10 I20-I25)	0.030 (-0.080 to 0.150)
						1883	Myocardial infarction (ICD10 I21-I23)	0.020 (-0.130 to 0.200)
						1673	Other ischemic heart disease (ICD10 I20, I24-I25)	0.040 (-0.120 to 0.220)
						744	Valvular heart disease (ICD10 I05–I08, I09.1, I34–I39)	0.450 (0.130 to 0.850)
						223	Rheumatic valvular heart disease (ICD10 I05–I08, I09.1)	0.960 (0.280 to 1.920)
						521	Non-rheumatic valvular heart disease (I34–I39)	0.240 (-0.080 to 0.680)
						1122	Hypertensive organ damage (ICD10 I11-I13)	0.360 (0.100 to 0.680)
						3334	Heart failure (ICD10 I50)	0.210 (0.070 to 0.370)
Japanese atomic bomb survivors 1958-2014	Takahashi *et al* [89]	~0.1 (0 to < 4)	Skin	Smoking, BMI, diabetes, blood pressure, total + low-LDL and high-LDL cholesterol, triglycerides, dyslipidaemia, high sensitivity CRP, white blood cell count, glomerular filtration rate, city	3,476 (NA)	79	Peripheral artery disease prevalence	-0.17 (-0.43 to 0.22)
Japanese atomic bomb survivors 1950-2003	Little *et al* [115]	~0.1 (0 to 3)	Lung	City	86,611 (3,294,210)	19,065	CVD (linear coefficient of linear-quadratic model, adjusted for female sex, age at exposure 20 y, years since exposure 30)	0.07 (-0.12 to 0.25)
Occupational studies								
International Agency for Research on Cancer15-country nuclear worker study	Vrijheid *et al* [13]	0.0207 (0.0 to 1.5)	Colon	Employer/facility, SES	275,312 (4,067,861)	8412	CVD (ICD10 I00-I99, J60-J69, O88.2, R00-R02, R57)	0.09 (-0.43 to 0.70)[c]
						5821	IHD (ICD10 I20-I25)	-0.01 (-0.59 to 0.69)[c]
						130	Heart failure (ICD10 I50)	-0.03 (<0 to 4.91)[c]
						104	Deep vein thrombosis and pulmonary embolism (ICD10 I26, I80, I82, O88.2)	-0.95 (-1.00 to 9.09)[c to d]
						1224	Cerebrovascular disease (ICD10 I60-I69)	0.88 (-0.67 to 3.16)[c]
						1133	All other CVD (ICD10 R00-R02, R57, I00-I99 excluding I20-26, I50, I60-69, I80, I82)	0.29 (<0 to 2.40)[c]
	Gillies *et al* [8]	0.0252 (0 to 1.932)		Employer/facility, SES	308,297 (8.2 x 10^6)	27,848	CVD (ICD10 I00-I99)	0.22 (0.08 to 0.37)[e]
						17,463	IHD (I20-I25)	0.18 (0.004 to 0.36)[e]

International Nuclear Workers Study (INWORKS)			Film badge ($H_p(10)$)			11,076 6238 4444	Acute myocardial infarction (I21) Chronic ischemic heart disease (I25) CeVD (I60-I69)	0.26 (0.03 to 0.51)[e] 0.07 (-0.19 to 0.36)[e] 0.50 (0.12 to 0.94)[e]
Mayak workers IHD	Azizova *et al* [5 10]	0.51 (0 to >4.5)[f]	External gamma	Smoking, BMI, hypertension alcohol consumption	22,377 (447,281)	7225	IHD incidence (ICD9 410-414) < 4 Gy IHD incidence (ICD9 410-414) < 4 Gy IHD incidence (ICD9 410-414) < 4 Gy	0.14 (0.08 to 0.21)[g] 0.15 (0.09 to 0.22)[c] 0.17 (0.10 to 0.25)[h]
					22,377 (836,048)	2848	IHD (ICD9 410-414) < 4 Gy IHD (ICD9 410-414) < 4 Gy IHD (ICD9 410-414) < 4 Gy	0.07 (<0 to 0.16)[g] 0.07 (>0 to 0.16)[c] 0.07 (<0 to 0.16)[h]
		0.43 (<0.1 to >3.0)	Liver external gamma	Smoking, BMI, diabetes, alcohol consumption	22,377 (890,132)	3481	IHD (ICD9 410-414)	0.04 (-0.02 to 0.11)[c]
Mayak workers CeVD	Azizova *et al* [9-11]	0.51 (0 to >4.5)[f]	External gamma	Smoking, BMI, hypertension, alcohol consumption	22,377 (425,735)	8717	CeVD incidence (ICD9 430-438) CeVD incidence (ICD9 430-438) CeVD incidence (ICD9 430-438)	0.46 (0.37 to 0.56)[g] 0.49 (0.39 to 0.60)[c] 0.53 (0.43 to 0.65)[h]
		0.43 (<0.1 to >3)	Liver external gamma	Smoking, BMI, diabetes, alcohol consumption	22,377 (459,520)	9469	CeVD incidence (ICD9 430-438)	0.39 (0.31 to 0.48)[c]
		0.51 (0 to >4.5)[f]	External gamma	Smoking, BMI, hypertension, alcohol consumption,	22,377 (836,078)	1578	CeVD (ICD9 430-438) CeVD (ICD9 430-438) CeVD (ICD9 430-438)	0.05 (-0.04 to 0.16)[g] 0.05 (-0.03 to 0.16)[c] 0.06 (-0.03 to 0.18)[h]
		0.43 (<0.1 to >3)	Liver external gamma	Smoking, BMI, diabetes, alcohol consumption	22,377 (890,132)	1808	CeVD (ICD9 430-438)	0.03 (-0.05 to 0.13)[c]
Mayak workers all cardiovascular disease	Azizova *et al* [6 10]	0.51 (0 to <4)	External gamma	Smoking, BMI, hypertension, alcohol consumption	22,334 (836,048)	5010	All cardiovascular disease (ICD9 390-459) < 4 Gy	0.08 (0.02 to 0.14)[g] 0.08 (0.02 to 0.15)[c] 0.09 (0.03 to 0.16)[h]
		0.43 (<0.1 to >3)	Liver external gamma	Smoking, BMI, diabetes, alcohol consumption	22,377 (890,132)	6019	All cardiovascular disease (ICD9 390-459)	0.03 (-0.01 to 0.09)[c]
Mayak workers stroke subtype	Moseeva *et al* [26]	0.44 (0 to >1.5)[i]	Liver (including plutonium alpha)	Smoking, BMI, diabetes, hypertension, alcohol consumption	22,377 (454,105)	221 1463 342	Intracerebral haemorrhage (ICD10 I61) incidence Brain cerebral infarction (ICD10 I63) incidence Stroke not specified as intracerebral haemorrhage or brain cerebral infarction (ICD10 I64) incidence	-0.01 (-0.17 to 0.15)[i] -0.07 (-0.17 to 0.03)[i] -0.24 (-0.35 to -0.14)[i]
Mayak workers lower extremity arterial disease	Azizova *et al* [52]	0.51 (0 to >4.5)	External gamma	Smoking, BMI, hypertension, alcohol consumption	21,122 (512,801)	943	Lower extremity arterial disease incidence (ICD9 440.2) Lower extremity arterial disease incidence (ICD9 440.2) Lower extremity arterial disease incidence (ICD9 440.2)	0.30 (0.13 to 0.53)[g] 0.28 (0.12 to 0.50)[c] 0.32 (0.14 to 0.57)[h]
Mayak part of combined nuclear worker study	Azizova *et al* [7]	0.52 (0 to 8.4)	External gamma	NA	22,374 (842,538)	5123 2905 1610	CVD (ICD10 I00-I99) IHD (ICD10 I20-I25) CeVD (ICD10 I60-I69)	0.04 (-0.00 to 0.09) 0.06 (0.01 to 0.13) 0.00 (-0.06 to 0.08)
Mayak workers hypertension	Azizova *et al* [53]	0.44 (0 to 5.82)	Liver external gamma	Smoking, BMI, alcohol consumption	22,377 (429,707)	8425	Hypertension incidence (ICD9 401-404)	0.14 (0.09 to 0.20)

Canadian National Dose Registry radiation workers	Zielinski *et al* [14]	0.0086 (0 to >0.5465) 0.0012 (0 to >0.2111)	Whole body including tritium	NA	169,256 (~2.8 x10^{6} [j]) 168,141 (~2.5 x10^{6} [j])	3018 515	All CVD (ICD9 390-459) males All CVD (ICD9 390-459) females	1.22 (0.47 to 2.10)[e] 7.37 (0.95 to 18.1)[e]
Sellafield part of combined nuclear worker study	Azizova *et al* [7]	0.07 (0 to 1.88)	Film badge ($H_p(10)$)	NA	23,443 (602,311)	2322 1560 438	CVD (ICD10 I00-I99) Ischemic heart disease (ICD10 I20-I25) Cerebrovascular disease (ICD10 I60-I69)	0.42 (0.12 to 0.78) 0.53 (0.14 to 1.00) 0.05 (-0.46 to 0.79)
UK NRRW heart disease	Zhang *et al* [2]	0.0232 (0 to >0.5)	Film badge	Industrial classification	174,541 (NA)	11,014 10,771 9814 9603 5991 5861 3823 3742 64 63 249 243 140 138 747 724	All heart disease (ICD9 393-398, 402, 404, 410-429) All heart disease (ICD9 393-398, 402, 404, 410-429) <0.4 Sv IHD (ICD9 410-414) IHD (ICD9 410-414) <0.4 Sv Myocardial infarction (ICD9 410) Myocardial infarction (ICD9 410) <0.4 Sv Other types of IHD (ICD9 411-414) Other types of IHD (ICD9 411-414) <0.4 Sv Rheumatic heart disease Rheumatic heart disease <0.4 Sv Heart failure (ICD9 428) Heart failure (ICD9 428) <0.4 Sv Hypertensive heart disease (ICD9 402, 404) Hypertensive heart disease (ICD9 402, 404) <0.4 Sv Other heart disease (ICD9 415-427, 429) Other heart disease (ICD9 415-427, 429) <0.4 Sv	0.37 (0.11 to 0.65) 0.64 (0.24 to 1.06) 0.32 (0.04 to 0.61) 0.70 (0.27 to 1.16) 0.54 (0.16 to 0.95) 1.00 (0.43 to 1.63) 0.01 (-0.36 to 0.45) 0.26 (-0.35 to 0.95) -0.59 (-1.89 to 4.6) -0.90 (-3.26 to 5.10) 0.72 (-0.77 to 3.21) 0.81 (-1.34 to 4.20) 0.06 (-1.57 to 4.00) -0.36 (-2.88 to 4.88) 1.08 (0.03 to 2.45) -0.003 (-1.31 to 1.73)
UK NRRW stroke	Hinksman *et al*[12]	0.0215[k] (0 to 1.9) 0.0192[k] (0 to 0.5)	Film badge	Industrial classification	166,812 (3,665,413)	3219 3169	CeVD (ICD10 I60-I69) CeVD (ICD10 I60-I69) dose <0.5 Sv	0.57 (0.00 to 1.31) 2.39 (-0.22 to 5.48)
French nuclear fuel cycle workers	Bouet *et al* [59]	0.01112 (0 to 0.21395)	External gamma	Smoking, BMI, glycemic level, hypertension, SES	4,541 (NA)	37 35 22	CVD (ICD10 I00-I99, G45-G46) (subgroup 2, adjusted for SES, blood pressure, BMI, smoking status, glycemic level) IHD (ICD10 I20-I25) (subgroup 1) CeVD (ICD10 I60-I69+G45 (exc G45.3, G45.4)+G46) (subgroup 1)	-0.1 (NA to 48.4) -4.0 (NA to 34.7) -0.3 (NA to 61.4)
French uranium miners case-control study	Drubay *et al* [39]	0.0662 (0 to 0.4701)	External gamma	Smoking, BMI, diabetes, hypertension, hyper-cholesterolaemia, hyper-triglyceridaemia, resting heart rate, chronic kidney disease hyperuricaemia, gamma glutamyl transpepsidase	76 cases, 237 counter-matched controls	76 26 16	All CVD (ICD10 I00-I99) IHD (ICD10 I20-I25) CeVD (ICD10 I60-I69)	0.4 (-1.6 to 2.9)[l] -1.0 (-3.9 to 3.3)[l] 2.4 (-0.6 to 11.4)[l]
French uranium miners cohort study	Rage *et al* [40]		External gamma	NA	5,086 (179,955)	442 167	All CVD (ICD10 I00-I99) IHD (ICD10 I20-I25)	0.3 (-1.1 to 2.4) -1.2 (NA to 1.5)

