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CARDIOVASCULAR DISEASE

Circulatory disease mortality in the Massachusetts tuberculosis fluoroscopy cohort study

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Abstract High-dose ionizing radiation is associated with circulatory disease. Risks from lower-dose fractionated exposures, such as from diagnostic radiation procedures, remain unclear. In this study we aimed to ascertain the relationship between fractionated low-to-medium dose radiation exposure and circulatory disease mortality in a cohort of 13,568 tuberculosis patients in Massachusetts, some with fluoroscopy screenings, between 1916 and 1961 and follow-up until the end of 2002. Analysis of mortality was in relation to cumulative thyroid (cerebrovascular) or lung (all other circulatory disease) radiation dose via Poisson regression. Over the full dose range, there was no overall radiation-related excess risk of death from circulatory disease (n = 3221; excess relative risk/Gy −0.023; 95 % CI −0.067, 0.028; $p = 0.3574$). Risk was somewhat elevated in hypertensive heart disease (n = 89; excess relative risk/Gy 0.357; 95 % CI −0.043, 1.030, $p = 0.0907$) and slightly decreased in ischemic heart disease (n = 1950; excess relative risk/Gy −0.077; 95 % CI −0.130, −0.012; $p = 0.0211$). However, under 0.5 Gy, there was a borderline significant increasing trend for all circulatory disease (excess relative risk/Gy 0.345; 95 % CI −0.032, 0.764; $p = 0.0743$) and for ischemic heart disease (excess relative risk/Gy 0.465; 95 % CI, −0.032, 1.034, $p = 0.0682$). Pneumolobectomy increased radiation–associated risk (excess relative risk/Gy 0.252; 95 % CI 0.024, 0.579). Fractionation of dose did not modify excess risk. In summary, we found no evidence of radiation-associated excess circulatory death risk overall, but there are indications of excess circulatory death risk at lower doses (<0.5 Gy). Although consistent with other radiation-exposed groups, the indications of higher risk at lower doses are unusual and should be confirmed against other data.

Keywords Ionizing radiation · Circulatory disease · Fluoroscopy · Tuberculosis · Hypertension

Introduction

Ionizing radiation can cause cancer [1, 2]. Therapeutic doses of ionizing radiation to the heart and large arteries are associated with various types of circulatory disease [3–6]. More recently, and controversially, studies on several groups exposed to low-to-moderate doses of radiation have reported excess mortality and morbidity from circulatory diseases, in particular the Life Span Study (LSS) of Japanese atomic bomb survivors [7] and several occupationally exposed cohorts [8]. There is biological data suggesting there might be a variant response for circulatory disease below *vs* above about 0.5 Gy [9]. However, the complicated, multifactorial nature of circulatory disease, possible contributions from unmeasured confounders and errors in dose estimates inevitably raise concerns about whether the observed associations are causal [8].

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Table 1 Causes of death for 13,568 patients in the Massachusetts tuberculosis fluoroscopy cohort more than 5 years after entry

Disease endpoint	ICD9 codes	Deaths
Cerebrovascular disease	430–438	472
Ischemic heart disease	410–414	1950
Non-ischemic heart disease	390–409, 415–429	588
Hypertensive heart disease	401–405	89
All other circulatory disease apart from heart + cerebrovascular	439–459	211
All circulatory disease	390–459	3221
Person years		345,948
Persons		13,568
Mean lung dose, Gy (range)		0.36 (0.00–8.56)
Mean thyroid dose, Gy (range)		0.20 (0.00–4.61)
Mean red bone marrow dose, Gy (range)		0.04 (0.00–0.92)

Individuals receiving fluoroscopic X-rays as part of treatment for tuberculosis in Canada and Massachusetts have been studied in relationship to cancer [10–14], but noncancerous diseases have not been so extensively examined. A recent analysis of the Canadian fluoroscopy cohort study indicated small radiation-associated excess relative risks (ERR) of ischemic heart disease (IHD) mortality, with the highest risk for those with the most prolonged period over which the fluoroscopies took place [15]. Radiation-related risks of IHD also decreased significantly with increasing time since first exposure and age at first exposure [15].

We therefore analyzed the Massachusetts tuberculosis fluoroscopy cohort study to assess circulatory disease mortality. We decided a priori to concentrate on the relationship between cumulative lung and thyroid tissue dose (surrogates for dose to the heart and carotid artery, respectively) and death from several circulatory diseases and on possible dose-fractionation associations and modifications by age at exposure and time since exposure. The dose response overall and under 0.5 Gy will be assessed.

Materials and methods

Cohort characteristics and follow-up

The methods used to assemble the Massachusetts tuberculosis fluoroscopy cohort are detailed elsewhere [10, 14, 16]. Briefly, data collected from the medical records of patients with a primary diagnosis of pulmonary tuberculosis between 1915 and 1968 and discharged alive from 12 Massachusetts hospitals were identified, and their medical records were abstracted (Table 1). Cohort entry was defined as the date of admission to one of the participating institutions for treatment of tuberculosis. Of the 13,716 members of the full cohort, 144 were excluded for lack of adequate follow-up information, and another 4 for missing last exposure date, leaving an analysis dataset of 13,568 persons. This dataset is a slightly larger cohort than that considered by Davis et al. [14], because we were more successful at tracing the cohort members originally assembled by Boice [16] and Davis et al. [14]. Data were obtained on pneumothorax treatments, fluoroscopic X-ray exposures (which took place between 1916 and 1961), smoking and alcohol use, and information to assist in locating study subjects. The vital status was determined as of December 31, 2002. Deaths were retrospectively ascertained from the Vital Statistics Offices in the state of last known residence by linking to the mortality files of the Social Security Administration and the National Death Index and by contacting relatives and friends [16]. Vital status was also confirmed through records from the post office, motor vehicle departments, credit bureaus, and other sources [14].

All causes of death on death certificates were coded again using the ninth revision of the International Classification of Diseases (ICD-9). The current analysis describes mortality from all circulatory diseases (ICD-9 codes 390–459), cerebrovascular diseases (CeVD) (ICD-9 430–438), IHD (ICD-9 codes 410–414), hypertensive heart disease (ICD9 401–405), all heart disease (ICD-9 390–429), and other cardiovascular (non-CeVD, non-heart) diseases (ICD-9 439–459) (see Table 1). These endpoints were chosen a priori because they might be radiogenic [8].

Dosimetry

Dosimetry is described elsewhere [14]. Briefly, exposure groups were defined by receipt of air-collapse therapy (pneumothorax/pneumoperitoneum) as indicated on treatment records. Air-collapse therapy was standard treatment for tuberculosis in the 1920s–1940s and involved injecting air into the pleural cavity to force lung tissue away from the chest wall. Typically this procedure was repeated, with the aid of a fluoroscopic examination, 2–3 times per month

Table 2 Excess relative risks for circulatory disease mortality in Massachusetts tuberculosis fluoroscopy cohort and modification by age at entry, years since entry, and dose rate

Model	ERR/Gy (+95 % CI)						
	All circulatory disease	CeVD	All heart disease	IHD	Heart disease excluding IHD	Hypertensive heart disease	All circulatory apart from heart and cerebrovascular
Linear ERR	−0.023 (−0.067, 0.028)	0.132 (−0.088, 0.415)	−0.042 (−0.088, 0.013)	−0.077 (−0.130[a], −0.012)	0.013 (−0.072, 0.127)	0.357 (−0.043, 1.030)	0.015 (−0.183[a], 0.243)
p value	0.3574	0.2668	0.1282	0.0211	0.7943	0.0907	0.8671
Linear ERR without background medical history adjustment	−0.008 (−0.052, 0.041)	0.124 (−0.092, 0.402)	−0.027 (−0.074, 0.027)	−0.063 (−0.116[a], 0.001)	0.048 (−0.046, 0.168)	0.376 (−0.027, 1.045)	0.036 (−0.113, 0.271)
p value	0.7301	0.2873	0.3130	0.0520	0.3512	0.0731	0.7034
Linear ERR adjusted for age at entry	−0.001 (−0.008[a], 0.005[a])	0.132 (−0.134[a], 0.398[a])	−0.042 (−0.093[a], 0.010[a])	−0.077 (−0.131[a], −0.023[a])	0.013 (−0.099[a], 0.127)	0.326 (−0.092[a], 0.951)	0.015 (−0.188[a], 0.218[a])
p value[b]	0.0801	1.0000	1.0000	0.9643	1.0000	0.6947	1.0000
Linear ERR adjusted for years since entry	−0.023 (−0.080[a], 0.035[a])	0.132 (−0.082, 0.459[a])	−0.042 (−0.103[a], 0.010)	−0.070 (−0.136[a], −0.007)	0.013 (−0.062, 0.119)	0.357 (−0.190[a], 0.904[a])	0.016 (−0.146[a], 0.220)
p value[b]	1.0000	0.9748	0.9748	0.6353	0.7301	0.9643	0.4696
Linear ERR adjusted for age at entry and years since entry	−0.001 (−0.008[a], 0.005[a])	0.132 (−0.243[a], 0.507[a])	−0.042 (−0.106[a], 0.023[a])	−0.071 (−0.141[a], −0.002[a])	0.008 (−0.097[a], 0.117)	0.326 (−0.286[a], 0.938[a])	0.019 (−0.168[a], 0.206[a])
p value[b]	0.2162	0.9995	0.9995	0.8204	0.8999	0.9259	0.7464
Linear ERR adjusted for dose rate	−0.024 (−0.074[a], 0.027[a])	0.170 (−0.070, 0.472)	−0.046 (−0.099[a], 0.007[a])	−0.081 (−0.136[a], −0.026[a])	0.006 (−1.859[a], 0.126)	0.212 (−7.163[a], 0.986)	0.007 (−3.797[a], 0.244)
p value[b]	0.2396	0.4099	0.2083	0.3048	0.8065	0.5189	0.9436