		0.0549 (0.0002 to 0.4701)				105	CeVD (ICD10 I60-I69)	4.9 (0.1 to 16.1)
French CEA tritium workers	Martin & Ségala[31]	0.0019 (0 to 0.047)	Effective dose (Heart)	Smoking, centre, socio-professional category	1746 (48,814)	52	All CVD (ICD10 I00-I99)	14.53 (-25.61 to 106.8)[m]
German uranium miner study	Kreuzer *et al* [75]	0.040 (0 to 0.909)	External gamma	Smoking, overweight, diabetes, radon	58,982 (2,180,639)	9039 4613 2073	All CVD (ICD10 I00-I99) IHD (ICD10 I20-I25) CeVD (ICD10 I60-I69)	-0.13 (-0.38 to 0.12)[c] -0.03 (-0.38 to 0.32)[c] 0.44 (-0.16 to 1.04)[c]
German and Canadian uranium processing worker study	Zablotska *et al* [95]	0.0615 (0 to 5.0988)	External gamma	Radon	7,431 (270,201)	1263 49 706 252	All CVD (ICD10 I00-I99) Hypertensive disease (ICD10 I10-I15) IHD (ICD10 I20-I25) CeVD (ICD10 I60-I69)	0.13 (-0.11 to 0.48)[g] 0.58 (<-1.10 to 5.12)[g] 0.21 (<-0.13 to 0.71)[g] -0.19 (<-1.12 to 0.50)[g]
Eldorado uranium miners and processing (male) workers	Lane *et al* [76]	0.0508 (<0.0234 to >0.1215)[n]	External gamma	Radon	16,236 (508,673)	1235 244 317	IHD Stroke All other CVD	0.15 (-0.14 to 0.58) -0.29 (<-0.29 to 0.27) 0.07 (<-0.33 to 0.77)
US uranium processing workers	Anderson *et al* [51]	0.044 (0 to 0.592)	Lung	SES, racial group	29,283 (NA)	3488 746	IHD (ICD9 410-414, 429.2) CeVD (ICD9 430-438)	0.28 (-0.45 to 1.1) 0.49 (-0.94 to 2.5)
Mallinckrodt uranium processing workers	Golden *et al* [66]	0.0475 (0 to 0.738)	Heart	SES, silica dust, internal exposures from uranium etc	2,514 (107,927)	521	IHD (ICD9 410-414)	1.3 (-0.1 to 2.8)
Mound workers	Boice *et al* [25]	0.0243 (0 to 0.9412)	Heart	Education, racial group, internal exposures from polonium etc	7,269 (293,462)	1189	Heart disease (ICD9 390-398, 404, 410-429)	0.601 (-16.31 to 17.51)[o]
US nuclear power workers	Boice *et al* [55]	0.0439 (0 to 1.1)	Heart	SES	135,193 (4,079,620)	5410	IHD (ICD9 410-414)	-0.1 (-0.6 to 0.4)
Los Alamos workers	Boice *et al*[43]	0.0135 (0 to 0.897) 0.0117 (0 to 0.764)	Heart Brain	Education, exposures from plutonium, tritium	26,328 (1,181,472)	2517 625	IHD (ICD9 410-414) CeVD (ICD9 430-438)	-0.6 (-1.6 to 0.4) -1.1 (-3.5 to 1.2)
US 8 series atomic test veterans	Boice *et al* [56]	0.0061[p] (0 to >0.025)	Heart	Pay grade, test area	114,270 (5,370,306)	22,592	Heart disease (ICD9 390–398, 404, 410–429)	-0.01 (-1.2 to 1.1)
UK atomic test veterans	Gillies & Haylock [32]	0.0099 (0 to >0.05)	Film badge	Service, employer, SES	~4900[q] (NA)	1166 690 233	All CVD (ICD10 I00-I99) IHD (ICD10 I20-I25) CeVD (ICD10 I60-I69)	0.240 (-4.447 to 5.948)[q] -1.597 (-7.409 to 6.084)[q] 8.012 (-3.608 to 24.56)[q]
US medical workers	Boice *et al* [57]	0.0146 (0 to 1.27) 0.0189 (0 to 1.08)	Heart Brain	Occupational category	109,019 (2,779,838)	1655 462	IHD (ICD9 410-414) CeVD (ICD9 430-438)	-1.0 (-2.7 to 0.6) 0.4 (-1.6 to 2.3)
NASA astronauts	Elgart *et al* [64]			Medical radiation dose	73 (3,120.8)	7	All cardiovascular disease (IHD, CeVD)	-123.5 (-491.6 to 16.9)

		0.002 (0 to 0.0741)	Effective dose			5 2	IHD CeVD	-62.7 (-411.8 to 32.6) -501.5 (-925.1 to 32.9)
Russian Chernobyl emergency workers	Ivanov *et al* [70 116]	0.109 (0 to >0.5)	External whole body gamma	NA	61,017 (NA)	15,484 11,910 7680 10,942 948 849 6613 7021 3572 12,832 3934 5572 32,189	Hypertension (ICD10 I10-I15) incidence Essential hypertension (ICD10 I10) incidence Hypertensive heart disease (ICD10 I11) incidence Ischemic heart disease (ICD10 I20-I25) incidence Acute myocardial infarction (ICD10 I21) incidence Other acute ischemic heart disease (ICD10 I24) incidence Angina pectoris (ICD10 I20) incidence Chronic ischemic heart disease (ICD10 I25) incidence Other heart disease (ICD10 I30-I52) incidence Cerebrovascular disease (ICD10 I60-I69) incidence Incidence from diseases of arteries, arterioles and capillaries (ICD10 I70-I79) Incidence from diseases of veins, lymphatic vessels and lymph nodes (ICD10 I80-I89) All CVD (ICD10 I00-I99) incidence	0.26 (-0.04 to 0.56) 0.36 (0.005 to 0.71) 0.04 (-0.36 to 0.44) 0.41 (0.05 to 0.78) 0.19 (-0.99 to 1.37) 0.82 (-0.62 to 2.26) 0.26 (-0.19 to 0.71) 0.20 (-0.23 to 0.63) -0.26 (-0.81 to 0.28) 0.45 (0.11 to 0.80) 0.47 (-0.15 to 1.09) -0.26 (-0.70 to 0.18) 0.18 (-0.03 to 0.39)
Russian Chernobyl emergency workers	Kashcheev *et al* [72]	0.161 (0.0001 to 1.24)	External whole body gamma	NA	53,772 (958,540.5)	23,264	CeVD (ICD10 I60-I69) incidence after no diabetes CeVD (ICD10 I60-I69) incidence after diabetes CeVD (ICD10 I60-I69) incidence after no atherosclerosis CeVD (ICD10 I60-I69) incidence after atherosclerosis CeVD (ICD10 I60-I69) incidence after no hypertensive disease CeVD (ICD10 I60-I69) incidence after hypertensive disease CeVD (ICD10 I60-I69) incidence after no IHD CeVD (ICD10 I60-I69) incidence after IHD CeVD (ICD10 I60-I69) incidence after no concomitant disease CeVD (ICD10 I60-I69) incidence	0.35 (0.18 to 0.53) 1.29 (0.63 to 1.94) 0.43 (0.25 to 0.62) 0.50 (0.09 to 0.90) 0.38 (0.08 to 0.68) 0.48 (0.27 to 0.68) 0.41 (0.14 to 0.68) 0.47 (0.25 to 0.69) 0.38 (0.13 to 0.64) 0.45 (0.28 to 0.62)
Russian Chernobyl emergency workers	Chekin *et al* and Kashcheev *et al* [101 105]	0.1610 (0.0001 to 1.42) 0.133 (NA)	External whole body gamma	NA	53,772 (940,204.5) 91,013 (2,408,812.5)	27,456 15,025	CVD (ICD10 I00-I99) incidence CVD (ICD10 I00-I99)	0.47 (0.31 to 0.63) 0.349 (0.146 to 0.564)
Russian Chernobyl emergency workers, including doses from their work at 10 other nuclear power plants	Shafransky *et al* [85]	0.0705 (0.0001 to 1.9856)	Film badge	NA	12,663 (234,548[r])	643	IHD (ICD10 I20-I25)	0.46 (-0.007 to 1.04)
Ukrainian Chernobyl emergency workers	Tatarenko [34]	0.152 (<0.05 to >0.195)	Film badge	Diabetes, hypercholesterolaemia, serum creatinine	796 (NA)	251	Myocardial infarction prevalence	1.450 (-4.311 to 7.700)[s]
					3623 (NA)	NA	Chronic cerebrovascular disease (ICD10 I67, I69) incidence	0.52 (0.35 to 0.77)

Ukrainian Chernobyl emergency workers	Krasnikova *et al* [73]	0.254 (<0.05 to >1.32)	External whole body	Smoking, diabetes, hypertension, hypercholesterolaemia, alcohol abuse, salt intake, thyroid disease, physical and emotional strain		NA	Cerebral atherosclerosis (ICD10 I67.2) incidence	1.13 (1.06 to 1.20)
Korean medical diagnostic workers	Cha *et al* [60]	0.0062 (0.000002 to 0.0729)	Heart	Smoking, BMI, blood glucose, systolic+diastolic blood pressure, total + low-density LDL + high-density LDL cholesterol, alcohol intake	11,500 (93,696)	2270	All CVD (ICD10 I00-I83, I85-I99) incidence	1.4 (-5.7 to 9.9)
						955	Hypertension (ICD10 I10-I15) incidence	-1.8 (-10.6 to 9.7)
						190	IHD (ICD10 I20-I25) incidence	12.2 (-7.1 to 47.3)
						109	Cerebrovascular disease (ICD10 I60-I69) incidence	31.0 (-7.5 to 115.9)
						755	Other CVD (ICD10 I70-I83, I85-I99) incidence	-0.6 (-15.7 to 21.7)
						1406	CVD excluding CeVD and others (ICD10 I53-I59, I70-I83, I85-I99) incidence	-0.7 (-8.3 to 8.8)
Korean radiation workers prevalence study	Park *et al*[108]	0.0118 (0 to ≥0.3929)	Film badge ($H_p(10)$)	Smoking, BMI, diabetes, alcohol consumption, hyperlipidaemia, cataracts, hepatitis, diseases of thyroid, musculoskeletal and respiratory systems, occupation, regular exercise, night shift work	20,608 (NA)	1855	All CVD (ICD10 I00-I99) prevalence	0 (-2 to 2)[t]
Environmental studies								
Techa River study	Krestinina *et al* [74]	0.034 (0 to 0.995)	Muscle	Ethnic group, settlement status	60,205 (1,836,203)		All CVD (ICD9 390-459)	0.12 (-0.70 to 0.32)[u to g]
						14,830	All CVD (ICD9 390-459)	0.19 (-0.50 to 0.40)[u to c]
							All CVD (ICD9 390-459)	0.30 (0.08 to 0.52)[u to h]
							IHD (ICD9 410-414)	0.64 (0.29 to 1.01)[u to g]
						6163	IHD (ICD9 410-414)	0.79 (0.42 to 1.19)[u to c]
							IHD (ICD9 410-414)	0.92 (0.54 to 1.35)[u to h]
							Cerebrovascular disease (ICD9 430-438)	0.23 (-0.16 to 0.67)[u to g]
						4388	Cerebrovascular disease (ICD9 430-438)	0.30 (-0.09 to 0.76)[u to c]
							Cerebrovascular disease (ICD9 430-438)	0.34 (-0.07 to 0.82)[u to h]
Semipalatinsk nuclear test study	Grosche *et al* [68]	0.09 (0 to 0.63)	External whole body	Ethnic group, settlement status	19,545 (582,656)	1721	Heart disease (ICD9 410-429): all settlements	3.22 (2.33 to 4.10)[c]
						878	Heart disease (ICD9 410-429): exposed settlements	0.06 (-0.39 to 0.52)[c]
						839	Stroke (ICD9 430-438): all settlements	2.96 (1.77 to 4.14)[c]
						453	Stroke (ICD9 430-438): exposed settlements	-0.06 (-0.65 to 0.54)[c]
						2856	Cardiovascular disease (ICD9 390-459): all settlements	3.15 (2.48 to 3.81)[c]
						1498	Cardiovascular disease (ICD9 390-459): exposed settlements	0.02 (-0.32 to 0.37)[c]
Semipalatinsk nuclear test hypertension study	Markabayeva *et al* [24]	0.059 (0 to 1.0)	Effective dose	Smoking, BMI, total cholesterol, alcohol consumption	2000 (NA)	655	Essential hypertension prevalence (ICD10 I10)	3.528 (-3.188 to 10.245)[v]

Semipalatinsk nuclear test stroke study	Semenova *et al*[33]	0.059[w] (0 to >0.186)	Effective dose	Diabetes, obesity, hypertension, atrial fibrillation, chronic heart failure, recurrent stroke, urban-rural status, income	10970 (NA)	6830	Ischemic stroke prevalence	15.70 (2.11 to 29.30) [x]
						1281	Haemorrhagic stroke prevalence	17.44 (-11.50 to 46.38)[x]

CI, Confidence Interval; ICD, International Classification of Diseases; $H_p(10)$, personal dose equivalent at 10 mm depth; SES, socioeconomic status; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; CRP, C-reactive protein.

[a]Analysis using underlying or contributing cause of death.

[b]Analysis derived from Table 3 of Yamada *et al* [94] with smoking and drinking in the stratification.

[c]Assuming a lag period of 10 years.

[d]Estimate derived from log-linear model, evaluated at 1 Sv.

[e]90% CI

[f]Doses given here are from Azizova *et al* [59].

[g]Assuming a lag period of 5 years.

[h]Assuming a lag period of 15 years.

[i]estimate derived by fitting a linear model by (inverse-variance) weighted least squares, applied to the ERR provided in Table 3 of Moseeva *et al* [26]. Mean gamma liver doses of 0.05, 0.15, 0.35, 0.75, 1.25 and 2 Gy were assumed for the groups with the following specified ranges of dose: 0-0.10, 0.10-0.20, 0.20-0.50, 0.50-1.0, 1.0-1.5, >1.5 Gy. Mean gamma liver dose derived by weighting assumed doses for males (0.46 Gy) and females (0.37 Gy) by proportions in cohort (75%:25%).

[j]estimate derived multiplying median/mean length of follow-up by number of persons.

[k]based on person year weighted median dose by dose group from data in Table 1 of Hinksman *et al*[12].

[l]Assuming a lag period of 0 years.

[m]ERR estimates are derived by fitting a Poisson model by maximum likelihood with given numbers of deaths and using as offsets the Poisson assuming mean badge doses of 0.0000005, 0.0000025, 0.000275, 0.00275 and 0.026 Sv for the groups with the following specified ranges of badge dose: <0.000001, 0.000001-0.00005, 0.00005-0.0005, 0.0005-0.005 and 0.005-0.047 Sv.

[n]estimate derived by weighting mean dose for males and females by numbers of each sex in the cohort.

[o]Analysis based on fitting a linear model by (inverse-variance) weighted least squares to RBE=1 data in Table 7 of Boice *et al* [25] assuming mean doses of 2.5 mSv, 27.5 mSv and 75 mSv in <5, 5-49, 50+ mSv dose groups.