Unless otherwise indicated, all 95 % CI are profile-likelihood based, and all *p* values are 2-sided. The background models are the optimal models given in Tables 8, 9, 10, 11, 12, 13 and 14

[a] Wald-based CI

[b] *p* value for modification of linear ERR coefficient by indicated variate

Table 3 Excess relative risks for all circulatory disease mortality in the Massachusetts tuberculosis fluoroscopy cohort and modification by groups of demographic (age at entry, years since entry, attained age) and lifestyle (cigarette smoking, alcohol consumption) variables

	Deaths	Person years of follow-up	ERR/Gy (+95 % CI)	*p* value
Overall	3221	345,948	−0.023 (−0.067, 0.028)	0.3574[a]
Age at first exposure, years				
0–9[b]	1741	168,727	−0.422 (−0.424[c], −0.420[c])	0.7143[d]
10–19	149	38,977	0.002 (−0.101[c], 0.105[c])	
20+	1331	138,244	−0.027 (−0.078[c], 0.024[c])	
Years since last exposure, years				
0–9[b]	1826	199,496	0.007 (−0.194[c], 0.260)	0.4817[d]
10–19	156	43,731	−0.081 (−0.192[c], 0.034)	
20+	1239	102,722	−0.013 (−0.062, 0.043)	
Age attained, years				
0–49	176	139,403	−0.036 (−0.191[c], 0.149)	0.1797[d]
50–69	1117	146,745	−0.067 (−0.131[c], 0.001)	
70+	1928	59,801	0.015 (−0.047, 0.087)	
Dose rate (Gy/year)				
0–0.29[b]	2220	223,803	−0.017 (−0.112, 0.093)	0.7189[d]
0.30–0.49	383	50,991	−0.003 (−0.065, 0.069)	
0.50–9.99	343	43,136	−0.043 (−0.103, 0.028)	
10.00+	275	28,019	0.224 (−0.392, 0.940)	
Cigarette smoking				
Never	774	119,892	−0.038 (−0.107, 0.051)	0.1635[d]
Ever	1492	164,861	−0.049 (−0.101, 0.017)	
Unknown	955	61,195	0.060 (−0.038, 0.178)	
Alcohol consumption				
No	1782	206,727	−0.042 (−0.092, 0.019)	0.0075[d]
Yes	669	82,340	−0.086 (−0.166[c], 0.006)	
Unknown	770	56,881	0.131 (0.013, 0.274)	

Unless otherwise indicated, all 95 % CI are profile-likelihood based, and all *p* values are 2-sided. The background model is the optimal model given in Table 8

[a] *p* value for linear ERR coefficient versus null

[b] Includes unexposed group

[c] Wald-based CI

[d] *p* value for modification of linear ERR coefficient by indicated variate

for over 2 years, and up to 5 years for patients with advanced disease. The radiation dose absorbed by several organs adjacent to the lung and exposed during the fluoroscopic procedures was estimated [17, 18]. This dosimetry method accounted for the number of fluoroscopies, calendar year of exposure, sex, age at treatment (<18, ≥18 years of age), and phantom studies of organ-specific doses using contemporary machine exposure settings to the extent possible.

Cumulative lagged doses to the lung, red bone marrow (RBM) and thyroid were estimated. We regard thyroid dose as a surrogate for dose to the carotid artery, and lung dose as a surrogate for dose to the heart; RBM dose was used because of suggestions of immunologic effects in circulatory disease [19, 20]. Therefore we used thyroid dose to analyze CeVD, and lung dose for all other circulatory disease endpoints, with RBM dose being used for certain sensitivity analyses (Table 6). For most analyses, cumulative dose was lagged by 5 years, as in most previous analyses of these endpoints [8].

Statistical methods

Each patient contributed person-years at risk from 5 years after starting treatment (or entry into the study for those unexposed) to December 31, 2002, or the date of death or last date contacted, whichever occurred earlier. In sensitivity analysis (not shown) we varied the exclusion period from 5 years to between 0 and 10 years. The fitted model assumed that the expected number of deaths in stratum i with cumulative lung/thyroid/RBM dose D_i (in Gy), lung dose rate DR_i (Gy y^{-1}), age at first exposure a_i, time since last exposure t_i, and associated other covariates $(X_{ij})_{j=1}^{n}$ is given by:

Table 4 Excess relative risks for all circulatory disease mortality in the Massachusetts tuberculosis fluoroscopy cohort and modification by surgical status (thoracoplasty, pneumolobectomy, other surgery) or maximal tuberculosis disease status

	Deaths	Person years of follow-up	ERR/Gy (+95 % CI)	*p* value
Overall	3221	345,948	−0.023 (−0.067, 0.028)	0.3574[a]
Thoracoplasty status				
No	2321	234,557	−0.026 (−0.079, 0.035)	0.5023[b]
Yes	609	56,283	0.026 (−0.075, 0.160)	
Unknown	291	55,109	−0.067 (−0.166[c], 0.054)	
Pneumolobectomy status				
No	2687	263,725	−0.036 (−0.084, 0.020)	0.0319[b]
Yes	187	22,056	0.252 (0.024, 0.579)	
Unknown	347	60,167	−0.060 (−0.150[c], 0.052)	
Other surgery status				
No	1448	153,388	−0.006 (−0.072, 0.075)	0.3891[b]
Yes	616	78,579	−0.007 (−0.081, 0.085)	
Unknown	1157	113,982	−0.081 (−0.168[c], 0.017)	
Maximal tuberculosis disease status at diagnosis				
Minimal	693	89,871	0.003 (−0.132[c], 0.137[c])	0.7673[b]
Moderate	1385	140,137	−0.009 (−0.079[c], 0.061[c])	
Advanced	1028	83,333	−0.049 (−0.116[c], 0.018[c])	
Childhood	76	27,556	−0.279 (−0.281[c], −0.278[c])	
Other	31	3437	0.255 (−1.167[c], 1.677[c])	
Unknown	8	1616	0.833 (−2.323[c], 3.989[c])	

Unless otherwise indicated, all 95 % CI are profile-likelihood based. The background model is the optimal model given in Table 8

[a] *p* value for linear ERR coefficient versus null

[b] *p* value for modification of linear ERR coefficient by indicated variate

[c] Wald-based CI

$$PY_i \exp\left[\sum_{j=1}^{n} X_{ij}\beta_j\right][1 + \alpha D_i \exp(\delta_1(a_i - 26.20) + \delta_2(t_i - 25.01) + \delta_3(DR_i - 10.44))] \quad (1)$$

where PY_i is the number of person-years of follow-up. Age at first exposure, years since last exposure and dose rate (defined as the total dose, multiplied by 365.24, and divided by the number of days of irradiation) were centered by subtracting their person-year weighted mean values over the exposed part of the cohort, 26.20, 25.01 years, and 10.44 Gy year^{-1}, respectively. For the purposes of the interaction analysis in Tables 3 and 4 we fitted a slight variant of this model in which for a given factor variable X_m taking values $1, \ldots, M_m$ the expected number of deaths is:

$$PY_i \exp\left[\sum_{j=1}^{n} X_{ij}\beta_j\right]\left[1 + \sum_{k=1}^{M_m} 1_{X_{im}=k}\alpha_k D_i \exp(\delta_1(a_i - 26.20) + \delta_2(t_i - 25.01) + \delta_3(DR_i - 10.44))\right] \quad (1')$$

It should be emphasized that the models used all incorporated the variables to be used (alcohol consumption, cigarette smoking status, thoracoplasty status, pneumolobectomy status, tuberculous disease status, etc.) in the background model, so that we are testing specifically the adjustment to the radiation dose response. The only exception related to the radiation-specific variables (age at first exposure, years since last exposure, dose rate), which cannot be incorporated in the background model.

Maximum likelihood techniques [21] were used to fit the models with EPICURE [22] and thereby to estimate all the above model parameters, in particular the ERR/Gy, α. All tests were 2-sided with a specified type I error of 0.05, and unless otherwise stated all confidence intervals for risk estimates were derived from the profile likelihood [21]. A forward stepwise procedure [21] determined the form of the model of the underlying risk for each endpoint, in relation to all factors other than radiation dose. Terms were selected for inclusion in the model if a p value of 0.1 or less was achieved by their incorporation. We only evaluated interactions of sex × age and sex × calendar year, and evaluated interactions as groups of variables, namely sex × {ln[age], ln[age]^2, …, ln[age]^k}, and sex × {year, year^2, …, year^m}); the maximal exponents of ln[age], year, namely k, m, were determined by the significance of the

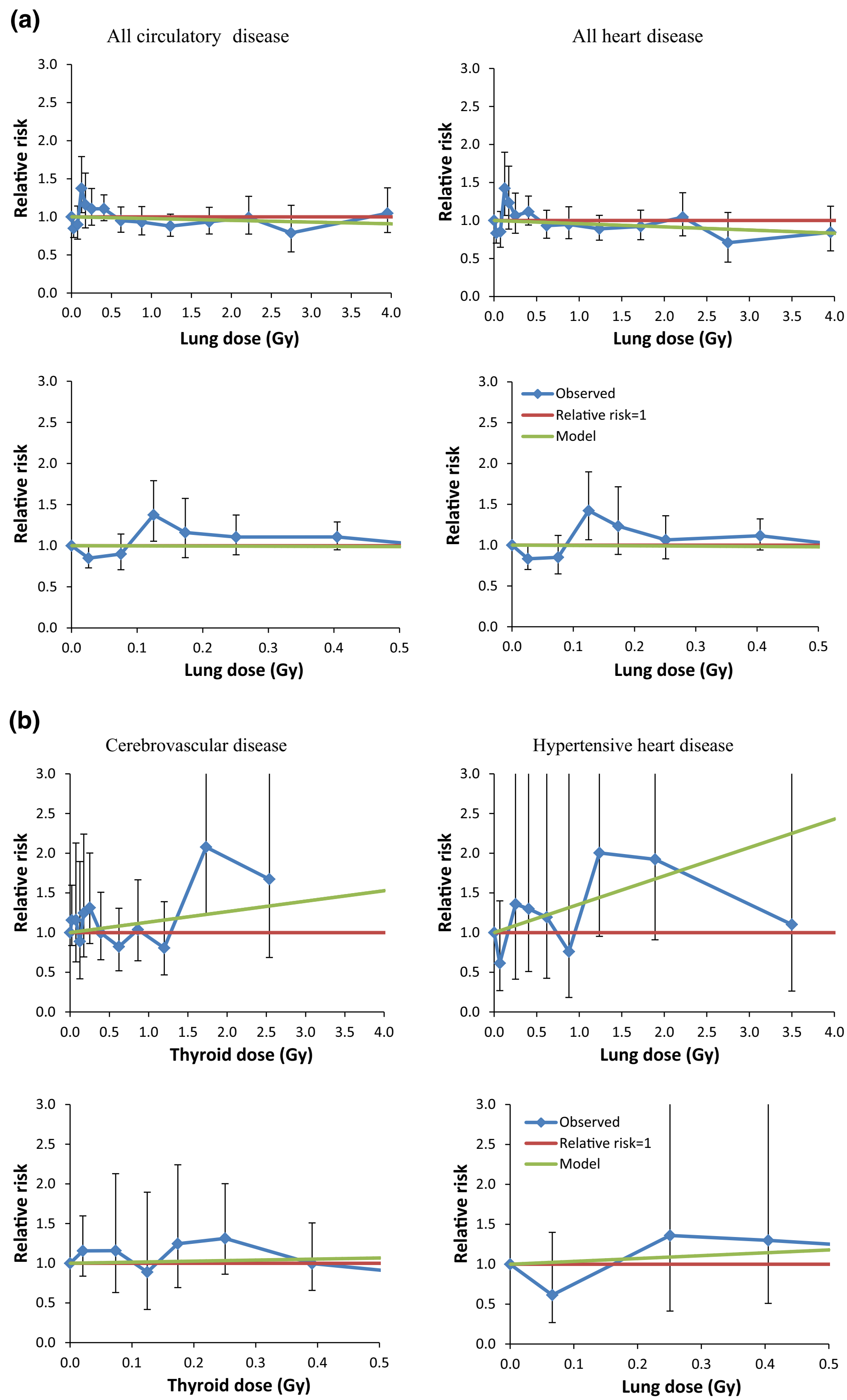

Fig. 1 **a** Dose response for all circulatory disease, and all heart disease, with 95 % CI. **b** Dose response for cerebrovascular disease, and hypertensive heart disease, with 95 % CI. *Lower panel* in each graph is low dose (<0.5 Gy) part of upper graph

Table 5 Excess relative risk (ERR) per Gy of various circulatory disease mortality endpoints by dose range examined

Dose range, Gy	ERR/Gy (+95 % CI), 2-sided p values				
	All circulatory disease	CeVD	All heart disease	IHD	Hypertensive heart disease
0–0.10	−1.998 (−4.189, 0.571)	3.453 (−3.636, 13.520)	−2.478 (−4.832, 0.350)	−2.144 (−4.940, 1.297)	0.300 (−16.990[a], 24.720)
p value	0.1213	0.3897	0.0828	0.2059	0.9643
0–0.20	0.866 (−0.484, 2.411)	1.206 (−1.622, 5.115)	1.056 (−0.449, 2.801)	2.337 (0.458, 4.543)	−4.968 (−8.420[a], 4.104)
p value	0.2205	0.4503	0.1794	0.0126	0.1711
0–0.30	0.646 (−0.165, 1.569)	1.202 (−0.472, 3.379)	0.574 (−0.317, 1.601)	1.324 (0.212, 2.624)	0.212 (−2.966, 7.929)
p value	0.1237	0.1770	0.2191	0.0177	0.9333
0–0.50	0.345 (−0.032, 0.764)	0.343 (−0.536, 1.473)	0.352 (−0.067, 0.824)	0.465 (−0.032, 1.034)	0.801 (−1.226, 4.638)
p value	0.0743	0.4808	0.1032	0.0682	0.5349

Unless otherwise indicated, all 95 % CI are profile-likelihood based, and all p values are 2-sided. The background models are the optimal models given in Tables 8, 9, 10, 11, 12, 13 and 14

[a] Wald-based CI

Table 6 Excess relative risk (ERR) per Gy of various circulatory disease mortality endpoints by organ dose used

Organ dose	ERR/Gy (+95 % CI), 2-sided p values				
	All circulatory disease	CeVD	All heart disease	IHD	Hypertensive heart disease
Lung	**−0.023 (−0.067, 0.028)**	0.075 (−0.050, 0.237)	**−0.042 (−0.088, 0.013)**	**−0.077 (−0.130[a], −0.012)**	**0.357 (−0.043, 1.030)**
Red bone marrow	−0.209 (−0.608, 0.247)	0.676 (−0.458, 2.137)	−0.378 (−0.797, 0.119)	−0.700 (−1.185[a], −0.118)	3.199 (−0.406, 9.271)
Thyroid	−0.040 (−0.118, 0.048)	**0.132 (−0.088, 0.415)**	−0.073 (−0.155, 0.023)	−0.136 (−0.230[a], −0.023)	0.615 (−0.082, 1.788)

Unless otherwise indicated all 95 % CI are profile-likelihood based. Optimal assignments of organ dose are shown in boldface. The background models are the optimal models given in Tables 8, 9, 10, 11, 12, 13 and 14

[a] Wald-based CI

associated main effect. The criteria for selection of these groups of interaction variables was the same as for all other variables, namely a p value of 0.1 or less. The results of the analysis of background rates are given in Tables 8, 9, 10, 11, 12, 13 and 14 by endpoint. The forward-stepwise variable selection procedure we used to construct the background rate models was not automated. Automatic variable selection procedures can result in models in which higher polynomial powers of a variable are used, but not all lower order terms, and likewise can add interaction terms without both the associated main effect terms, both of them undesirable features of a model. Certain more automatic forms of the variable selection procedure use a mixture of forward (variable selection) and backward (variable elimination) methods, with different p value thresholds for selection and dropping of variables [23]; the choice of p values requires some care. We have used an alternative fully automatic method, described in "Appendix 2", using Akaike's information criterion (AIC) [24, 25] to choose an optimal background model. Minimizing AIC is a standard method of variable selection that avoids over-parameterised (and therefore over-fitted) models. AIC penalises against overfitting by adding 2 × [number of fitted parameters] to the model deviance. The selected variables for each endpoint are given in Table 15. The results of using this automatically selected set of models are shown in Table 16. A mixed forward–backward stepwise procedure was used, implemented in R [26].