[p]Mean heart doses of 0.00125, 0.00375, 0.0075, 0.0175, and 0.035 Sv were assumed for the groups with the following specified ranges of heart dose: 0-0.0025, 0.0025-0.005, 0.005-0.010, 0.010-0.0250, >0.025 Gy, and weighted by the number of veterans in each group, using data from Table 6 of Boice *et al*[56].

[q]The number of test participants is estimated from the total number of test participants, assuming that ~23% have film badges. ERR estimates are derived by fitting a Poisson model by maximum likelihood with given numbers of deaths and using as offsets the expected number of deaths by endpoint, as given in Table S7A in Gillies & Haylock[32] assuming mean badge doses of 0.000005, 0.0005, 0.0003, 0.0075, 0.03 and 0.07 Sv for the groups with the following specified ranges of badge dose: <0.00001, 0.00001-0.00099, 0.001-0.00499, 0.005-0.00999, 0.01-0.0499 and >0.05 Sv.

[r]based on person-year total of Shafransky *et al* [117],

[s]estimate derived by dividing ln[odds ratio] (for >50 mSv vs <50 mSv) from Tatarenko *et al*[34] by difference in mean doses for the >50 mSv and <50 mSv groups (91, 31 mSv), and similarly for the CI.

[t]prevalence excess odds ratio per Gy.

[u]Analysis based on dose to muscle.

[v]estimate derived by fitting a linear model by (inverse-variance) weighted least squares, applied to the adjusted odds ratio (OR) provided in Table 2 of Markabayeva *et al* [24]. Median cardiac doses of 0.009, 0.041, 0.070, and 0.326 Sv were assumed for the respective groups with the following specified ranges of effective doses: <20, 20-59, 60-185, >185 mSv, as given by Markabayeva *et al* [24].

[w]derived from Markabayeva *et al* [24].

[x]estimate derived by fitting a linear model by (inverse-variance) weighted least squares, applied to the adjusted hazard ratio (HR) provided in Table 5 of Semenova *et al*[33]. Mean doses of 0.01, 0.04, 0.123, and 0.3 Sv were assumed for the respective groups with the following specified ranges of effective doses: <20, 20-59, 60-185, >186 mSv, as given by Semenova *et al*[33].

Table S3.6. Estimated excess relative risk of cardiovascular diseases in relation to alternative target organs in various therapeutically treated groups, exposed at moderate or high doses and high dose rates. All data are in relation to underlying cause of death, unless otherwise indicated.

Study	Reference	Average Organ Dose (Gy) mean/median (range)	Organ used	Variables (other than age, sex, year) available to assess possible confounding	Persons (person years of follow-up)	Deaths/ cases	Endpoint (mortality unless otherwise indicated, mean heart dose unless otherwise indicated)	Excess relative risk Gy^{-1} (95% CI)
EORTC 9-cohort Hodgkin lymphoma study	Maraldo *et al* [107]	23.3 (<2.2 to >32.5)	Heart	Anthracyclines, vinca alkaloids. country	6039 (~54,000[a])	1238	All cardiovascular event incidence	0.015 (0.006 to 0.024)
						639	Major cardiovascular event incidence	0.019 (0.009 to 0.028)
		17.3 (<2.4 to >20.9)	Left internal carotid			1238	All cardiovascular event incidence	0.007 (-0.009 to 0.023)
		17.7 (<2.3 to >21.7)	Right internal carotid			1238	All cardiovascular event incidence	-0.003 (-0.017 to 0.012)
Netherlands Hodgkin lymphoma heart failure case-control study	van Nimwegen *et al* [17]	20.1[b] (0 to >33)	Heart EQD2	Smoking, BMI, diabetes, hypertension, hyper-cholesterolaemia, physical activity, anthracyclines, splenectomy	NA	91 cases, 278 controls	Heart failure incidence CTCAE v3.0, v4.0 grades ≥2	0.038 (-0.001 to 0.146)[c]
		13.8[b] (0 to >30)	Left ventricle					0.069 (0.009 to 0.239)[c]
Nordic breast cancer case–control study	Darby *et al* [61]	4.9 (0.03 to 27.72)	Heart	Smoking, BMI, diabetes, hypertension, analgesic medication, thyroid medication, surgery, HRT, chemotherapy, ovarian ablation, history of IHD or COPD	NA	963 cases, 1205 controls	Ischemic heart disease incidence (ICD10 I20-I25)	0.074 (0.029 to 0.145)
		3.9 (0.1 to 30.4)	Heart EQD2					0.084 (0.036 to 0.159)
William Beaumont hospital breast cancer study	Zureick *et al*[96]	0.8 (<0.6 to >1.4)	Heart	Smoking, BMI, diabetes, hypertension, hyperlipidaemia, COPD, previous CVD or liver disease, paraplegia, hemiplegia,	375 (~1500[b])	23	Major cardiac events (MCE) (cardiogenic death, myocardial infarction, coronary revascularisation, unstable angina, development of heart failure)	0.68 (0.24 to 2.77)
						36	MCE + valvular disease requiring surgical intervention, dysrhythmias, pericarditis	0.86 (0.12 to 2.08)
		1.9 (<1.3 to >5.1)	LAD			23	Major cardiac events (MCE)	0.08 (0.01 to 0.17)

				dementia, chemotherapy, anti-HER2 immunotherapy, racial group		36	(cardiogenic death, myocardial infarction, coronary revascularisation, unstable angina, development of heart failure) MCE + valvular disease requiring surgical intervention, dysrhythmias, pericarditis	0.09 (0.02 to 0.17)
William Beaumont Hospital breast cancer study	Tagami *et al*[87]	1.48 (0.69 to 2.64) 3.0 (0.5 to 12.8)	Heart LAD	Smoking, BMI, diabetes, hypertension, hyperlipidaemia, chronic kidney disease, chemotherapy, statin use, aspirin use, beta blocker use, family history of premature CVD	94 (NA)	NA	Cardiovascular Computed Tomography grade ≥3 LAD stenosis	0.08 (0.00 to 0.17) 0.49 (0.03 to 1.17)
University of North Carolina non-small cell lung cancer study	Wang *et al*[27]	12.3 (<1.6 to >48.6) 4.0 (<3,9 to >9.5)	Heart Left ventricle	Smoking, diabetes, hypertension, chemotherapy, previous CAD	112 (~990[a])	26	Symptomatic cardiac event (shortness of breath, myocardial infarction, unstable angina, pericarditis, significant arrhythmia, heart failure) incidence	0.04 (0.013 to 0.067)[d] 0.02 (-0.002 to 0.042)[d]
University of North Carolina non-small cell lung cancer study	Wang *et al*[113]	12.3 (<12.3 to >24.5) 4.0 (<4.0 to >11.7) 24.7 (<24.7 to >49.4) 11.6 (<11.6 to >37.8)	Heart Left ventricle Left atrium Right atrium	Chemotherapy, baseline CAD	112 (~990[a])	9	Pericardial event incidence	0.04 (0.01 to 0.07) 0.01 (-0.02 to 0.05) 0.04 (0.02 to 0.07) 0.03 (0.01 to 0.06)
		12.3 (<12.3 to >24.5) 4.0 (<4.0 to >11.7) 24.7 (<24.7 to >49.4) 11.6 (<11.6 to >37.8)	Heart Left ventricle Left atrium Right atrium			7	Ischemic event incidence	0.04 (-0.004 to 0.08) 0.05 (0.01 to 0.09) 0.02 (-0.02 to 0.05) 0.00 (-0.03 to 0.03)
		12.3 (<12.3 to >24.5) 4.0 (<4.0 to >11.7) 24.7 (<24.7 to >49.4) 11.6 (<11.6 to >37.8)	Heart Left ventricle Left atrium Right atrium			12	Arrhythmic event incidence	0.02 (0.00 to 0.05) 0.00 (-0.03 to 0.04) 0.01 (-0.004 to 0.03) 0.02 (-0.001 to 0.03)
University of Michigan non-small cell lung cancer study	Xue *et al* [93]	13.9 (0.2 to 46.9)	Heart Pericardium	Smoking, hypertension, COPD, chemotherapy, previous CVD, KPS	94 (~450[b])	38	Pericardial effusion incidence	0.041 (0.004 to 0.079) 0.050 (0.009 to 0.093)

Singapore non-small cell lung cancer study	Lee *et al* [77]	12.55 (<4.75 to >19.48) 17.17 (<14.71 to >18.66)	Heart Lung	Smoking, diabetes, COPD, previous IHD, chemotherapy, use of PET-CT, brain imaging	120 (~180[a])	5	Acute myocardial infarction incidence (ICD9 410, ICD10 I21, I22)	0.03 (0.01 to 0.06) -0.02 (-0.11 to 0.08)
Medical College of Wisconsin lung cancer study	Borkenhagen *et al* [58]	NA (>0 to >26.22) NA (>0 to >26.22[e]) NA (>0 to >26.22)	Pericardium Atrium Ventricle	Smoking, diabetes, previous cardiac or vascular disease, chemotherapy, surgery	76 (~90[a])	16	Pericardial disease, arrhythmia, valvular disease	0.052 (0.010 to 0.097) 0.031 (0.004 to 0.059) 0.047 (0.010 to 0.085)
Shanghai non-small cell lung cancer study	Chen *et al* [102]	13.2 (7.8 to 18.5) 5.6 (2.4 to 8.9)	Heart Left ventricle	Smoking, diabetes, systolic blood pressure, cholesterol, chemotherapy, pre-existing CAD	112 (~280[a])	14	CTCAE v4.0 grade ≥3 cardiac incidence (among patients without previous radiotherapy with fields including heart, persistent pericardial effusions or atrial fibrillation)	0.779 (0.151 to 1.750) 0.957 (0.266 to 2.033)
New Jersey non-small cell lung cancer study	Yegya-Raman *et al* [111]	15.8[f] (<4.5 to >53.2)	Heart	Smoking, blood pressure, diabetes, chemotherapy, pre-treatment CAD	140 (~550[a])	47	First symptomatic cardiac event (myocardial infarction, unstable angina, significant arrhythmia, symptomatic pericardial effusion, pericarditis, congestive heart failure) incidence	0.059 (0.032 to 0.086)
		15.8[f] (<4.5 to >53.2) 3.3[f] (<1.7 to >10.1) 9.2[f] (<4.1 to >16.3) 3.6[f] (<1.7 to >16.3)	Heart Left ventricle Right ventricle LAD			20	Myocardial infarction, unstable angina, congestive heart failure	0.067 (0.031 to 0.105) 0.044 (0.017 to 0.071) 0.057 (0.026 to 0.090) 0.042 (0.018 to 0.066)
		15.8[f] (<4.5 to >53.2) 27.5[f] (<16.9 to >37.0) 14.7[f] (<5.7 to >29.2)	Heart Left atrium Right atrium			41	Myocardial infarction, unstable angina, congestive heart failure, supraventricular arrhythmic event	0.028 (-0.010 to 0.067) 0.015 (-0.013 to 0.044) 0.007 (-0.013 to 0.028)
Duke Cancer Institute head and neck cancer study	Dorth *et al* [62]	57 (<57 to >67) 50 (NA)	Carotid bulb +2 cm Carotid	Smoking, diabetes, hypertension, hyperlipidaemia, cardio/peripheral vascular disease, atrial fibrillation, chemotherapy	224 (810[a])	35	Carotid stenosis incidence	0.04 (-0.02 to 0.14) 0.02 (-0.03 to 0.10)
Peptic ulcer study	Little *et al* [78]	1.08 (0.0 to 6.20) 0.079 (0.0 to 0.46) 8.06 (0.0 to 46.1)	Heart Thyroid Kidney	Smoking, alcohol consumption, marital status	3600 (76,571.7)	1003	IHD (ICD9 410-414)	0.102 (0.039 to 0.174) 1.696 (0.651 to 2.907) 0.033 (0.012 to 0.056)

		6.69 (0.0 to 38.0)	Pancreas					0.020 (0.008 to 0.035)
		1.08 (0.0 to 6.20)	Heart			226	CeVD (ICD9 430-438)	0.028 (-0.085 to 0.186)
		0.079 (0.0 to 0.46)	Thyroid					0.422 (-1.455 to 3.039)
		0.013 (0.0 to 0.074)	Brain					2.649 (-8.912 to 18.740)
		1.08 (0.0 to 6.20)	Heart			240	All other CVD (ICD9 390-409, 415-429, 439-459)	0.050 (-0.053 to 0.194)
		1.08 (0.0 to 6.20)	Heart			1469	All CVD (ICD9 390-459)	0.082 (0.031 to 0.140)
Israeli tinea capitis prevalence study	Sadetzki *et al*[84]	0.0071 (0 to 0.074)	Breast	Smoking, BMI, diabetes, hypertension, SES	17,734 (NA)	1261	IHD	7 (1 to 14)[g]
		0.6266 (0 to 6)	Brain			1089	CeVD	0.20 (0.12 to 0.29)[g]
		0.3258 (0 to 2.8)	Salivary			321	Carotid artery stenosis	0.33 (0.04 to 0.71)[g]
		0.0376 (0 to 0.5)	Thyroid			321	Carotid artery stenosis	2 (0 to 5)[g]

CTCAE v, Common Terminology Criteria for Adverse Events version; CVD, cardiovascular disease; LAD, left anterior descending artery; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HER2, human epidermal growth factor receptor 2; KPS, Karnovsky performance score; CAD, coronary artery disease; NA, not available.

[a]estimate derived multiplying median/mean length of follow-up by number of persons.

[b]using mean dose to controls.

[c]estimate derived by fitting a linear binomial odds model to aggregate numbers of cases and controls, and assuming mean heart doses of 0, 16, 23, 28, 33 Gy for the 0, 1-20, 21-25, 26-30, ≥31 Gy mean heart dose groups, and 0, 13, 19, 23, 30 Gy for the 0, 1-15, 16-20, 21-25, ≥26 Gy mean left ventricle dose groups and given in Table 2 of van Nimwegen *et al* [17]: see Supplements S1 and S2.

[d]CI derived by using the 2-sided *p*-value and central estimate of hazard ratio adjusted for baseline coronary artery disease given in Table 4 of Wang *et al* [27].