We also fitted a simple generalized additive model (GAM) [27], in which the expected number of deaths is:

$$PY_i\left\{\exp\left[\sum_{j=1}^{n} X_{ij}\beta_j\right] + \kappa D_i \times \exp\begin{pmatrix}\theta_1(a_i - 26.20) + \theta_2(t_i - 25.01) \\ + \theta_3(DR_i - 10.44)\end{pmatrix}\right\} \quad (2)$$

Table 7 Estimated excess relative risks of circulatory disease in the present study and in various other studies of moderate- and low-dose radiation exposure

Data	Reference	Average heart/brain dose (range) (Sv)	Numbers in cohort (person years follow-up)	Endpoint (mortality unless otherwise indicated)	ERR/Sv (and 95 % CI)
Present study					
		0.36 (0–8.56)[a]	13,572 (345,948)	IHD (ICD9 410–414) <0.5 Gy	0.465 (−0.032, 1.034)[a]
				Hypertensive heart disease (ICD9 401–405) <0.5 Gy	0.801 (−1.266, 4.638)[a]
				CeVD (ICD9 430–438) <0.5 Gy	0.343 (−0.536, 1.473)[b]
				All circulatory disease (ICD9 390–459) <0.5 Gy	0.345 (−0.032, 0.764)[a]
				IHD (ICD9 410–414) full dose range	−0.077 (−0.130, −0.012)[a]
				Hypertensive heart disease (ICD9 401–405) full dose range	0.357 (−0.043, 1.030)[a]
				CeVD (ICD9 430–438) full dose range	0.132 (−0.088, 0.415)[b]
				All circulatory disease (ICD9 390–459) full dose range	−0.023 (−0.067, 0.028)[a]
Japanese atomic bomb survivors					
Mortality	Shimizu et al. [7]	0.1 (0–4)[c]	86,611 (3,294,280)	Heart disease total (ICD9 393–429 excluding 401, 403, 405)	0.18 (0.11, 0.25)[d]
				CeVD (ICD9 430–438)	0.12 (0.05, 0.19)[d]
				All circulatory disease (ICD9 390–459)	0.15 (0.10, 0.20)[d]
Morbidity	Yamada et al. [48]	0.1 (0–4)[e]	10,339 (n.a.)	IHD incidence, 1958–1998 (ICD9 410–414)	0.05 (−0.05, 0.16)[e]
				Stroke incidence, 1958–1998 (ICD9 430, 431, 433, 434, 436)	0.07 (−0.08, 0.24)[e]
Occupational studies					
Mayak workers	Azizova et al. [49, 50]	0.83 (0–5.92)[f]	12,210 (205,249)	IHD morbidity (ICD9 410–414)	0.119 (0.051, 0.186)[f, g]
			22,377 (425,735)	CeVD morbidity (ICD9 430–438)	0.46 (0.36, 0.56)[f, g]
BNFL workers	McGeoghegan et al. [54]	0.0569 (0– >0.729)	38,779 (1,081,570)	IHD (ICD9 410–414)	0.70 (0.37, 1.07)[d, h]
				CeVD (ICD9 430–438)	0.66 (0.17, 1.27)[d,h]
				Other circulatory diseases (ICD9 390–398, 415–429, 440–459)	0.83 (−0.10, 1.12)[h]
				Circulatory diseases apart from CeVD (ICD9 390–429, 439–459)	0.72 (0.39, 1.10)[h]
				All circulatory disease (ICD9 390–459)	0.54 (0.30, 0.82)[d, h]
3rd analysis of UK National Registry for radiation workers	Muirhead et al. [55]	0.0249 (<0.01– >0.4)	174,541 (3.9×10^6)	All circulatory disease (ICD9 390–459)	0.251 (−0.01, 0.54)
				Ischemic heart disease (ICD9 410–414)	0.259 (−0.05, 0.61)
				CeVD (ICD9 430–438)	0.161 (−0.42, 0.91)

Table 7 continued

Data	Reference	Average heart/brain dose (range) (Sv)	Numbers in cohort (person years follow-up)	Endpoint (mortality unless otherwise indicated)	ERR/Sv (and 95 % CI)
IARC 15-country nuclear worker study	Vrijheid et al. [56]	0.0207 (0.0– >0.5)	275,312 (4,067,861)	Circulatory disease (ICD10 I00–I99, J60–J69, O88.2, R00–R02, R57)	0.09 (−0.43, 0.70)
				IHD (ICD10 I20–I25)	−0.01 (−0.59, 0.69)
				CeVD (ICD10 I60–I69)	0.88 (−0.67, 3.16)
				All other circulatory disease (ICD10 R00–R02, R57, I00–I99 excluding I20–26, I50, I60–69, I80, I82)	0.29 (<0, 2.40)
Environmental studies					
Techa River study	Krestinina et al. [57]	0.035 (0–0.51)[i]	29,735 (901,563)	All circulatory disease (ICD9 390–459)[g]	0.24 (−0.08, 0.59)
				IHD (ICD9 410–414)[g]	0.40 (−0.11, 0.99)
Semipalatinsk nuclear test study	Grosche et al. [58]	0.09 (0–0.63)[f]	19,545 (582,656)	Heart disease (ICD9 410–429): exposed settlements	0.06 (−0.39, 0.52)[f]
				CeVD (ICD9 430–438): exposed settlements	−0.06 (−0.65, 0.54)[f]
				Cardiovascular disease (ICD9 390–459): exposed settlements	0.02 (−0.32, 0.37)[f]
Diagnostic medical studies					
Canadian tuberculosis fluoroscopy	Zablotska et al. [15]	0.79 (0–11.60)[a]	63,707 (1,902,252)	IHD (ICD9 410–414, 429.2)	0.007 (−0.044, 0.072)[a]
				Hypertensive disease and other non-CeVD (ICD9 390–409, 415–429.1, 429.3–429.9, 439–459)	0.027 (−0.064, 0.167)[a]
				All circulatory disease apart from CeVD (ICD9 390–429, 439–459)	0.020 (−0.025, 0.074)[a]

All data are in relation to underlying cause of death, unless otherwise indicated

[a] Lung dose

[b] Analysis based on thyroid dose

[c] Analysis based on colon dose

[d] Analysis using underlying or contributing cause of death

[e] Analysis based on stomach dose, derived from Table 4 of Yamada et al. [48] with smoking and drinking in the stratification

[f] Risk estimates in relation to cumulative whole body external gamma dose

[g] Assuming a lag period of 10 years

[h] 90 % CI

[i] Analysis based on dose to muscle

However, models other than that with the simplest possible radiation effect term, with $\theta_1 = \theta_2 = \theta_3 = 0$, proved generally numerically unstable (results not shown). Therefore we present results only for this special case, the constant excess absolute risk (EAR) model:

$$PY_i \left\{ \exp\left[\sum_{j=1}^{n} X_{ij}\beta_j \right] + \kappa D_i \right\} \quad (2')$$

Inference relates to the EAR coefficient κ. Further details are given in Table 17. GAMs were fitted using EPICURE [22] and R [26].

Results

Among persons followed for 5 or more years (345,948 person-years of follow-up), 3221 died of circulatory diseases (Table 1). Overall, radiation had no marked effects on the circulatory system when adjusting for various lifestyle and environmental factors in the background (as per Tables 8, 9, 10, 11, 12, 13 and 14). For all circulatory disease, the ERR/Gy was −0.023 (95 % CI −0.067, 0.028, $p = 0.3574$, Table 2). There are stronger indications of excess risk for hypertensive heart disease (ERR/Gy = 0.357, 95 % CI −0.043, 1.030, $p = 0.0907$, Table 2). On the other hand, the dose–response for IHD was negative (ERR/Gy = −0.077, 95 % CI −0.130, −0.012, $p = 0.0211$, Table 2). The fits of the GAM (Table 17) were also generally non-significant, and some were numerically unstable.

Risk did not change significantly for any endpoint with continuous modification by dose fractionation, age at entry, or time since entry (Table 2). This lack of a marked effect was also the case when factor (grouped) modifications of the temporal and dose rate variables were employed (Table 3).

Cigarette smoking did not significantly modify radiation risk, but the category of alcohol consumption did ($p = 0.0075$), with statistically significant excess radiation risk in the group whose alcohol consumption was unknown (Table 3).

Thoracoplasty, other surgery, and tuberculosis status did not significantly modify all circulatory disease radiation risk ($p > 0.2$), but pneumolobectomy did ($p = 0.0319$), with radiation risk highest (and statistically significant) among those reporting a pneumolobectomy (ERR/Gy = 0.252; 95 % CI 0.024, 0.579; Table 4).

Risk in the low-dose region fluctuated considerably, with indications of excess risk for some endpoints (Fig. 1). If the dose range was restricted to less than 0.5 Gy, borderline significant elevations in ERR were associated with all circulatory disease (ERR/Gy = 0.345; 95 % CI −0.032, 0.764; $p = 0.0743$), IHD (ERR/Gy = 0.465; 95 % CI −0.032, 1.034; $p = 0.0682$), and for all heart disease (ERR/Gy = 0.352; 95 % CI −0.067, 0.824; $p = 0.1032$) (Table 5).

Different organ doses were associated with a considerable range in risks (Table 6). Risks are particularly large in relation to RBM dose, the use of which increases the ERR/Gy for CeVD more than five-fold (to 0.676, compared with 0.132 for thyroid dose).

The main results used a follow-up period starting 5 years after entry (for those not exposed) or 5 years after last exposure (for those exposed), with cumulative doses lagged by 5 years. The results were essentially unchanged when these exclusion and lagging periods were varied between 0 and 10 years (results not shown). The results of using an automatically selected set of background models, selected to minimize AIC, are shown in Table 16. Comparison of this table with Table 2 indicates that very similar inference results from using this alternative set of background models.

Discussion

We found no strong evidence of radiation-associated excess risks for the all-circulatory disease mortality endpoint. Over the full dose range, there were borderline significant ($p \approx 0.1$) indications of an excess risk for hypertensive heart disease. Borderline significant ($0.05 < p \leq 0.10$) increasing trends were found for all circulatory disease, IHD, and all heart disease when dose was restricted to <0.5 Gy. Significant excess risk was found for pneumolobectomy. Dose fractionation, age at entry, and time since entry, did not modify radiation risk for circulatory mortality.

The absence of any fractionation effect in the present data contrasts with the inverse fractionation effect observed in the Canadian tuberculosis data [15]. However, the cohorts and analytical methods of these two studies differ in several ways. The significant dose-fractionation effect observed in the Canadian study was estimated for 10-year lagged lung doses, whereas we used 5-year lagged doses. When Canadian data were re-analyzed with the 5-year lag, the dose-fractionation was attenuated and no longer significant [15]. Whereas the Canadian study used time-dependent annual lung doses [15], we relied on cumulative lung and thyroid doses. We also defined dose rate differently. The Canadian study used actual days under treatment and fluoroscopy screening [15], and we defined duration of exposure as the difference between the dates of the first and last fluoroscopy. The two populations also differ, e.g., the Canadian cohort has different calendar times of exposure (1930–1952 vs 1901–1962 in our study). However, risks in the present cohort are entirely consistent with the overall pattern of risk (without adjusting for fractionation) in the Canadian data (Table 7).

Several authors and committees have reviewed evidence for excess risk of circulatory disease in groups exposed to low and moderate doses of radiation (mean dose < 0.5 Gy) [8, 9, 28]. For example, a recent systematic review and meta-analysis [8] documented statistically significant excess risk for three of the four major subtypes of circulatory disease. The risks in the present study, when evaluated over the full dose range or when restricted to less than 0.5 Gy, are similar to results in most other radiation-exposed groups (Table 7).

The candidate biological mechanisms for the circulatory disease effects of radiation have been recently reviewed [9, 28, 29]. At high radiotherapeutic doses (>5 Gy), the cell-killing effect on capillaries and endothelial cells plausibly explains effects on the heart and other parts of the circulatory system [29]. At lower doses (0.5–5 Gy), in humans and in in vivo and in vitro experiments, many inflammatory markers are upregulated long after exposure to radiation, although for exposures less than about 0.5 Gy, the balance shifts toward anti-inflammatory effects [9, 28, 30], implying that the initiating mechanisms for adverse effects in this dose range would not directly result from inflammation. A recent analysis of death from renal failure in the Life Span Study suggests that radiation-induced renal dysfunction may be a factor in increasing the risk of circulatory disease [31], and some experimental data support this suggestion [32].

We used thyroid dose (a surrogate for dose to the carotid artery) to analyze CeVD, and (as in the Canadian tuberculosis analysis [15]) lung dose (a surrogate for heart dose) to analyze all other endpoints. One would expect carotid artery dose to be higher than thyroid dose, but that lung dose is probably lower than heart dose; estimates of both the heart and carotid dose may be wrong by a factor of 2 [33].

Dose-related variations in T cell and B-cell populations in Japanese atomic-bomb survivors suggest that radiation may harm the immune system [34] at doses > 1.5 Gy, implying that whole-body or RBM dose might be the most relevant to the radiation effects of the associated systems. Although other evidence implicates infections and the immune system in cardiovascular disease [19, 35, 36], the negative findings of two randomized-controlled trials of antibiotic administration [37, 38] suggest that bacterial infection is not likely involved in circulatory disease. The somewhat high (albeit non-significant) risks for hypertensive heart disease and CeVD if RBM dose is used (Table 6) (weakly) suggest that dose to this tissue may not be relevant for these endpoints. There is biological data suggesting radiation-associated senescence of monocytes [39], and a somewhat similar mechanism based on monocyte cell killing in the arterial intima suggests that the arterial intima may be causally associated with initiating atheroma in the arterial wall [40] (although there are many other stages between that point and plaque rupture [41, 42]), so that mean arterial dose might be the most relevant organ or tissue dose for studying circulatory disease.

Several recent reviews [8, 9, 28, 43] describe the abundant radiobiological reasons for considering the studies of moderate and low doses separately from studies of high doses. The mechanisms relevant for lower doses are likely to differ from those relevant at higher (e.g., radiotherapeutic) doses. However, risks in studies of medically-exposed groups, with relevant organ doses usually well above 0.5 Gy, are generally consistent with those in populations exposed at the much lower doses and dose rates discussed above [3–6, 44], suggesting that mechanisms operating at high doses and high dose rates may be similar to those at low doses and dose rates. The fact that the IHD risks using mean heart dose in these high-dose/partial-body exposed groups are similar to the risks in the generally uniformly whole-body-exposed groups using whole-body dose discussed above (Table 7) also suggests that mean dose to the heart is the most relevant metric for predicting radiation-associated IHD [44]. In the current analysis, we used lung dose as a surrogate for heart dose.

Epidemiological research has identified specific hereditary and lifestyle risk factors for circulatory disease, including male sex, family history of heart disease, cigarette smoking, diabetes, high blood pressure, obesity, increased low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol plasma concentrations [45–47]. Many studies lack this information on lifestyle factors. Of the studies considered in Table 7 only those of the Japanese atomic-bomb survivors [7, 48], Mayak workers [49, 50], and Canadian fluoroscopy patients [15] had such information. Some lifestyle factors were included in the Nordic breast cancer case–control study [4], and specific medical factors (surgery, thoracoplasty, pneumolobectomy), alcohol consumption, and cigarette smoking were included in the cohort considered here. Cigarette smoking did not modify the dose response in the present cohort, although unknown alcohol consumption and pneumolobectomy did (Tables 3, 4). However, the importance of these findings is unclear, and they may best be interpreted as the effects of chance. In all other radiation-exposed groups with such information there is no evidence that lifestyle factors interacted with radiation risk [4, 7, 48–50].

Strengths of the study include the fact that results are based on a long-term follow-up of a large cohort of subjects of both sexes exposed at different ages. Risks could be evaluated from low-to-moderate radiation doses protracted over time. Dose was evaluated to a number of organs, in particular to the lung, which should be a reasonable surrogate to dose to the heart (as discussed above). The outcome and exposure information are both register-based, so most biases (e.g., due to misclassification of exposure or outcome) are unlikely. As noted above we have information on certain lifestyle and medical variables. A weakness of the study is that there are many other lifestyle and medical risk factors for circulatory disease that we lack information on. These include diabetes, hypertension, and obesity (and related to that exercise). It is possible that these may confound the radiation dose response that we observe. However, as discussed above, there is little information in other studies to suggest interactions of such variables with radiation risk.