[e]dose to ventricles.

[f]median dose.

[g]prevalence excess odds ratio per Gy.

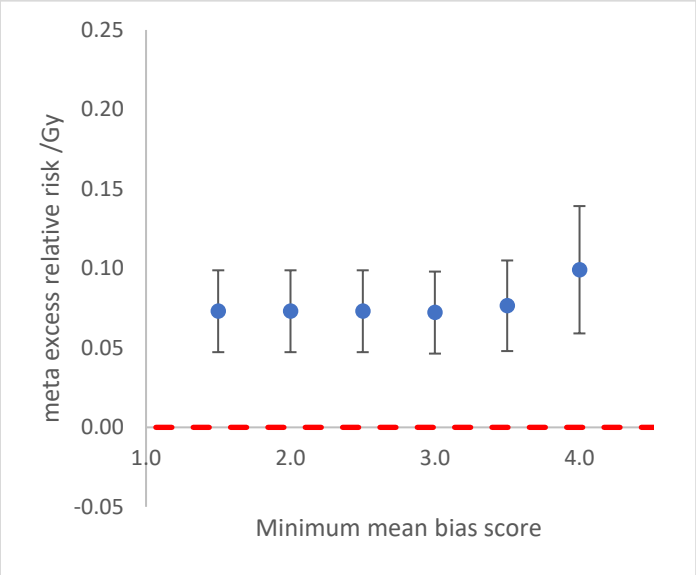
Table S3.7. Restricted maximum likelihood meta-analysis of mERR/Gy (+95% CI) with various datasets excluded from main meta-analysis or certain auxiliary data added

Endpoint	Full main analysis	Excluding Mayak morbidity data	Excluding Mayak mortality data	Excluding Canadian National Dose Register study[14]	Including Los Alamos[43] and Rochester thymus[44] data
	mERR / Gy (+95% CI)				
Ischemic heart disease	0.0730 (0.0473 to 0.0988)	0.0626 (0.0394 to 0.0857)	0.0741 (0.0468 to 0.1014)	0.0730 (0.0473 to 0.0988)	0.0684 (0.0422 to 0.0947)
Other heart disease[a]	0.0344 (0.0202 to 0.0486)	0.0344 (0.0202 to 0.0486)	0.0344 (0.0202 to 0.0486)	0.0344 (0.0202 to 0.0486)	0.0344 (0.0202 to 0.0486)
Cerebrovascular disease	0.1879 (0.0927 to 0.2831)	0.1612 (0.0724 to 0.2499)	0.1989 (0.0987 to 0.2992)	0.1879 (0.0927 to 0.2831)	0.1863 (0.0913 to 0.2812)
Other cardiovascular disease [b]	0.1720 (-0.0288 to 0.3729)	0.1583 (-0.1211 to 0.4377)	0.1785 (-0.0595 to 0.4165)	0.1720 (-0.0288 to 0.3729)	0.1720 (-0.0288 to 0.3729)
All cardiovascular disease (using maximal cardiovascular disease data per study)	0.1057 (0.0763 to 0.1352)	0.0879 (0.0624 to 0.1133)	0.1065 (0.0757 to 0.1372)	0.1047 (0.0759 to 0.1336)	0.1028 (0.0735 to 0.1322)

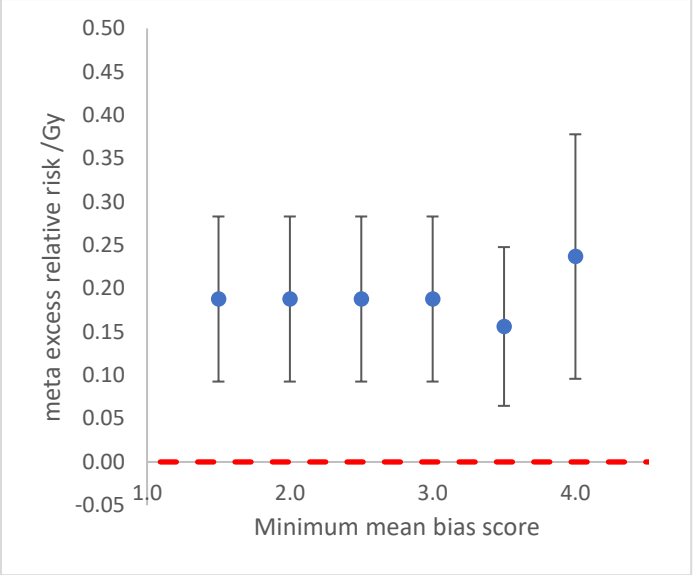
heart disease other than ischaemic heart disease.
[b]cardiovascular disease other than heart disease and cerebrovascular disease.

Fig. S3.1. Meta excess relative risk / Gy (+95% CI) in relation to the minimum mean bias score, by four major cardiovascular disease endpoints. All model fits are by restricted maximum likelihood. Dashed red line is mERR/Gy = 0.

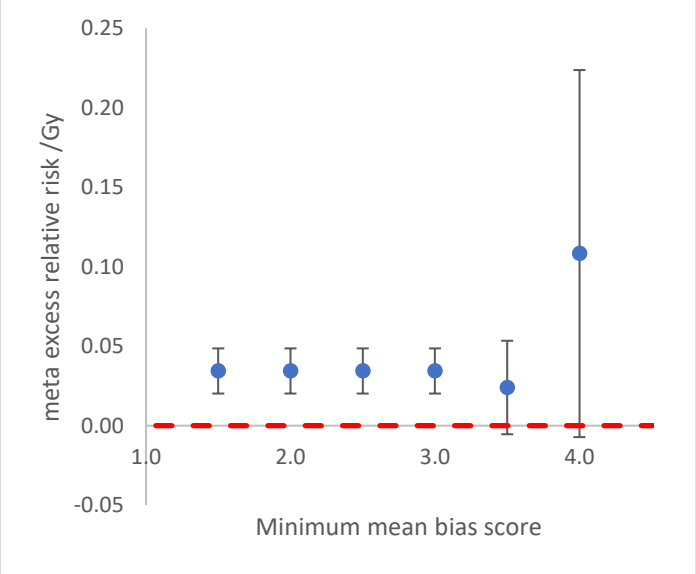
Ischaemic heart disease



Cerebrovascular disease



Heart disease other than ischaemic heart disease



Cardiovascular disease apart from heart or cerebrovascular

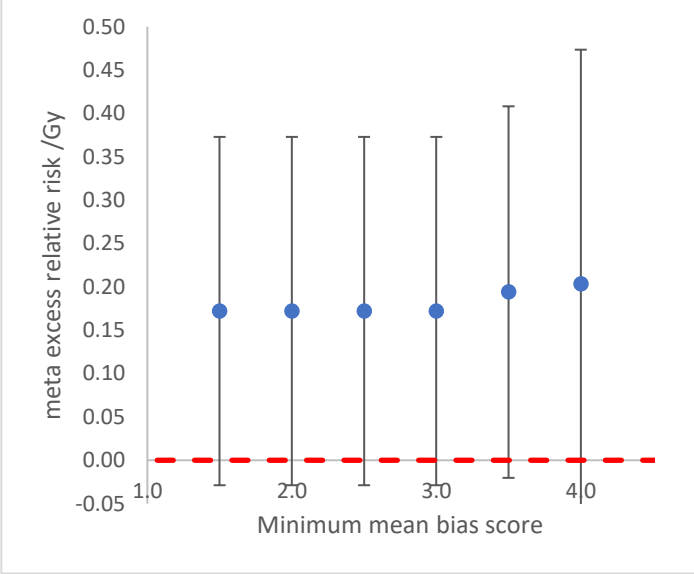
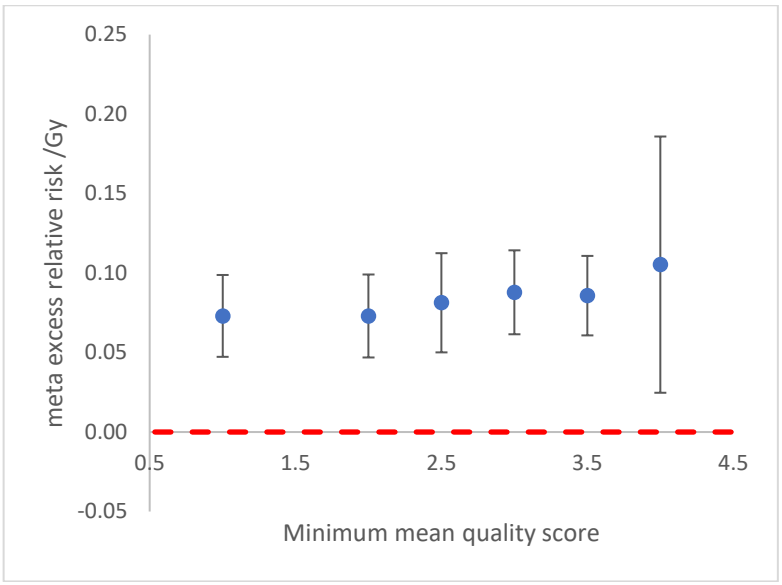
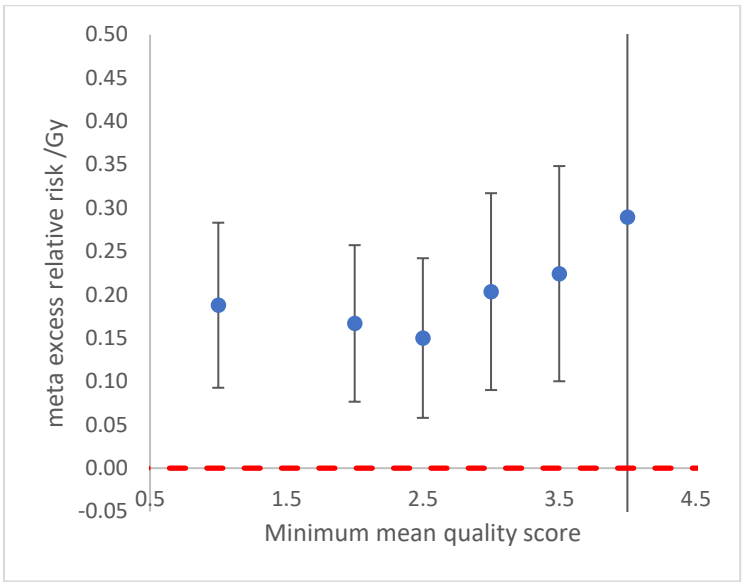


Fig. S3.2. Meta excess relative risk /Gy (+95% CI) in relation to the minimum mean quality score, by four major cardiovascular disease endpoints. All model fits are by restricted maximum likelihood. Dashed red line is mERR/Gy = 0.

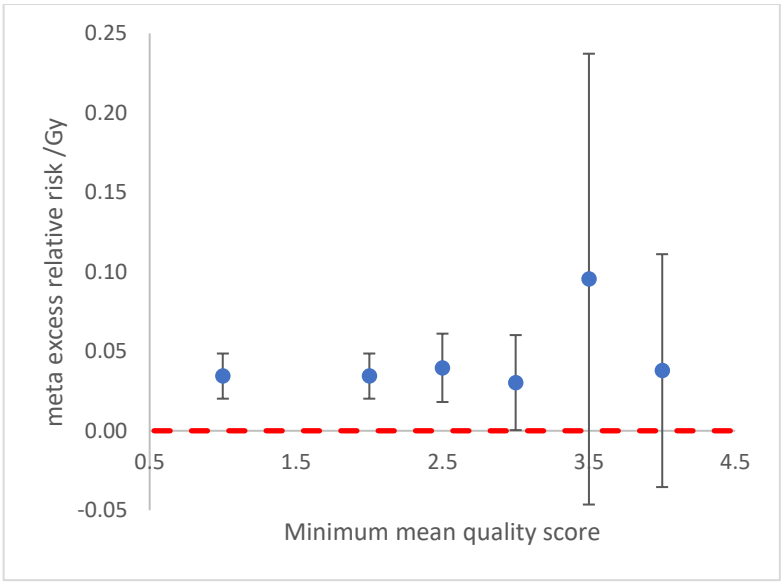
Ischaemic heart disease



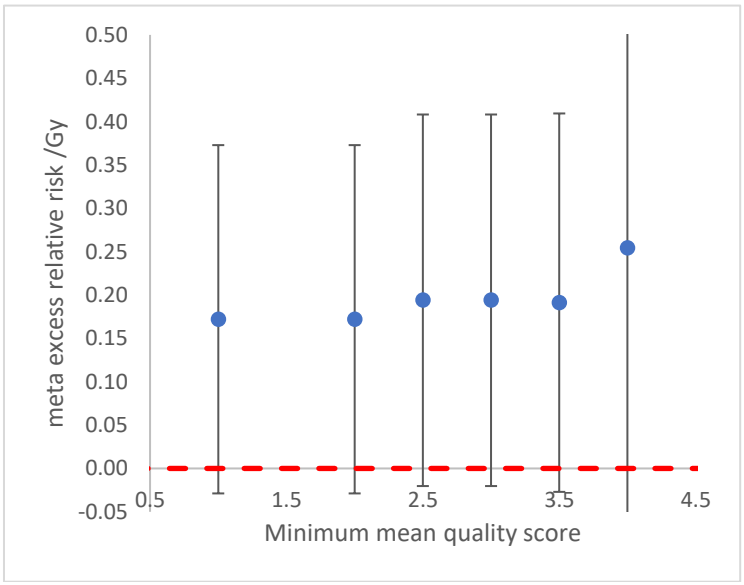
Cerebrovascular disease



Heart disease other than ischaemic heart disease



Cardiovascular disease apart from heart or cerebrovascular



Supplement S4. Supplementary discussion of study-specific risks.
Therapeutically exposed groups

Childhood cancer Survivors cohorts

Studies of childhood cancer survivor cohorts are summarised in Supplement S3 Table S3.4. Studies of Mueller *et al*, [19] Fullerton *et al*, [20] and Mulrooney *et al*, [21 23] analysing the Childhood Cancer Survivor Study (CCSS), a largely US-based cohort of persons treated for cancer in childhood, do not exhibit significant increasing trend with dose, nevertheless show significant excess risk, generally above 15 Gy. The heart and brain dosimetry in these studies, which relied on measurements in physical phantoms, was not fully individualised, in that treatment blocking data was not taken into account. [118] It was also reliant on self-reported information on CVD outcomes.