The International Commission on Radiological Protection has classified circulatory disease as a tissue reaction effect [51], with a threshold dose of 0.5 Gy. The threshold was derived by fitting a linear model to epidemiologic data and selecting the dose below which there was less than a 1 % chance of an effect. As such this does not represent a true no-effect dose threshold. Schöllnberger et al. [52], analyzing somewhat older Japanese atomic bomb survivor data, concluded that for CeVD and cardiovascular disease, risk estimates are compatible with no risk below threshold doses of 0.62 and 2.19 Gy respectively. However, this analysis is controversial [53]. The analysis of Table 5 suggests that a threshold of the order of 0.5 Gy is marginally inconsistent with the pattern of radiogenic excess risk observed in the Massachusetts tuberculosis fluoroscopy sub-cohort.

In summary, we found no strong evidence of radiation-associated excess risks for the circulatory disease overall. In contrast to the findings in the generally similar (although somewhat larger) Canadian TB fluoroscopy cohort, there was no indication of an inverse fractionation effect. However, borderline significant increasing trends were observed for all circulatory disease, ischemic heart disease, and all heart disease when dose was restricted to <0.5 Gy. The magnitude of the trends both overall and <0.5 Gy are consistent with those in other groups exposed at moderate and low doses. However, the indications of a much steeper low dose slope are unexpected, and should be tested against other data.

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Compliance with ethical standards

Conflict of interest The authors report no financial conflicts of interest.

Appendix 1: Background models selected

See Tables 8, 9, 10, 11, 12, 13 and 14.

Table 8 Analysis of deviance of all circulatory disease mortality

Model number	Model description	Deviance (*df*)	*p* value
1	Constant	29,716.61 (233,803)	
2	Constant + ln[age]	25,531.27 (233,802)	<0.0001
3	Constant + ln[age] + $ln[age]^2$	25,487.47 (233,801)	<0.0001
4	Constant + ln[age] + $ln[age]^2$ + $ln[age]^3$	25,486.09 (233,800)	0.2415
5	Constant + ln[age] + $ln[age]^2$ + $ln[age]^3$ + $ln[age]^4$	25,484.81 (233,799)	0.2572
6	Constant + ln[age] + $ln[age]^2$ + $ln[age]^3$ + $ln[age]^4$ + $ln[age]^5$	25,484.73 (233,798)	0.7828
7	Constant + ln[age] + $ln[age]^2$ + $ln[age]^3$ + $ln[age]^4$ + $ln[age]^5$ + $ln[age]^6$	25,480.38 (233,797)	0.0369
8	Constant + ln[age] + $ln[age]^2$ + sex	25,065.83 (233,800)	<0.0001[a]
9	Constant + ln[age] + $ln[age]^2$ + sex + year	24,758.67 (233,799)	<0.0001
10	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$	24,758.64 (233,798)	0.8648
11	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$	24,739.99 (233,797)	<0.0001
12	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$	24,733.20 (233,796)	0.0091
13	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$	24,729.77 (233,795)	0.0643
14	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + $year^6$	24,729.14 (233,794)	0.4244
15	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + smoking	24,535.55 (233,793)	<0.0001[b]
16	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + smoking + alcohol	24,483.18 (233,791)	<0.0001
17	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + smoking + alcohol + other lung surgery	24,471.18 (233,789)	0.0025
18	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + smoking + alcohol + other lung surgery + thoracoplasty	24,439.04 (233,787)	<0.0001
19	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy	24,430.88 (233,785)	0.0168
20	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort	24,424.82 (233,783)	0.0484
21	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type	24,398.03 (233,778)	<0.0001
22	**Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age], $ln[age]^2$}**	**24,332.45 (233,776)**	**<0.0001**
23	Constant + ln[age] + $ln[age]^2$ + sex + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age], $ln[age]^2$, year, $year^2$, …, $year^5$}	24,330.94 (233,771)	0.9114

Unless otherwise stated, all *p* values refer to the improvement in fit of the model in a given row of the table over that in the row above. Optimal model is shown in boldface

[a] *p* value for improvement in fit of model 8 versus model 3

[b] *p* value for improvement in fit of model 15 versus model 13

Table 9 Analysis of deviance of all cerebrovascular disease mortality

Model number	Model description	Deviance (*df*)	*p* value
1	Constant	6177.75 (233,803)	
2	Constant + ln[age]	5367.14 (233,802)	<0.0001
3	Constant + ln[age] + ln[age]^2	5351.22 (233,801)	<0.0001
4	Constant + ln[age] + ln[age]^2 + ln[age]^3	5349.29 (233,800)	0.1656
5	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4	5345.56 (233,799)	0.0533
6	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + ln[age]^5	5345.40 (233,798)	0.6910
7	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + ln[age]^5 + ln[age]^6	5341.21 (233,797)	0.0408
8	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex	5323.92 (233,798)	<0.0001[a]
9	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year	5254.32 (233,797)	<0.0001
10	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2	5254.28 (233,796)	0.8495
11	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3	5230.12 (233,795)	<0.0001
12	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4	5216.82 (233,794)	0.0003
13	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + year^5	5214.61 (233,793)	0.1374
14	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + year^5 + year^6	5213.26 (233,792)	0.2448
15	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + smoking	5170.95 (233,792)	<0.0001[b]
16	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + smoking + alcohol	5166.39 (233,790)	0.1024
17	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + smoking + alcohol + other lung surgery	5162.63 (233,788)	0.1527
18	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + smoking + alcohol + other lung surgery + thoracoplasty	5157.97 (233,786)	0.0973
19	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy	5157.04 (233,784)	0.6281
20	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort	5155.73 (233,782)	0.5187
21	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type	5152.19 (233,777)	0.6176
22	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age] + … + ln[age]^4}	5142.72 (233,773)	0.0503
23	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age] + … + ln[age]^4 + year + … + year^4}	5141.40 (233,768)	0.9324
24	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + smoking + thoracoplasty + sex × {ln[age] + … + ln[age]^4}	5157.25 (233,786)	–

Unless otherwise stated, all *p* values refer to the improvement in fit of the model in a given row of the table over that in the row above. Optimal model is given at the bottom of the table

[a] *p* value for improvement in fit of model 8 versus model 5

[b] *p* value for improvement in fit of model 15 versus model 12

Table 10 Analysis of deviance of all heart disease mortality

Model number	Model description	Deviance (*df*)	*p* value
1	Constant	24,590.22 (233,803)	
2	Constant + ln[age]	21,549.82 (233,802)	<0.0001
3	Constant + ln[age] + ln[age]^2	21,525.00 (233,801)	<0.0001
4	Constant + ln[age] + ln[age]^2 + ln[age]^3	21,524.36 (233,800)	0.4226
5	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4	21,522.15 (233,799)	0.1374
6	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + ln[age]^5	21,520.66 (233,798)	0.2222
7	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + ln[age]^5 + ln[age]^6	21,518.27 (233,797)	0.1221
8	Constant + ln[age] + ln[age]^2 + sex	21,160.96 (233,800)	<0.0001[a]
9	Constant + ln[age] + ln[age]^2 + sex + year	20,946.52 (233,799)	<0.0001
10	Constant + ln[age] + ln[age]^2 + sex + year + year^2	20,946.50 (233,798)	0.8795
11	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3	20,939.50 (233,797)	0.0081
12	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + year^4	20,937.76 (233,796)	0.1873
13	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + year^4 + year^5	20,937.06 (233,795)	0.4028
14	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + year^4 + year^5 + year^6	20,937.06 (233,794)	0.9563
15	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + smoking	20,803.95 (233,795)	<0.0001[b]
16	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + smoking + alcohol	20,752.00 (233,793)	<0.0001
17	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery	20,742.81 (233,791)	0.0101
18	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty	20,710.96 (233,789)	<0.0001
19	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy	20,697.25 (233,787)	0.0011
20	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort	20,691.33 (233,785)	0.0519
21	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type	20,670.75 (233,780)	0.0010
22	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age], ln[age]^2}	20,602.52 (233,778)	<0.0001
23	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age], ln[age]^2, year,…, year^3}	20,602.51 (233,775)	0.9998
24	Constant + ln[age] + ln[age]^2 + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age], ln[age]^2}	20,602.52 (233,778)	–

Unless otherwise stated, all *p* values refer to the improvement in fit of the model in a given row of the table over that in the row above. Optimal model is given at the bottom of the table