The French/French-UK studies of Tukenova *et al*[109], Haddy *et al*[69], Haddy *et al*[104], El-Fayech *et al*[63] and Mansouri *et al*[80] document significant excess mortality and incidence risks of cardiac and cerebrovascular endpoints in childhood cancer survivors, and do not have the weaknesses of the CCSS studies, [19-21 23] in that diagnostic information is obtained via national mortality registries (in France and UK). However, the incidence analyses of Haddy *et al*, [104] El-Fayech *et al*, [63] and Mansouri *et al*, [80] within the French/French-UK cohorts ascertained endpoint information via patient contact and medical record validation as in the CCSS. The radiotherapy organ dosimetry in all five French/French-UK studies[63 69 80 104 109] is also of somewhat higher quality, in that it is fully individualised. [119 120] The St Jude Lifetime cohort had the most complete adjustment for lifestyle/environmental/medical risk factors, with data on physical fitness (assayed in part via a treadmill test), smoking, drinking, dyslipidemia, diabetes, body mass index (BMI) and blood pressure. [22] The CCSS study of Mueller *et al*[19] adjusted for diabetes, hypertension, sex and race, the study of Fullerton *et al*[20] for diabetes, hypertension and smoking, that of Mulrooney *et al*[21] for diabetes, hypertension, smoking, dyslipidemia and BMI, although the study of Shrestha *et al*[23] only adjusted for smoking. A

weakness of all CCSS studies is that for an appreciable fraction (11% of the cohort) the cardiac event was reported but the participant did not report the age at which the event occurred. [19-21]

Hodgkin lymphoma cohorts

The three Dutch case-control studies, of Cutter *et al*, [16] van Nimwegen *et al*, [92] and van Nimwegen *et al*, [17] assessed incidence from valvular heart disease, IHD and heart failure, respectively, in a group of survivors of HL. In all three studies, in the European Organisation for Research and Treatment of Cancer (EORTC) 9-cohort HL study, [107] the Toronto HL study[42] and the French HL case-control study[81] there were modest but generally significantly increasing trends in various types of CVD with dose. Incidence in the Dutch studies was assessed via a postal questionnaire completed by the patients' general practitioner and/or cardiologist. As such there may be variation in ascertainment over time, also by whether a cardiologist or general practitioner responded to the questionnaire; as case-control matching was by year of HL diagnosis, at least the variation in ascertainment over time should not affect the derived risks. In the Dutch cohort there was borderline significant (p=0.03) upward curvature in the dose-response for valvular heart disease[16] and heart failure[17] but no significant curvature for IHD (p=0.356). [92]

Adult cancer survivor cohorts

The Nordic case-control study of Darby *et al*[61] assessed IHD incidence in a group of women treated for breast cancer, as did similar studies in the Netherlands, [71 83 112] Denmark, [79] and Germany[99]. Another Dutch case-control study assessed heart failure[54] and a Swedish study assessed a heterogeneous group of cardiac disease both for incidence and mortality. [106] A major strength of the Nordic study is that national incidence registries in Sweden and Denmark were used to assess incidence of IHD. Dosimetry reconstruction in all these studies was based on individual radiotherapy charts. Another strength of all four studies of IHD, also the study of Boekel *et al*[54] is the rich covariate lifestyle and medical information, in particular the standard

risk factors for CVD that are available and used for the analysis. However, the Swedish and German studies lacked any lifestyle/medical risk factor data. [99 106]

There were a number of small studies of CVD after radiotherapy for various other types of cancer[18 27-30 41 58 62 65 77 87 91 93 96-98 100 102 103 110 111 113 114] most of which demonstrated significant increases in various types of CVD with increasing dose (Supplement S3 Table S3.4).

Cohorts exposed for treatment of non-malignant disease

The US study of patients treated for peptic ulcer, who were given mostly a single treatment course of X-rays to the stomach, of Little *et al*[78] documented significant excess mortality risks for all CVD (ERR Gy^{-1} = 0.082, 95% CI 0.031 to 0.140), and IHD (ERR Gy^{-1} = 0.102; 95% CI 0.039 to 0.174), and indications of excess risk for stroke. There were no significant (p>0.2) differences between risks by endpoint, and few indications of curvature in dose response. [78]. Doses to several target tissues, specifically heart, thyroid, kidney, pancreas, and brain, were used to assess radiation effects. Using thyroid dose (a surrogate for carotid artery dose) for CeVD and heart dose for other CVD endpoints resulted in significant heterogeneity of risk (p=0.011) between endpoints, which was not the case when heart dose was used throughout (p=0.28). [78] Using brain or thyroid dose resulted in somewhat higher risks per unit dose for CeVD, risk being particularly high for brain dose (Supplement S3 Table S3.6). A study of Israel tinea capitis patients found large and significant excess risks of IHD in relation to breast dose (ERR Gy^{-1} = 7, 95% CI 1 to 14), and much more modest (but still significant) elevated risks of CeVD (ERR Gy^{-1} = 0.20, 95% CI 0.12 to 0.29) and carotid stenosis (a subset of CeVD) in relation to salivary gland dose (ERR Gy^{-1} = 0.33, 95% CI 0.04 to 0.71). [84] Arguably breast dose may not be as relevant as heart or coronary artery dose, which were not employed. A much larger risk for carotid stenosis was obtained using thyroid dose (ERR Gy^{-1} = 2, 95% CI 0 to 5) (see Supplement S3 Table S3.6). [84] A cohort of persons receiving X-rays in infancy in

Rochester for treatment of an enlarged thymus received a number of questionnaire based surveys, also linkage with the National Death Index, the conjunction used to determine incidence of CVD. [44] ERR were generally non-significant, whether adjusted or not for various lifestyle/medical risk factors (smoking, dyslipidaemia, diabetes, hypertension, family history of myocardial infarction) (see Supplement S3 Table S3.4). There were borderline significant indications of curvature in the dose response (p=0.11), which appeared to increase and then turn over at higher levels of dose.

Diagnostically exposed groups

The two major studies of CVD mortality in relation to medical diagnostic exposure are both of groups that received repeated fluoroscopic doses as part of the lung collapse treatment for tuberculosis (TB) in Canada[121] and in Massachusetts[122]. In the Massachusetts cohort there were additional analyses employing thyroid dose (a surrogate for carotid artery dose) and red bone marrow dose. A novel finding in the Canadian data, but only when a 10-year lag was employed, was a significant inverse dose fractionation effect for IHD, after adjustment for which the IHD dose-response was significant. [121] There were no indications of such effects in the Massachusetts data[122] or the pooled analysis, [1] on which we focus on henceforth. In both groups, lung dose was used as a surrogate for heart dose. Although there is no dose-response overall in the two datasets, if analysis is restricted to persons with <0.5 Gy the dose response trends for all CVD and IHD become much steeper, and statistically significant (Supplement S3 Table S3.4). In both cohorts there is limited medical and lifestyle information. This was more extensive in the Massachusetts data, and included smoking and alcohol consumption, thoracoplasty, and pneumolobectomy; some of these variables were included in baseline models for certain disease endpoints. [122] Carotid dose would be a preferable dose metric to use for CeVD, but this was only available for the Massachusetts cohort. However, analysis in the

Massachusetts cohort in which stroke was analysed in relation to dose to either the lung or the thyroid suggested no more than a factor of 2 difference. [122]

Moderate/low-dose exposed groups

Japanese Atomic Bomb Survivors

Excess radiation-associated mortality from heart disease and stroke has been observed in the LSS cohort (Supplement S3 Table S3.5). [86 88] In the latest follow-up of the Adult Health Study (AHS), a subset of the LSS subject to biennial clinical examinations, Yamada *et al*[94] observed generally non-significant, radiation-associated excess risks of hypertension and myocardial infarction incidence, although among those exposed in early childhood there was significantly increased incidence of non-fatal stroke or myocardial infarction, [90] as also of hypertension in early life (age 9-19 y) after exposure *in utero*[82] (Supplement S3 Table S3.5). A puzzling feature of the mortality data is that the ERR/Gy is much higher among those with cancer or diabetes as a contributing (non-underlying) cause of death; [123] this may suggest an interaction with conditions such as obesity, which are risk factors for both.

Some aspects of the Japanese atomic bomb survivor data imply that risks may not necessarily apply to other exposed populations. Survivors suffered from burns, epilation, and other acute injuries caused by the radiation, heat, and blast of the bombs, respectively, lived in a war-torn country (subject to malnutrition, deprivation, infectious diseases and other conditions), and these injuries, in addition to radiation, may have contributed to the development of non-cancer diseases in later life. In addition to the direct effect of the injuries, these and other trauma might introduce selection bias. Although selection bias cannot be entirely discounted, the general consistency of risks in the Japanese and other groups suggests that it does not have a major impact (Supplement S3 Tables S3.4, S3.5). [4] One notable feature of the dose response for CVD mortality is the indication of downward curvature, although this is not statistically significant. [115]

There is rich lifestyle information available in the LSS, including smoking, alcohol consumption, education, occupation for household, obesity and diabetes, ascertained via a mail survey in 1978, partway through the follow-up [86]. Adjustment for these risk factors made little difference (<15%) to ERR for the main disease endpoints (heart disease, stroke). [86]

Occupationally Exposed Groups

15-country Study of Radiation Workers, International Nuclear Workers Study (INWORKS), and Subcohorts

The 15-country study conducted by the International Agency for Research on Cancer (IARC) of radiation workers found increasing dose-related trends for mortality from all CVD, CeVD, and other types of CVD and negative trends for IHD, heart failure, deep vein thrombosis, and pulmonary embolism[13] (Supplement S3 Table S3.5), although none of these trends was significant (1-sided $p \geq 0.20$). The findings for cancer in this cohort have been controversial, with indications of missing dosimetric data. [124] A more recent study, the International Nuclear Workers Study (INWORKS), comprises substantially extended follow-up of the three largest national groups of workers in France, UK and US. [8] This study has demonstrated significant risks of CVD, IHD, acute myocardial infarction and CeVD in relation to external gamma and neutron dose. [8] Internal dose is not taken into account; indeed for many workers only the fact of monitoring for such internal exposures is known. [8] There is some evidence of downward curvature in the dose response for CeVD ($p=0.017$), but not for any other endpoint. [8]

Analysis of heart disease and CeVD in the UK National Registry for Radiation Workers (NRRW), part of the INWORKS and IARC 15-Country cohorts, has been recently reported. [2] [12] Follow-up extends to 2011, 10 years past the end of follow-up of this cohort in INWORKS. Zhang *et al*[2] report significant excess risk for all heart disease (ERR Gy^{-1} = 0.37, 95% CI 0.11, 0.65), also for IHD and myocardial infarction, with some evidence of downward curvature for IHD ($p=0.048$), although not for other types of heart disease. Hinksman *et al*[12] reported

borderline significant excess risk of CeVD (ERR Gy^{-1} = 0.57, 95% CI 0.00 to 1.31) with again significant (p=0.016) downward curvature in the dose response. Wakeford[125] and Little *et al*[3] discuss the issue of inter-country and inter-facility heterogeneity within INWORKS for all CVD, but not IHD and CeVD separately, which suggests that the heterogeniety for CVD may be explained by differences between IHD and CeVD risks and the differing numbers of these endpoints in the various subcohorts.

A problem with the INWORKS[8] and NRRW[2 12] analyses reported here is that there is only limited account taken of lifestyle/medical risk factors, via the standard industrial/non-industrial (blue collar/white collar) coding. A case-control study within the industrial workers at two UK nuclear plants (Sellafield, Springfield) that had information on numerous lifestyle and environmental risk factors including shift work, BMI, smoking status, diastolic and systolic blood pressure did not suggest that adjusting for any of these made appreciable difference to IHD risk. [126] A case-control study within the French nuclear fuel cycle workers found almost no effect on trend estimates after adjustments for BMI, blood pressure, smoking, total cholesterol or glycaemic level. [59] A small study of French tritium workers did not find significant excess risks of CVD when adjusted for smoking and standard demographic risk factors. [31]

Russian Mayak nuclear worker cohort

In the last few years, there have been several analyses of the cohort of workers at the nuclear reactors and radiochemical and plutonium production plant at the Mayak Production Association, the first nuclear materials production complex in Russia. [5-7 9-11 52 127-129] As noted in the Supplementary Methods, in this systematic review among the most recent studies of IHD and CeVD at the time of literature search are used, in particular the studies of Azizova *et al*[5] and Azizova *et al,* [9] a study of lower extremity arterial disease, [52] and the Mayak part of a pooled analysis (with the Sellafield workers) [7] which are cited in Supplement S3 Table S3.5. The results of the most recent studies of Azizova *et al*[10 11] use external gamma dose to the liver,

which may not be the most relevant target tissue, particularly for CeVD. The difference made may be judged by the fact that in slightly earlier CeVD incidence analysis using external gamma dose[9] the ERR Gy^{-1} (for a 10 y lag) is 0.49 (95% CI 0.39 to 0.60), compared with an ERR Gy^{-1} in the later analysis (using the same lag) of 0.39 (95% CI 0.31 to 0.48). For these and other reasons outlined in the Supplementary Methods we do not employ these most current results in the meta-analysis, although they are given in Supplement S3 Table S3.5. A significant trend with dose was seen for IHD and CeVD incidence in the Mayak workers, although the trend of IHD and CeVD mortality is much lower than for incidence, and generally non-significant (Supplement S3 Table S3.5). [5 7 9 10] Wakeford[125] discusses the findings of the recent mortality study of Azizova *et al*, [10] noting in particular the fact that CeVD ERR are low both for persons who continued to live in Ozyorsk and those who emigrated, and apparent inconsistency of the CeVD mortality risk among Ozyorsk residents with CeVD incidence risk in the analysis of Azizova *et al*. [11] This has also been addressed in some detail in a recent review of Little *et al*. [3], who noted the general consistency of mortality and incidence risks for IHD among those who remain resident in Ozyorsk. [5] This suggests particular issues with definition of CeVD in this study, which may be quite different for incidence and mortality. The study is unusual in that doses to certain internal organs, especially the lung and liver, were dominated by doses from internally deposited radionuclides; in particular, the α-particle-emitting plutonium. Doses in this study are among the highest for the occupationally-exposed groups considered here, and arguably more comparable with at least the medical-diagnostic or even the radiotherapy-exposed groups considered above: average whole body doses for external γ rays were 0.5 to 0.6 Gy (Supplement S3 Table S3.5), although all at <5 mGy/hour, and therefore low dose-rate exposures. [45] Hypertension in the Mayak worker cohort is associated with external γ dose to the liver, although there is no trend with internal α-particle dose. [53]

Nonetheless, interpreting the results of the Mayak cohort is complicated by the large and highly heterogeneous internal α-particle dose from plutonium. The dose response for IHD and CeVD was significant, both in relation to the external γ dose and the internal (α-particle) dose to the liver. [5 9]

There is rich lifestyle and environmental risk factor information available in the Mayak worker data, including blood pressure, smoking, diabetes mellitus and BMI (Supplement S3 Table S3.5). Adjustment for these made little difference to trend risk estimates, although for some analyses the unadjusted analyses were not reported, and not all these variables were used for all analyses.

Chernobyl worker cohorts

Radiation-associated excess IHD and CeVD incidence was observed in a group of Russian Chernobyl recovery workers, [72 85 105] as also in a much smaller group of Ukrainian liquidators[34 73] (Supplement S3 Table S3.5). CVD mortality in this cohort has also been recently studied. [101] A remarkable feature of the Russian cohort is the relatively high rates of CVD, including for example 23,264 cases of CeVD in a cohort of 53,772 people, [72], contrasting with 15,025 deaths in a cohort of 91,013, [101] reflecting the substantially elevated CVD incidence (but not mortality) rates in the Russian population relative to those in other developed countries. [130] Both cohort studies were performed using personal data from the National Radiation and Epidemiological Registry (NRER) which provides a unified federal diagnostic system for Chernobyl recovery workers. [131] As shown by Supplement S3 Table S3.5, there are several lifestyle/medical factors that markedly modify radiation risk, most notably diagnosed diabetes; Chernobyl recovery workers with diagnosed diabetes had a 3.7 times higher risk than the ones without this diagnosis (Supplement S3 Table S3.5). There remain concerns about many design aspects of the Russian study, including cohort selection, diagnosis confirmation and source of dose information. There is also a complete lack of any lifestyle or environmental risk factor data.

Other radiation worker studies

There are several other groups of workers, in particular a large study of US nuclear power workers, [55] a large study of US medical workers, [57] a study of workers at Los Alamos, [43] various groups of uranium miners and uranium processing workers, [39 40 51 59 66 75 76 95] in which internal doses were probably mainly to the lung, a US plant in which workers were exposed to ^{210}Po, ^{3}H and various plutonium isotopes, [25] and two studies of nuclear test veterans, [32 56] in all of which there were generally no statistically significant trends of CVD with external gamma dose (Supplement S3 Table S3.5). A recent review of occupational studies revealed no clear and consistent relationship between uranium work and CVD. [132]

A notable feature of all the analyses of the various Million Person Study (MPS) cohorts, a number of which are included here [43 55-57 66] is the general absence of strong positive trends not only for all CVD endpoints but also for well-established radiogenic malignancies such as leukaemia excluding chronic lymphocytic leukaemia, lung, female breast, stomach, colorectal, brain/CNS and all solid cancers; only for lung cancer in the medical workers, [57] for leukaemia in the US nuclear power workers, [55] for oesophageal cancer in the Los Alamos cohort, [43] and for IHD in the Mallinckrodt workers[66] are there indications (albeit borderline-significant in all cases) of positive trends, and for brain cancer in the test veterans study[56] there is a significant negative trend with dose. Some of these cohorts are of considerable size, with appreciable mean and maximum doses (see Supplement S3 Table S3.5).

Environmentally Exposed Groups

A study of a cohort of environmentally exposed individuals in the Southern Ural Mountains reported a statistically significant, or borderline significant, increase (depending on the latent period used) of both all CVD mortality and IHD mortality[133] (Supplement S3 Table S3.5).

Grosche *et al*[68] studied CVD mortality in a Kazakhstan group exposed to fallout from nuclear weapons tests at the Semipalatinsk site (Supplement S3 Table S3.5). No statistically

significant excess risk for all CVD, heart disease and stroke was found. A more recent study has assessed essential hypertension in a small subset of this population and found weak indications (with large uncertainties) of excess risk[24] (Supplement S3 Table S3.5). This study unlike the earlier one has rich lifestyle risk factor data, including smoking, alcohol consumption, cholesterol and BMI. Adjusting for these made little difference to hypertension risk. [24] The dosimetry in this cohort is problematic because it is based on assessments of residence, estimates of time spent outdoors, and diet, all of which were collected by interviews more than 30 years after the bomb tests. As such, the results of these studies may be less informative than others considered here. Another prevalence study of persons exposed near Semipalatinsk yielded very large excess risks of ischaemic CeVD. [33] The design of the study, with a single cross sectional assay, makes these results quite difficult to interpret. There are very few details given on the dosimetry.

References

1. Tran V, Zablotska LB, Brenner AV, et al. Radiation-associated circulatory disease mortality in a pooled analysis of 77,275 patients from the Massachusetts and Canadian tuberculosis fluoroscopy cohorts. *Sci Rep* 2017;7:44147. doi: 10.1038/srep44147
2. Zhang W, Haylock RGE, Gillies M, et al. Mortality from heart diseases following occupational radiation exposure: analysis of the National Registry for Radiation Workers (NRRW) in the United Kingdom. *J Radiol Prot* 2019;39(2):327-53. doi: 10.1088/1361-6498/ab02b2 [published Online First: 2019/03/13]
3. Little MP, Azizova TV, Hamada N. Low- and moderate-dose non-cancer effects of ionizing radiation in directly exposed individuals, especially circulatory and ocular diseases: a review of the epidemiology. *Int J Radiat Biol* 2021;97(6):782-803. doi: 10.1080/09553002.2021.1876955 [published Online First: 2021/01/21]
4. Little MP, Azizova TV, Bazyka D, et al. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. *Environ Health Perspect* 2012;120(11):1503-11. doi: 10.1289/ehp.1204982 [doi]
5. Azizova TV, Grigoryeva ES, Haylock RGE, et al. Ischaemic heart disease incidence and mortality in an extended cohort of Mayak workers first employed in 1948-1982. *Br J Radiol* 2015;88(1054):20150169. doi: 10.1259/bjr.20150169
6. Azizova TV, Grigorieva ES, Hunter N, et al. Risk of mortality from circulatory diseases in Mayak workers cohort following occupational radiation exposure. *J Radiol Prot* 2015;35(3):517-38. doi: 10.1088/0952-4746/35/3/517
7. Azizova TV, Batistatou E, Grigorieva ES, et al. An Assessment of Radiation-Associated Risks of Mortality from Circulatory Disease in the Cohorts of Mayak and Sellafield Nuclear Workers. *Radiat Res* 2018;189(4):371-88. doi: 10.1667/RR14468.1
8. Gillies M, Richardson DB, Cardis E, et al. Mortality from Circulatory Diseases and other Non-Cancer Outcomes among Nuclear Workers in France, the United Kingdom and the United States (INWORKS). *Radiat Res* 2017;188(3):276-90. doi: 10.1667/RR14608.1
9. Azizova TV, Haylock RGE, Moseeva MB, et al. Cerebrovascular diseases incidence and mortality in an extended Mayak Worker Cohort 1948-1982. *Radiat Res* 2014;182(5):529-44. doi: 10.1667/RR13680.1
10. Azizova TV, Bannikova MV, Grigoryeva ES, et al. Mortality from various diseases of the circulatory system in the Russian Mayak nuclear worker cohort: 1948-2018. *J Radiol Prot* 2022;42(2) doi: 10.1088/1361-6498/ac4ae3 [published Online First: 20220309]
11. Azizova TV, Moseeva MB, Grigoryeva ES, et al. Incidence risks for cerebrovascular diseases and types of stroke in a cohort of Mayak PA workers. *Radiat Environ Biophys* 2022;61(1):5-16. doi: 10.1007/s00411-022-00966-6 [published Online First: 20220219]
12. Hinksman CA, Haylock RGE, Gillies M. Cerebrovascular Disease Mortality after occupational Radiation Exposure among the UK National Registry for Radiation Workers Cohort. *Radiat Res* 2022;197(5):459-70. doi: 10.1667/RADE-20-00204.1 [published Online First: 2022/02/10]
13. Vrijheid M, Cardis E, Ashmore P, et al. Mortality from diseases other than cancer following low doses of ionizing radiation: results from the 15-Country Study of nuclear industry workers. *Int J Epidemiol* 2007;36(5):1126-35. doi: dym138 [pii];10.1093/ije/dym138 [doi]
14. Zielinski JM, Ashmore PJ, Band PR, et al. Low dose ionizing radiation exposure and cardiovascular disease mortality: cohort study based on Canadian national dose registry of radiation workers. *Int J Occup Med Environ Health* 2009;22(1):27-33. doi: 316K63836525U89Q [pii];10.2478/v10001-009-0001-z [doi]
15. Gilbert ES. Invited commentary: studies of workers exposed to low doses of radiation. *Am J Epidemiol* 2001;153(4):319-22.
16. Cutter DJ, Schaapveld M, Darby SC, et al. Risk of valvular heart disease after treatment for Hodgkin lymphoma. *J Natl Cancer Inst* 2015;107(4):djv008. doi: 10.1093/jnci/djv008
17. van Nimwegen FA, Ntentas G, Darby SC, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. *Blood* 2017;129(16):2257-65. doi: 10.1182/blood-2016-09-740332 [published Online First: 2017/02/02]
18. Liao J, Liu T, Zhang H, et al. The role of postoperative radiation therapy for completely resected stage III thymoma and effect of higher heart radiation dose on risk of cardiovascular disease: A retrospective cohort study. *Int J Surg* 2018;53:345-49. doi: 10.1016/j.ijsu.2018.04.018 [published Online First: 2018/04/21]
19. Mueller S, Fullerton HJ, Stratton K, et al. Radiation, atherosclerotic risk factors, and stroke risk in survivors of pediatric cancer: a report from the Childhood Cancer Survivor Study. *Int J Radiat Oncol Biol Phys* 2013;86(4):649-55. doi: 10.1016/j.ijrobp.2013.03.034
20. Fullerton HJ, Stratton K, Mueller S, et al. Recurrent stroke in childhood cancer survivors. *Neurology* 2015;85(12):1056-64. doi: 10.1212/WNL.0000000000001951 [published Online First: 2015/08/28]

21. Mulrooney DA, Hyun G, Ness KK, et al. Major cardiac events for adult survivors of childhood cancer diagnosed between 1970 and 1999: report from the Childhood Cancer Survivor Study cohort. *BMJ* 2020;368:l6794. doi: 10.1136/bmj.l6794 [published Online First: 2020/01/17]
22. Mulrooney DA, Armstrong GT, Huang S, et al. Cardiac Outcomes in Adult Survivors of Childhood Cancer Exposed to Cardiotoxic Therapy: A Cross-sectional Study. *Ann Intern Med* 2016;164(2):93-101. doi: 10.7326/M15-0424 [published Online First: 2016/01/10]
23. Shrestha S, Bates JE, Liu Q, et al. Radiation therapy related cardiac disease risk in childhood cancer survivors: Updated dosimetry analysis from the Childhood Cancer Survivor Study. *Radiother Oncol* 2021;163:199-208. doi: https://doi.org/10.1016/j.radonc.2021.08.012
24. Markabayeva A, Bauer S, Pivina L, et al. Increased prevalence of essential hypertension in areas previously exposed to fallout due to nuclear weapons testing at the Semipalatinsk Test Site, Kazakhstan. *Environ Res* 2018;167:129-35. doi: 10.1016/j.envres.2018.07.016 [published Online First: 2018/07/18]
25. Boice JD, Jr., Cohen SS, Mumma MT, et al. Mortality among mound workers exposed to polonium-210 and other sources of radiation, 1944-1979. *Radiat Res* 2014;181(2):208-28. doi: 10.1667/RR13395.1
26. Moseeva MB, Azizova TV, Grigoryeva ES, et al. Analysis of incidence risk of different types of stroke among the Mayak worker cohort. *Biology Bull* 2020;47(11):1516-23. doi: 10.1134/S1062359020110102
27. Wang K, Eblan MJ, Deal AM, et al. Cardiac Toxicity After Radiotherapy for Stage III Non-Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy. *J Clin Oncol* 2017;35(13):1387-94. doi: 10.1200/JCO.2016.70.0229 [published Online First: 2017/01/24]
28. Cho S-G, Kim Y-H, Park H, et al. Prediction of cardiac events following concurrent chemoradiation therapy for non-small-cell lung cancer using FDG PET. *Annals Nucl Med* 2022;36(5):439-49. doi: 10.1007/s12149-022-01724-w
29. Kim K, Chung SY, Oh C, et al. Automated coronary artery calcium scoring in patients with breast cancer to assess the risk of heart disease following adjuvant radiation therapy. *The Breast* 2022;65:77-83. doi: https://doi.org/10.1016/j.breast.2022.07.003
30. Ni L, Koshy M, Connell P, et al. Heart V5 predicts cardiac events in unresectable lung cancer patients undergoing chemoradiation. *J Thorac Dis* 2019;11(6):2229-39. doi: 10.21037/jtd.2019.06.29 [published Online First: 2019/08/03]
31. Martin S, Segala C. Epidemiological Study of Mortality Among Workers Exposed to Tritium in France. *Radiat Res* 2021;195(3):284-92. doi: 10.1667/RR15353.1
32. Gillies M, Haylock RGE. Mortality and cancer incidence 1952-2017 in United Kingdom participants in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes. *J Radiol Prot* 2022;42(2):021507. doi: 10.1088/1361-6498/ac52b4 [published Online First: 20220223]
33. Semenova Y, Rakhimova I, Nurpeissov T, et al. Epidemiology of stroke and transient ischemic attacks in the population of the territories adjacent to the former Semipalatinsk Nuclear Test Site, Kazakhstan. *Radiat Environ Biophys* 2022;61(1):17-28. doi: 10.1007/s00411-021-00955-1
34. Tatarenko O. Expert evaluation of cases of myocardial infarction in the Chernobyl clean-up workers with hypertension. *Kardiologija v Belarusi* 2018;10(4):470-76.
35. Karpov AB, Semenova YV, Takhauov RM, et al. The risk of acute myocardial infarction and arterial hypertension in a cohort of male employees of a Siberian group of chemical enterprises exposed to long-term irradiation. *Health Phys* 2012;103:15-23.
36. Karpov AB, Semyonova YV, Dubln VV, et al. The risk of arterial hypertension development in Siberian group of chemical enterprises personnel. *Radiats Biol Radioecol* 2008;48(4):456-63. [published Online First: 2008]
37. Torquati L, Mielke GI, Brown WJ, et al. Shift work and the risk of cardiovascular disease. A systematic review and meta-analysis including dose–response relationship. *Scand J Work Environ Health* 2018(3):229-38. doi: 10.5271/sjweh.3700
38. Burns DM. Epidemiology of smoking-induced cardiovascular disease. *Prog Cardiovasc Dis* 2003;46(1):11-29. doi: 10.1016/S0033-0620(03)00079-3
39. Drubay D, Caer-Lorho S, Laroche P, et al. Mortality from Circulatory System Diseases among French Uranium Miners: A Nested Case-Control Study. *Radiat Res* 2015;183(5):550-62. doi: 10.1667/RR13834.1 [published Online First: 2015/03/26]
40. Rage E, Caer-Lorho S, Drubay D, et al. Mortality analyses in the updated French cohort of uranium miners (1946-2007). *Int Arch Occup Environ Health* 2015;88(6):717-30. doi: 10.1007/s00420-014-0998-6 [published Online First: 2014/11/21]
41. Chung SY, Oh J, Chang JS, et al. Risk of Cardiac Disease in Patients With Breast Cancer: Impact of Patient-Specific Factors and Individual Heart Dose From Three-Dimensional Radiation Therapy Planning. *Int J Radiat Oncol Biol Phys* 2021;110(2):473-81. doi: https://doi.org/10.1016/j.ijrobp.2020.12.053
42. Hahn E, Jiang H, Ng A, et al. Late Cardiac Toxicity After Mediastinal Radiation Therapy for Hodgkin