[a] *p* value for improvement in fit of model 8 versus model 3

[b] *p* value for improvement in fit of model 15 versus model 11

Table 11 Analysis of deviance of ischemic heart disease mortality

Model number	Model description	Deviance (*df*)	*p* value
1	Constant	19,962.28 (233,803)	–
2	Constant + ln[age]	17,622.59 (233,802)	<0.0001
3	Constant + ln[age] + ln[age]^2	17,621.53 (233,801)	0.3030
4	Constant + ln[age] + ln[age]^2 + ln[age]^3	17,618.35 (233,800)	0.0745
5	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4	17,618.32 (233,799)	0.8744
6	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + ln[age]^5	17,618.25 (233,798)	0.7828
7	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + ln[age]^5 + ln[age]^6	17,617.22 (233,797)	0.3111
8	Constant + ln[age] + sex	17,208.56 (233,801)	<0.0001[a]
9	Constant + ln[age] + sex + year	16,959.94 (233,800)	<0.0001
10	Constant + ln[age] + sex + year + year^2	16,935.89 (233,799)	<0.0001
11	Constant + ln[age] + sex + year + year^2 + year^3	16,929.17 (233,798)	0.0096
12	Constant + ln[age] + sex + year + year^2 + year^3 + year^4	16,928.68 (233,797)	0.4808
13	Constant + ln[age] + sex + year + year^2 + year^3 + year^4 + year^5	16,928.19 (233,796)	0.4839
14	Constant + ln[age] + sex + year + year^2 + year^3 + year^4 + year^5 + year^6	16,928.18 (233,795)	0.9563
15	Constant + ln[age] + sex + year + year^2 + year^3 + smoking	16,804.03 (233,796)	<0.0001[b]
16	Constant + ln[age] + sex + year + year^2 + year^3 + smoking + alcohol	16,770.13 (233,794)	<0.0001
17	Constant + ln[age] + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery	16,763.74 (233,792)	0.0410
18	Constant + ln[age] + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty	16,741.30 (233,790)	<0.0001
19	Constant + ln[age] + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy	16,729.41 (233,788)	0.0026
20	Constant + ln[age] + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort	16,725.24 (233,786)	0.1246
21	Constant + ln[age] + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type	16,715.12 (233,781)	0.0720
22	Constant + ln[age] + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × ln[age]	16,658.69 (233,780)	<0.0001
23	Constant + ln[age] + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age], year, …, year^3}	16,658.48 (233,777)	0.9761
24	Constant + ln[age] + sex + year + year^2 + year^3 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + TB type + sex × ln[age]	16,663.45 (233,782)	–

Unless otherwise stated, all *p* values refer to the improvement in fit of the model in a given row of the table over that in the row above. Optimal model is given at the bottom of the table

[a] *p* value for improvement in fit of model 8 versus model 2

[b] *p* value for improvement in fit of model 15 versus model 11

Table 12 Analysis of deviance of non-ischemic heart disease mortality

Model number	Model description	Deviance (*df*)	*p* value
1	Constant	7366.20 (233,803)	–
2	Constant + ln[age]	6665.48 (233,802)	<0.0001
3	Constant + ln[age] + ln[age]^2	6583.47 (233,801)	<0.0001
4	Constant + ln[age] + ln[age]^2 + ln[age]^3	6559.59 (233,800)	<0.0001
5	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4	6558.31 (233,799)	0.2577
6	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + ln[age]^5	6558.28 (233,798)	0.8769
7	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + ln[age]^5 + ln[age]^6	6553.72 (233,797)	0.0326
8	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex	6552.92 (233,799)	0.0098[a]
9	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year	6551.67 (233,798)	0.2647
10	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2	6483.65 (233,797)	<0.0001
11	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3	6483.65 (233,796)	0.9563
12	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4	6480.64 (233,795)	0.0829
13	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5	6471.74 (233,794)	0.0029
14	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + year^6	6471.47 (233,793)	0.6027
15	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + smoking	6454.44 (233,792)	0.0002[b]
16	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + smoking + alcohol	6431.96 (233,790)	<0.0001
17	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + smoking + alcohol + other lung surgery	6428.94 (233,788)	0.2215
18	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + smoking + alcohol + other lung surgery + thoracoplasty	6419.01 (233,786)	0.0070
19	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy	6416.42 (233,784)	0.2739
20	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort	6411.68 (233,782)	0.0934
21	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type	6396.62 (233,777)	0.0101
22	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age],…, ln[age]^3}	6391.00 (233,774)	0.1317
23	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age],…, ln[age]^3, year, …, year^5}	6385.20 (233,769)	0.3259
24	Constant + ln[age] + ln[age]^2 + ln[age]^3 + sex + year + year^2 + year^3 + year^4 + year^5 + smoking + alcohol + thoracoplasty + study cohort + TB type	6399.26 (233,781)	–

Unless otherwise stated, all *p* values refer to the improvement in fit of the model in a given row of the table over that in the row above. Optimal model is given at the bottom of the table

[a] *p* value for improvement in fit of model 8 versus model 3

[b] *p* value for improvement in fit of model 15 versus model 13

Table 13 Analysis of deviance of hypertensive heart disease mortality

Model number	Model description	Deviance (*df*)	*p* value
1	Constant	1469.58 (233,803)	<0.0001
2	Constant + ln[age]	1375.80 (233,802)	<0.0001
3	Constant + ln[age] + $\ln[age]^2$	1373.74 (233,801)	0.1510
4	Constant + ln[age] + $\ln[age]^2$ + $\ln[age]^3$	1372.71 (233,800)	0.3111
5	Constant + ln[age] + $\ln[age]^2$ + $\ln[age]^3$ + $\ln[age]^4$	1372.63 (233,799)	0.7680
6	Constant + ln[age] + $\ln[age]^2$ + $\ln[age]^3$ + $\ln[age]^4$ + $\ln[age]^5$	1371.48 (233,798)	0.2831
7	Constant + ln[age] + $\ln[age]^2$ + $\ln[age]^3$ + $\ln[age]^4$ + $\ln[age]^5$ + $\ln[age]^6$	1370.21 (233,797)	0.2600
8	Constant + ln[age] + sex	1374.38 (233,801)	0.2334[a]
9	Constant + ln[age] + year	1345.40 (233,801)	<0.0001
10	Constant + ln[age] + year + $year^2$	1331.55 (233,800)	0.0002
11	Constant + ln[age] + year + $year^2$ + $year^3$	1321.21 (233,799)	0.0013
12	Constant + ln[age] + year + $year^2$ + $year^3$ + $year^4$	1319.51 (233,798)	0.1911
13	Constant + ln[age] + year + $year^2$ + $year^3$ + $year^4$ + $year^5$	1317.96 (233,797)	0.2142
14	Constant + ln[age] + year + $year^2$ + $year^3$ + $year^4$ + $year^5$ + $year^6$	1317.05 (233,796)	0.3393
15	Constant + ln[age] + year + $year^2$ + $year^3$ + smoking	1316.86 (233,797)	0.1134[b]
16	Constant + ln[age] + year + $year^2$ + $year^3$ + smoking + alcohol	1311.78 (233,795)	0.0790
17	Constant + ln[age] + year + $year^2$ + $year^3$ + smoking + alcohol + other lung surgery	1311.68 (233,793)	0.9498
18	Constant + ln[age] + year + $year^2$ + $year^3$ + smoking + alcohol + other lung surgery + thoracoplasty	1304.13 (233,791)	0.0229
19	Constant + ln[age] + year + $year^2$ + $year^3$ + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy	1303.99 (233,789)	0.9333
20	Constant + ln[age] + year + $year^2$ + $year^3$ + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort	1300.08 (233,787)	0.1409
21	Constant + ln[age] + year + $year^2$ + $year^3$ + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type	1292.96 (233,782)	0.2124
22	Constant + ln[age] + sex + year + $year^2$ + $year^3$ + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × ln[age]	1291.51 (233,780)	0.4834
23	Constant + ln[age] + sex + year + $year^2$ + $year^3$ + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age], year, …, $year^3$}	1289.67 (233,777)	0.6069
24	Constant + ln[age] + year + $year^2$ + $year^3$ + alcohol + thoracoplasty	1310.12 (233,795)	–

Unless otherwise stated, all *p* values refer to the improvement in fit of the model in a given row of the Table over that in the row above. Optimal model is given at the bottom of the table

[a] *p* value for improvement in fit of model 8 versus model 2

[b] *p* value for improvement in fit of model 15 versus model 11

Table 14 Analysis of deviance of all circulatory disease mortality apart from heart disease and cerebrovascular disease