Lymphoma: Contributions of Coronary Artery and Whole Heart Dose-Volume Variables to Risk Prediction. *Int J Radiat Oncol Biol Phys* 2017;98(5):1116-23. doi: 10.1016/j.ijrobp.2017.03.026 [published Online First: 2017/07/20]
43. Boice JD, Jr., Cohen SS, Mumma MT, et al. Mortality among workers at the Los Alamos National Laboratory, 1943-2017. *Int J Radiat Biol* 2022;98(4):722-49. doi: 10.1080/09553002.2021.1917784 [published Online First: 2021/05/29]
44. Adams MJ, Fisher SG, Lipshultz SE, et al. Risk of Coronary Events 55 Years after Thymic Irradiation in the Hempelmann Cohort. *Cardio-Oncology* 2018;4 doi: 10.1186/s40959-018-0027-0 [published Online First: 20180217]
45. Wakeford R, Tawn EJ. The meaning of low dose and low dose-rate. *J Radiol Prot* 2010;30(1):1-3. doi: 10.1088/0952-4746/30/1/E02 [doi]
46. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919. doi: 10.1136/bmj.i4919 [published Online First: 2016/10/14]
47. Prentice RL, Pyke R. Logistic disease incidence models and case-control studies. *Biometrika* 1979;66(3):403-11.
48. McCullagh P, Nelder JA. Generalized linear models. 2nd edition. Boca Raton, FL: Chapman and Hall/CRC 1989:1-526.
49. Epicure version 2.0.1.0. 55 Metcalfe, K1P 6L5, Canada: Risk Sciences International, 2015.
50. Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ* 1980 32:1-350.
51. Anderson JL, Bertke SJ, Yiin J, et al. Ischaemic heart and cerebrovascular disease mortality in uranium enrichment workers. *Occup Environ Med* 2021;78(2):105-11. doi: 10.1136/oemed-2020-106423
52. Azizova TV, Bannikova MV, Grigorieva ES, et al. Risk of lower extremity arterial disease in a cohort of workers occupationally exposed to ionizing radiation over a prolonged period. *Radiat Environ Biophys* 2016;55(2):147-59. doi: 10.1007/s00411-016-0645-6
53. Azizova T, Briks K, Bannikova M, et al. Hypertension Incidence Risk in a Cohort of Russian Workers Exposed to Radiation at the Mayak Production Association Over Prolonged Periods. *Hypertension* 2019;73(6):1174-84. doi: doi:10.1161/HYPERTENSIONAHA.118.11719
54. Boekel NB, Duane FK, Jacobse JN, et al. Heart failure after treatment for breast cancer. *Eur J Heart Failure* 2020;22(2):366-74. doi: 10.1002/ejhf.1620 [published Online First: 2019/11/14]
55. Boice JD, Jr., Cohen SS, Mumma MT, et al. Mortality from leukemia, cancer and heart disease among U.S. nuclear power plant workers, 1957-2011. *Int J Radiat Biol* 2022;98(4):657-78. doi: 10.1080/09553002.2021.1967507 [published Online First: 2021/10/21]
56. Boice JD, Cohen SS, Mumma MT, et al. Mortality among U.S. military participants at eight aboveground nuclear weapons test series. *Int J Radiat Biol* 2022;98(4):679-700. doi: 10.1080/09553002.2020.1787543 [published Online First: 2020/07/01]
57. Boice JD, Jr., Cohen SS, Mumma MT, et al. Mortality among medical radiation workers in the United States, 1965-2016. *Int J Radiat Biol* 2023;99(2):183-207. doi: 10.1080/09553002.2021.1967508 [published Online First: 20220516]
58. Borkenhagen JF, Bergom C, Rapp CT, et al. Dosimetric Predictors of Cardiotoxicity in Thoracic Radiotherapy for Lung Cancer. *Clin Lung Cancer* 2019;20(6):435-41. doi: 10.1016/j.cllc.2019.05.014 [published Online First: 2019/07/16]
59. Bouet S, Davesne E, Samson E, et al. Analysis of the association between ionizing radiation and mortality in uranium workers from five plants involved in the nuclear fuel production cycle in France. *Int Arch Occup Environ Health* 2019;92(2):249-62. doi: 10.1007/s00420-018-1375-7 [published Online First: 2018/11/06]
60. Cha ES, Zablotska LB, Bang YJ, et al. Occupational radiation exposure and morbidity of circulatory disease among diagnostic medical radiation workers in South Korea. *Occup Environ Med* 2020;77(11):752-60. doi: 10.1136/oemed-2019-106326
61. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368(11):987-98. doi: 10.1056/NEJMoa1209825 [doi]
62. Dorth JA, Patel PR, Broadwater G, et al. Incidence and risk factors of significant carotid artery stenosis in asymptomatic survivors of head and neck cancer after radiotherapy. *Head Neck* 2014;36(2):215-9. doi: 10.1002/hed.23280 [published Online First: 2013/04/05]
63. El-Fayech C, Haddy N, Allodji RS, et al. Cerebrovascular Diseases in Childhood Cancer Survivors: Role of the Radiation Dose to Willis Circle Arteries. *Int J Radiat Oncol Biol Phys* 2017;97(2):278-86. doi: 10.1016/j.ijrobp.2016.10.015 [published Online First: 2017/01/10]
64. Elgart SR, Little MP, Chappell LJ, et al. Radiation Exposure and Mortality from Cardiovascular Disease and Cancer in Early NASA Astronauts. *Sci Rep* 2018;8(1):8480. doi: 10.1038/s41598-018-25467-9

65. Errahmani MY, Locquet M, Spoor D, et al. Association Between Cardiac Radiation Exposure and the Risk of Arrhythmia in Breast Cancer Patients Treated With Radiotherapy: A Case–Control Study. *Frontiers Oncol* 2022;12 doi: 10.3389/fonc.2022.892882
66. Golden AP, Ellis ED, Cohen SS, et al. Updated mortality analysis of the Mallinckrodt uranium processing workers, 1942-2012. *Int J Radiat Biol* 2022;98(4):701-21. doi: 10.1080/09553002.2019.1569773 [published Online First: 2019/01/18]
67. Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms' tumor: A report from the National Wilms' Tumor Study Group. *J Clin Oncol* 2001;19(7):1926-34.
68. Grosche B, Lackland DT, Land CE, et al. Mortality from cardiovascular diseases in the Semipalatinsk historical cohort, 1960-1999, and its relationship to radiation exposure. *Radiat Res* 2011;176(5):660-69. doi: 10.1667/RR2211.1 [pii]
69. Haddy N, Mousannif A, Tukenova M, et al. Relationship between the brain radiation dose for the treatment of childhood cancer and the risk of long-term cerebrovascular mortality. *Brain* 2011;134(Pt 5):1362-72. doi: awr071 [pii];10.1093/brain/awr071 [doi]
70. Ivanov VK, Maksioutov MA, Chekin SY, et al. The risk of radiation-induced cerebrovascular disease in Chernobyl emergency workers. *Health Phys* 2006;90(3):199-207. doi: 10.1097/01.HP.0000175835.31663.ea [doi];00004032-200603000-00001 [pii]
71. Jacobse JN, Duane FK, Boekel NB, et al. Radiation Dose-Response for Risk of Myocardial Infarction in Breast Cancer Survivors. *Int J Radiat Oncol Biol Phys* 2019;103(3):595-604. doi: 10.1016/j.ijrobp.2018.10.025 [published Online First: 2018/11/06]
72. Kashcheev VV, Chekin SY, Maksioutov MA, et al. Radiation-epidemiological study of cerebrovascular diseases in the cohort of Russian recovery operation workers of the Chernobyl accident. *Health Phys* 2016;111(2):192-7. doi: 10.1097/HP.0000000000000523
73. Krasnikova LI, Buzunov VO, Solonovitch SI. Radiation and non-radiation factors impact on development of cerebrovascular diseases in the Chornobyl clean-up workers. The epidemiological study results. *Problemy radiatsiinoi medytsyny ta radiobiolohii* 2013(18):89-101. [published Online First: 2014/09/06]
74. Krestinina LY, Silkin SS, Degteva M, et al. Risk of death from circulatory system diseases in a Ural population cohort exposed to accidental radiation between 1950 and 2015. *Radiatsionnaya Gygiena* 2019;12(1):52-61. doi: 10.21514/1998-426X-2019-12-1-52-61 [doi]
75. Kreuzer M, Dufey F, Sogl M, et al. External gamma radiation and mortality from cardiovascular diseases in the German WISMUT uranium miners cohort study, 1946-2008. *Radiat Environ Biophys* 2013;52(1):37-46. doi: 10.1007/s00411-012-0446-5 [doi]
76. Lane RSD, Frost SE, Howe GR, et al. Mortality (1950-1999) and cancer incidence (1969-1999) in the cohort of Eldorado uranium workers. *Radiat Res* 2010;174(6):773-85. doi: 10.1667/RR2237.1 [pii];10.1667/RR2237.1 [doi]
77. Lee CC, Zheng H, Soon YY, et al. Association between radiation heart dosimetric parameters, myocardial infarct and overall survival in stage 3 non-small cell lung cancer treated with definitive thoracic radiotherapy. *Lung Cancer* 2018;120:54-59. doi: https://doi.org/10.1016/j.lungcan.2018.03.024
78. Little MP, Kleinerman RA, Stovall M, et al. Analysis of dose response for circulatory disease after radiotherapy for benign disease. *Int J Radiat Oncol Biol Phys* 2012;84(5):1101-09. doi: S0360-3016(12)00123-X [pii];10.1016/j.ijrobp.2012.01.053 [doi]
79. Lorenzen EL, Rehammar JC, Jensen M-B, et al. Radiation-induced risk of ischemic heart disease following breast cancer radiotherapy in Denmark, 1977–2005. *Radiother Oncol* 2020;152:103-10. doi: https://doi.org/10.1016/j.radonc.2020.08.007
80. Mansouri I, Allodji RS, Hill C, et al. The role of irradiated heart and left ventricular volumes in heart failure occurrence after childhood cancer. *Eur J Heart Failure* 2019;21(4):509-18. doi: 10.1002/ejhf.1376 [published Online First: 2018/12/29]
81. Moignier A, Broggio D, Derreumaux S, et al. Coronary stenosis risk analysis following Hodgkin lymphoma radiotherapy: A study based on patient specific artery segments dose calculation. *Radiother Oncol* 2015;117(3):467-72. doi: 10.1016/j.radonc.2015.07.043 [published Online First: 2015/08/19]
82. Nakashima E, Akahoshi M, Neriishi K, et al. Systolic blood pressure and systolic hypertension in adolescence of atomic bomb survivors exposed in utero. *Radiat Res* 2007;168(5):593-99. doi: RR1060 [pii];10.1667/RR1060.1 [doi]
83. Roos CTG, van den Bogaard VAB, Greuter MJW, et al. Is the coronary artery calcium score associated with acute coronary events in breast cancer patients treated with radiotherapy? *Radiother Oncol* 2018;126(1):170-76. doi: 10.1016/j.radonc.2017.10.009 [published Online First: 2017/11/02]
84. Sadetzki S, Chetrit A, Boursi B, et al. Childhood Exposure to Low to Moderate Doses of Ionizing Radiation and the Risk of Vascular Diseases. *Am J Epidemiol* 2021;190(3):423-30. doi: 10.1093/aje/kwaa177
85. Shafransky IL, Tukov AR, Sidorin IV, et al. Analysis of the risk of death from ischemic heart disease among

the liquidators of the consequences of the accident at Chernobyl NPP and workers in the nuclear industry. *Radiat Risk* 2020;29(3):129-41.
86. Shimizu Y, Kodama K, Nishi N, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. *BMJ* 2010;340:b5349. doi: 10.1136/bmj.b5349
87. Tagami T, Almahariq MF, Balanescu DV, et al. Usefulness of Coronary Computed Tomographic Angiography to Evaluate Coronary Artery Disease in Radiotherapy-Treated Breast Cancer Survivors. *Am J Cardiol* 2021;143:14-20. doi: https://doi.org/10.1016/j.amjcard.2020.12.038
88. Takahashi I, Shimizu Y, Grant EJ, et al. Heart disease mortality in the Life Span Study, 1950-2008. *Radiat Res* 2017;187(3):319-32. doi: 10.1667/RR14347.1
89. Takahashi I, Cologne J, Haruta D, et al. Association Between Prevalence of Peripheral Artery Disease and Radiation Exposure in the Atomic Bomb Survivors. *J Am Heart Assoc* 2018;7(23):e008921. doi: 10.1161/JAHA.118.008921 [published Online First: 2018/11/30]
90. Tatsukawa Y, Nakashima E, Yamada M, et al. Cardiovascular disease risk among atomic bomb survivors exposed in utero, 1978-2003. *Radiat Res* 2008;170(3):269-74. doi: RR1434 [pii];10.1667/RR1434.1 [doi]
91. van Aken ESM, van der Laan HP, Bijl HP, et al. Risk of ischaemic cerebrovascular events in head and neck cancer patients is associated with carotid artery radiation dose. *Radiother Oncol* 2021;157:182-87. doi: https://doi.org/10.1016/j.radonc.2021.01.026
92. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. *J Clin Oncol* 2016;34(3):235-43. doi: 10.1200/JCO.2015.63.4444
93. Xue J, Han C, Jackson A, et al. Doses of radiation to the pericardium, instead of heart, are significant for survival in patients with non-small cell lung cancer. *Radiother Oncol* 2019;133:213-19. doi: 10.1016/j.radonc.2018.10.029 [published Online First: 2018/11/13]
94. Yamada M, Wong FL, Fujiwara S, et al. Noncancer disease incidence in atomic bomb survivors, 1958-1998. *Radiat Res* 2004;161(6):622-32. doi: 10.1667/RR3183
95. Zablotska LB, Fenske N, Schnelzer M, et al. Analysis of mortality in a pooled cohort of Canadian and German uranium processing workers with no mining experience. *Int Arch Occup Environ Health* 2018;91(1):91-103. doi: 10.1007/s00420-017-1260-9 [published Online First: 2017/09/25]
96. Zureick AH, Grzywacz VP, Almahariq MF, et al. Dose to the Left Anterior Descending Artery Correlates With Cardiac Events After Irradiation for Breast Cancer. *Int J Radiat Oncol Biol Phys* 2022;114(1):130-39. doi: https://doi.org/10.1016/j.ijrobp.2022.04.019
97. Abraham A, Sanghera KP, Gheisari F, et al. Is Radiation-Induced Cardiac Toxicity Reversible? Prospective Evaluation of Patients With Breast Cancer Enrolled in a Phase 3 Randomized Controlled Trial. *Int J Radiat Oncol Biol Phys* 2022;113(1):125-34. doi: https://doi.org/10.1016/j.ijrobp.2022.01.020
98. Atkins KM, Bitterman DS, Chaunzwa TL, et al. Statin Use, Heart Radiation Dose, and Survival in Locally Advanced Lung Cancer. *Pract Radiat Oncol* 2021;11(5):e459-e67. doi: 10.1016/j.prro.2020.12.006
99. Baaken D, Merzenich H, Schmidt M, et al. A nested case-control study on radiation dose-response for cardiac events in breast cancer patients in Germany. *The Breast* 2022;65:1-7. doi: 10.1016/j.breast.2022.05.007
100. Cai G, Li C, Yu J, et al. Heart Dosimetric Parameters Were Associated With Cardiac Events and Overall Survival for Patients With Locally Advanced Esophageal Cancer Receiving Definitive Radiotherapy. *Frontiers Oncol* 2020;10:153. doi: 10.3389/fonc.2020.00153 [published Online First: 2020/04/01]
101. Chekin SY, Maksyutov MA, Kashcheyev VV, et al. Effect of dose uncertainty on the assessment of the radiation risk of nononcological diseases among Russian workers involved in cleaning up the consequences of the accident at the Chernobyl nuclear power plant (NPP). *Radiat Risk* 2022;31:21-35. doi: 10.21870/0131-3878-2022-31-2-21-35 [published Online First: 1/2022]
102. Chen L, Ta S, Wu W, et al. Prognostic and Added Value of Echocardiographic Strain for Prediction of Adverse Outcomes in Patients with Locally Advanced Non-Small Cell Lung Cancer after Radiotherapy. *Ultrasound Med Biol* 2019;45(1):98-107. doi: 10.1016/j.ultrasmedbio.2018.09.012 [published Online First: 2018/10/28]
103. Dess RT, Sun Y, Matuszak MM, et al. Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2017;35(13):1395-402. doi: 10.1200/JCO.2016.71.6142 [published Online First: 2017/03/17]
104. Haddy N, Diallo S, El-Fayech C, et al. Cardiac Diseases Following Childhood Cancer Treatment: Cohort Study. *Circulation* 2016;133(1):31-8. doi: 10.1161/CIRCULATIONAHA.115.016686 [published Online First: 2015/10/22]
105. Kashcheev VV, Chekin SY, Karpenko SV, et al. Radiation risk of cardiovascular diseases in the cohort of Russian emergency workers of the Chernobyl accident. *Health Phys* 2017;113(1):23-29. doi: 10.1097/HP.0000000000000670

106. Killander F, Wieslander E, Karlsson P, et al. No Increased Cardiac Mortality or Morbidity of Radiation Therapy in Breast Cancer Patients After Breast-Conserving Surgery: 20-Year Follow-up of the Randomized SweBCGRT Trial. *Int J Radiat Oncol Biol Phys* 2020;107(4):701-09. doi: 10.1016/j.ijrobp.2020.04.003 [published Online First: 2020/04/18]
107. Maraldo MV, Giusti F, Vogelius IR, et al. Cardiovascular disease after treatment for Hodgkin's lymphoma: an analysis of nine collaborative EORTC-LYSA trials. *Lancet Haematol* 2015;2(11):e492-502. doi: 10.1016/S2352-3026(15)00153-2 [published Online First: 2015/12/22]
108. Park S, Lee DN, Jin YW, et al. Non-cancer disease prevalence and association with occupational radiation exposure among Korean radiation workers. *Sci Rep* 2021;11(1):22415. doi: 10.1038/s41598-021-01875-2
109. Tukenova M, Guibout C, Oberlin O, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol* 2010;28(8):1308-15. doi: JCO.2008.20.2267 [pii];10.1200/JCO.2008.20.2267 [doi]
110. Wang X, Palaskas NL, Yusuf SW, et al. Incidence and Onset of Severe Cardiac Events After Radiotherapy for Esophageal Cancer. *J Thorac Oncol* 2020;15(10):1682-90. doi: 10.1016/j.jtho.2020.06.014 [published Online First: 2020/07/01]
111. Yegya-Raman N, Wang K, Kim S, et al. Dosimetric Predictors of Symptomatic Cardiac Events After Conventional-Dose Chemoradiation Therapy for Inoperable NSCLC. *J Thorac Oncol* 2018;13(10):1508-18. doi: 10.1016/j.jtho.2018.05.028 [published Online First: 2018/06/09]
112. van den Bogaard VAB, Spoor DS, van der Schaaf A, et al. The Importance of Radiation Dose to the Atherosclerotic Plaque in the Left Anterior Descending Coronary Artery for Radiation-Induced Cardiac Toxicity of Breast Cancer Patients? *Int J Radiat Oncol Biol Phys* 2021;110(5):1350-59. doi: https://doi.org/10.1016/j.ijrobp.2021.03.004
113. Wang K, Pearlstein KA, Patchett ND, et al. Heart dosimetric analysis of three types of cardiac toxicity in patients treated on dose-escalation trials for Stage III non-small-cell lung cancer. *Radiother Oncol* 2017;125(2):293-300. doi: 10.1016/j.radonc.2017.10.001 [published Online First: 2017/10/21]
114. Atkins KM, Rawal B, Chaunzwa TL, et al. Cardiac Radiation Dose, Cardiac Disease, and Mortality in Patients With Lung Cancer. *J Am Coll Cardiol* 2019;73(23):2976-87. doi: 10.1016/j.jacc.2019.03.500 [published Online First: 2019/06/15]
115. Little MP, Pawel D, Misumi M, et al. Lifetime mortality risk from cancer and circulatory disease predicted from the Japanese atomic bomb survivor Life Span Study data taking account of dose measurement error. *Radiat Res* 2020;194(3):259-76. doi: 10.1667/RR15571.1 [published Online First: 2020/09/18]
116. Ivanov VK. Late cancer and noncancer risks among Chernobyl emergency workers of Russia. *Health Phys* 2007;93(5):470-79. doi: 10.1097/01.HP.0000282195.34508.b0 [doi];00004032-200711000-00012 [pii]
117. Shafransky IL, Tukov AR, Prokhorova ON, et al. Analysis of the risk of death from ischemic due to cerebrovascular diseases among workers involved in cleaning up the consequences of the accident at Chernobyl NPP (ChNPP), nuclear industry workers. *Radiat Risk* 2022;67(1):60-64. doi: 10.12737/1024-6177-2022-67-1-60-64
118. Stovall M, Weathers R, Kasper C, et al. Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies. *Radiat Res* 2006;166(1 Pt 2):141-57. doi: RR3525 [pii];10.1667/RR3525.1 [doi]
119. Shamsaldin A, Grimaud E, Hardiman C, et al. Dose distribution throughout the body from radiotherapy for Hodgkin's disease in childhood. *Radiother Oncol* 1998;49(1):85-90. doi: S0167-8140(98)00110-8 [pii]
120. Diallo I, Lamon A, Shamsaldin A, et al. Estimation of the radiation dose delivered to any point outside the target volume per patient treated with external beam radiotherapy. *Radiother Oncol* 1996;38(3):269-71. doi: 0167814096017136 [pii]
121. Zablotska LB, Little MP, Cornett RJ. Potential increased risk of ischemic heart disease mortality with significant dose fractionation in the Canadian fluoroscopy cohort study. *Am J Epidemiol* 2014;179(1):120-31. doi: 10.1093/aje/kwt244
122. Little MP, Zablotska LB, Brenner AV, et al. Circulatory disease mortality in the Massachusetts tuberculosis fluoroscopy cohort study. *Eur J Epidemiol* 2016;31(3):287-309. doi: 10.1007/s10654-015-0075-9
123. Takamori A, Takahashi I, Kasagi F, et al. Mortality Analysis of the Life Span Study (LSS) Cohort Taking into Account Multiple Causes of Death Indicated in Death Certificates. *Radiat Res* 2017;187(1):20-31. doi: 10.1667/RR14314.1
124. Zablotska LB, Lane RS, Thompson PA. A reanalysis of cancer mortality in Canadian nuclear workers (1956-1994) based on revised exposure and cohort data. *Br J Cancer* 2014;110(1):214-23. doi: 10.1038/bjc.2013.592
125. Wakeford R. Risk of diseases of the circulatory system after low-level radiation exposure-an assessment of evidence from occupational exposures. *J Radiol Prot* 2022;42(2) doi: 10.1088/1361-6498/ac6275

[published Online First: 20220516]
126. de Vocht F, Hidajat M, Martin RM, et al. Ischemic heart disease mortality and occupational radiation exposure in a nested matched case-control study of British Nuclear Fuel cycle workers: investigation of confounding by lifestyle, physiological traits and occupational exposures. *Radiat Res* 2020;194:431-44. doi: 10.1667/RADE-19-00007.1 [published Online First: 2020/08/28]
127. Moseeva MB, Azizova TV, Grigoryeva ES, et al. Risks of circulatory diseases among Mayak PA workers with radiation doses estimated using the improved Mayak Worker Dosimetry System 2008. *Radiat Environ Biophys* 2014;53(2):469-77. doi: 10.1007/s00411-014-0517-x
128. Simonetto C, Azizova TV, Grigoryeva ES, et al. Ischemic heart disease in workers at Mayak PA: latency of incidence risk after radiation exposure. *PloS One* 2014;9(5):e96309. doi: 10.1371/journal.pone.0096309
129. Simonetto C, Schöllnberger H, Azizova TV, et al. Cerebrovascular Diseases in Workers at Mayak PA: The Difference in Radiation Risk between Incidence and Mortality. *PloS One* 2015;10(5):e0125904. doi: 10.1371/journal.pone.0125904
130. World Health Organization (WHO). World Health Organization Statistical Information System (WHOSIS) (updated 17 November 2015)(http://www.who.int/gho/en/), 2015.
131. Ivanov VK, Kashcheev VV, Maksioutov MA, et al. Clinical and dosimetric information to support long-term cohort study of Chernobyl clean-up workers in Russia. *Radiat Prot Dosimetry* 2018;182(1):163-69. doi: 10.1093/rpd/ncy133
132. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). UNSCEAR 2019 Report. Annex A. Evaluation of selected health effects and inference of risk due to radiation exposure. New York: United Nations, 2020:21-192.
133. Krestinina LY, Epifanova S, Silkin S, et al. Chronic low-dose exposure in the Techa River Cohort: risk of mortality from circulatory diseases. *Radiat Environ Biophys* 2013;52(1):47-57. doi: 10.1007/s00411-012-0438-5 [doi]