Model number	Model description	Deviance (*df*)	*p* value
1	Constant	3098.22 (233,803)	–
2	Constant + ln[age]	2724.37 (233,802)	<0.0001
3	Constant + ln[age] + ln[age]^2	2723.32 (233,801)	0.3069
4	Constant + ln[age] + ln[age]^2 + ln[age]^3	2722.53 (233,800)	0.3744
5	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4	2717.74 (233,799)	0.0286
6	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + ln[age]^5	2717.65 (233,798)	0.7592
7	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + ln[age]^5 + ln[age]^6	2717.30 (233,797)	0.5570
8	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex	2666.79 (233,798)	<0.0001[a]
9	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year	2638.89 (233,797)	<0.0001
10	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2	2636.39 (233,796)	0.1137
11	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3	2635.99 (233,795)	0.5276
12	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4	2635.89 (233,794)	0.7483
13	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + year^5	2632.17 (233,793)	0.0539
14	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + year^2 + year^3 + year^4 + year^5 + year^6	2632.17 (233,792)	0.9496
15	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + smoking	2622.52 (233,795)	0.0003[b]
16	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + smoking + alcohol	2621.84 (233,793)	0.7128
17	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + smoking + alcohol + other lung surgery	2621.65 (233,791)	0.9053
18	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + smoking + alcohol + other lung surgery + thoracoplasty	2620.31 (233,789)	0.5120
19	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy	2618.68 (233,787)	0.4429
20	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort	2617.34 (233,785)	0.5115
21	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type	2605.43 (233,780)	0.0360
22	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age], …, ln[age]^4}	2603.31 (233,776)	0.7139
23	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + smoking + alcohol + other lung surgery + thoracoplasty + pneumolobectomy + study cohort + TB type + sex × {ln[age], …, ln[age]^4, year}	2603.24 (233,775)	0.7973
24	Constant + ln[age] + ln[age]^2 + ln[age]^3 + ln[age]^4 + sex + year + smoking + TB type	2610.69 (233,790)	–

Unless otherwise stated, all *p* values refer to the improvement in fit of the model in a given row of the Table over that in the row above. Optimal model is given at the bottom of the table

[a] *p* value for improvement in fit of model 8 versus model 5

[b] *p* value for improvement in fit of model 15 versus model 9

Appendix 2: Effect of alternative background models selected via minimizing Akaike information criterion

In this appendix we consider an alternative set of explanatory background models for each endpoint, selected via an automatic variable selection process, by minimizing the Akaike information criterion (AIC) [24, 25]. Minimizing AIC is a standard method of variable selection that avoids over-parameterised (and therefore over-fitted) models. AIC penalizes against overfitting by adding 2 × [number of fitted parameters] to the model deviance. We used an iterative mixed-forward–backward stepwise procedure to minimize AIC using models with Poisson error via R [26].

The models used the set of candidate variables listed in Table 15, in which the optimal models chosen are also indicated. We provide the analog of Table 2 using these alternative background models in Table 16.

Table 15 Candidate variables for fits to various circulatory disease mortality endpoints in analysis using minimization of AIC to select the background model

Candidate variables	All circulatory disease	CeVD	All heart disease	IHD	Heart disease excluding IHD	Hypertensive heart disease	All circulatory apart from heart and cerebrovascular
ln[age]	X	X	X	X	X	X	X
$ln[age]^2$	X	X	X	X	X		X
$ln[age]^3$	X				X		X
$ln[age]^4$	X						X
$ln[age]^5$							
$ln[age]^6$		X	X				
sex	X		X	X	X		X
year	X	X	X	X		X	X
$year^2$	X	X	X	X	X	X	X
$year^3$				X	X		
$year^4$					X		
$year^5$	X	X	X		X	X	
$year^6$	X	X			X		
Smoking	X	X	X	X	X		X
Alcohol	X		X	X	X	X	
Other lung surgery		X					
Thoracoplasty	X		X	X	X		
Pneumolobectomy							
Study cohort	X		X	X	X		X
Tuberculosis type	X		X	X			
Sex × ln[age]	X		X	X	X		
Sex × $ln[age]^2$	X		X	X	X		
Sex × $ln[age]^3$							
Sex × $ln[age]^4$	X						X
Sex × $ln[age]^5$							
Sex × $ln[age]^6$							
Sex × year							
Sex × $year^2$							
Sex × $year^3$							
Sex × $year^4$							
Sex × $year^5$							
Sex × $year^6$					X		

The variables used for each circulatory disease endpoint are indicated by X

Table 16 Excess relative risks for circulatory disease mortality in the Massachusetts tuberculosis fluoroscopy cohort and modification by age at entry, years since entry, and dose rate, using alternative optimal models selected to minimize AIC as in Table 15

Model	ERR/Gy (+95 % CI)						
	All circulatory disease	CeVD	All heart disease	IHD	Heart disease excluding IHD	Hypertensive heart disease	All circulatory apart from heart and cerebrovascular
Linear ERR	−0.023 (−0.066, 0.027)	0.099 (−0.115, 0.378)	−0.044 (−0.089, 0.009)	−0.074 (−0.127[a], −0.010)	0.054 (−0.043, 0.178)	0.374 (−0.028, 1.040)	0.060 (−0.103, 0.315)
p value	0.3521	0.4008	0.1022	0.0256	0.3088	0.0747	0.5435
Linear ERR without background medical history adjustment	−0.008 (−0.053, 0.041)	0.124 (−0.092, 0.400)	−0.027 (−0.074, 0.027)	−0.062 (−0.116[a], 0.001)	0.046 (−0.048, 0.165)	0.374 (−0.028, 1.040)	0.033 (−0.114, 0.266)
p value	0.7269	0.2901	0.3120	0.0531	0.3687	0.0747	0.7216
Linear ERR adjusted for age at entry	−0.001 (−0.007[a], 0.005[a])	0.099 (−0.160[a], 0.359[a])	−0.044 (−0.094[a], 0.006[a])	−0.074 (−0.128[a], −0.020[a])	0.054 (−0.066[a], 0.177)	0.337 (−0.004, 0.985)	0.060 (−0.169[a], 0.289[a])
p value[b]	0.0927	0.9748	1.0000	0.9643	1.0000	0.6429	1.0000
Linear ERR adjusted for years since entry	−0.023 (−0.080[a], 0.022)	0.099 (−0.223[a], 0.421[a])	−0.044 (−0.104[a], 0.016[a])	−0.065 (−0.133[a], −0.004)	0.039 (−0.124[a], 0.202[a])	0.374 (−0.174[a], 0.921[a])	0.027 (−0.068, 0.250)
p value[b]	0.9748	0.9748	1.0000	0.5833	0.5801	0.9643	0.2169
Linear ERR adjusted for age at entry and years since entry	−0.001 (−0.007[a], 0.005[a])	0.099 (−0.267[a], 0.465[a])	−0.044 (−0.108[a], 0.020[a])	−0.067 (−0.137[a], 0.003[a])	0.034 (−0.122[a], 0.165)	0.338 (−0.274[a], 0.949[a])	0.032 (−0.147[a], 0.211[a])
p value[b]	0.2434	0.9995	1.0000	0.7835	0.8361	0.8981	0.4148
Linear ERR adjusted for dose rate	−0.023 (−0.073[a], 0.026[a])	0.139 (−0.101, 0.439)	−0.048 (−0.100[a], 0.004[a])	−0.078 (−0.133[a], −0.022[a])	0.028 (−2.151[a], 0.173)	0.186 (−7.519[a], 1.001)	0.038 (−1.790[a], 0.316)
p value[b]	0.2422	0.4543	0.2049	0.3149	0.6185	0.5519	0.9244

Unless otherwise indicated, all 95 % CI are profile-likelihood based, and all *p* values are 2-sided

[a] Wald-based CI

[b] *p* value for modification of linear ERR coefficient by indicated variate

Appendix 3: Generalized additive models (GAM)

See Table 17.

Table 17 GAM fitted to circulatory disease mortality in the Massachusetts tuberculosis fluoroscopy cohort

Model	Excess absolute risk (EAR)/10^4 person year Gy (+95 % CI)						
	All circulatory disease	CeVD	All heart disease	IHD	Heart disease excluding IHD	Hypertensive heart disease	All circulatory apart from heart and cerebrovascular
Linear EAR	−0.380 (−1.849[a], 0.679)	0.597 (−0.601[a], 2.210)	−0.180 (−1.600[a], 0.589)	0.313 (−0.566[a], 1.428)	0.000 (−0.938[a], 0.726)	0.230 (−0.195[a], 0.867)	–[b]
p value	0.2919	0.3401	0.3778	0.4183	1.0000	0.2755	–[b]
Linear ERR without background medical history adjustment	−0.323 (−1.754[a], 0.977)	0.584 (−0.611[a], 2.181)	−0.137 (−1.521[a], 0.730)	0.359 (−0.548[a], 1.498)	–[b]	0.285 (−0.169[a], 0.964)	–[b]
p value	0.4405	0.3364	0.4862	0.3370	–[b]	0.2359	–[b]

Unless otherwise indicated, all 95 % CI are profile-likelihood based, and all *p* values are 2-sided. The background models used are the optimal models indicated in Tables 8, 9, 10, 11, 12, 13 and 14

[a] Wald-based CI

[b] Non-convergence

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