

**Supplementary Appendix.**

**Table S1. Estimated excess relative risk of circulatory disease in various therapeutically and diagnostically exposed groups, exposed at high doses, with mean dose generally > 0.5 Gy. All data are in relation to underlying cause of death, unless otherwise indicated.**

Study	Reference	Average Dose to Heart (Gy) (mean, range)	Persons (person years of follow-up)	Endpoint (mortality unless otherwise indicated)	Excess relative risk Gy <sup>-1</sup> (95% CI)
<b>Therapeutically treated groups</b>					
US Childhood Cancer Survivor Study	Mulrooney <i>et al</i> (Mulrooney et al. 2009)	NA (<5 - >35)	14,358 (NA)	Congestive heart failure incidence	0.084 (0.062, 0.106) <sup>a</sup>
				Myocardial infarction incidence	0.062 (0.040, 0.084) <sup>a</sup>
				Pericardial disease incidence	0.091 (0.068, 0.115) <sup>a</sup>
				Valvular heart disease incidence	0.109 (0.091, 0.127) <sup>a</sup>
French-UK childhood cancer study	Tukenova <i>et al</i> (Tukenova et al. 2010)	11.1 <sup>b</sup> (<1 - >15)	4122 (NA)	All cardiac disease	0.6 (0.2, 2.5)
Institut Gustave Roussy childhood cancer cardiac study	Haddy <i>et al</i> (Haddy et al. 2016)	7.5 (<1 - >15)	3162 (82,200)	Cardiac disease (ICD9 391, 393-397, 410-413, 420, 423-424, 426-428; ICD10 I05-I09, I20-I25, I30-I32, I44-I50): without anthracyclines	0.49 (0.26, 1.3)
				Cardiac disease: with anthracyclines	0.07 (0.03, 0.13)
Institut Gustave Roussy childhood cancer stroke study	El-Fayech <i>et al</i> (El-Fayech et al. 2017)	7.7 (0 - >40)	3172 (82,500)	All stroke (ICD9 430-439)	0.24 (0.11, 0.53)
				Ischemic stroke	0.42 (0.16, 1.20)
Peptic ulcer study	Little <i>et al</i> (Little et al. 2012)	1.01 (0.0 - 6.20)	3600 (76,571.7)	Ischemic heart disease ICD9 410-414 using heart dose	0.102 (0.039, 0.174)
				Ischemic heart disease ICD9 410-414 using thyroid dose	1.696 (0.651, 2.907)
				Ischemic heart disease ICD9 410-414 using kidney dose	0.033 (0.012, 0.056)
				Ischemic heart disease ICD9 410-414 using pancreas dose	0.020 (0.008, 0.035)
				Cerebrovascular disease ICD9 430-438 using heart dose	0.028 (-0.085, 0.186)
				Cerebrovascular disease ICD9 430-438 using thyroid dose	0.422 (-1.455, 3.039)
				Cerebrovascular disease ICD9 430-438 using brain dose	2.649 (-8.912, 18.740)
				All other circulatory disease ICD9 390-409, 415-429, 439-459 using heart dose	0.050 (-0.053, 0.194)

				All circulatory disease ICD9 390-459 using heart dose	0.082 (0.031, 0.140)
Nordic breast cancer case-control study	Darby <i>et al</i> (Darby et al. 2013)	4.9 (0.03 – 27.72) <sup>c</sup> 3.9 (0.1 – 30.4) <sup>d</sup>	963 cases, 1205 controls	Ischemic heart disease incidence ICD10 I20-I25	0.074 (0.029, 0.145) <sup>c</sup> 0.084 (0.036, 0.159) <sup>d</sup>
Netherlands Hodgkin lymphoma valvular disease case-control study	Cutter <i>et al</i> (Cutter et al. 2015)	30.7 <sup>e</sup> (0 – >40)	89 cases, 200 controls	Valvular heart disease incidence	0.141 (0.024, 1.013) <sup>d,t</sup>
Netherlands Hodgkin lymphoma heart disease case-control study	van Nimwegen <i>et al</i> (van Nimwegen et al. 2016)	20.4 <sup>g</sup> (0 – >35)	325 cases, 1204 controls	Coronary heart disease incidence	0.074 (0.033, 0.148) <sup>d</sup>
Netherlands Hodgkin lymphoma heart failure case-control study	van Nimwegen <i>et al</i> (van Nimwegen et al. 2017)	20.9 (0 – >33)	91 cases, 278 controls	Heart failure CTCAE grades 3-4	0.038 (-0.001, 0.146) <sup>h</sup>
Netherlands breast cancer case-control study	Jacobse <i>et al</i> (Jacobse et al. 2019)	8.5 (4.3 – 15.0)	183 cases, 183 controls	Myocardial infarction incidence	0.064 (0.013, 0.160)
<b>Diagnostically exposed groups</b>					
Canadian and Massachusetts TB fluoroscopy cohorts	Tran <i>et al</i> (Tran et al. 2017)	0.18 (0, 0.50) [ $<0.5$ Gy] / 1.16 (0, 27.77) [total]	77,275 (1,945,041)	All circulatory disease ICD9 390-459 All circulatory disease ICD9 390-459: $<0.5$ Gy Ischemic heart disease ICD9 410-414 Ischemic heart disease ICD9 410-414: $< 0.5$ Gy Cerebrovascular disease ICD9 430-438 Cerebrovascular disease ICD9 430-438: $< 0.5$ Gy Hypertensive heart disease ICD9 401-405 Hypertensive heart disease ICD9 401-405: $< 0.5$ Gy Heart disease apart from hypertensive and IHD ICD9 390-400, 406-410 Heart disease apart from hypertensive and IHD ICD9 390-400, 406-410: $< 0.5$ Gy All circulatory disease apart from heart and cerebrovascular ICD9 439-459 All circulatory disease apart from heart and cerebrovascular ICD9 439-459: $< 0.5$ Gy	-0.024 (-0.042, -0.005) <sup>i</sup> 0.246 (0.036, 0.469) <sup>i</sup> -0.037 (-0.060, -0.013) <sup>i</sup> 0.268 (0.003, 0.552) <sup>i</sup> -0.014 (-0.067, 0.044) <sup>i</sup> 0.441 (-0.119, 1.090) <sup>i</sup> -0.035 (-0.152, 0.153) <sup>i</sup> 1.121 (-0.351, 3.228) <sup>i</sup> -0.010 (-0.064, 0.043) <sup>i</sup> -0.226 (-0.679, 0.307) <sup>i</sup> 0.055 (-0.028, 0.164) <sup>i</sup> 0.507 (-0.322, 1.541) <sup>i</sup>

<sup>a</sup>estimate derived by fitting a linear model by weighted least squares, applied to the aggregate data provided in Table 5 of Mulrooney *et al.* (Mulrooney et al. 2009). Average cardiac doses of 0, 2.5, 10, 25, and 40 Gy were assumed for the respective groups with the following specified ranges of cardiac doses: 0, 0-4, 5-14, 15-34 Gy,  $\geq 35$  Gy.

<sup>b</sup>mean dose to heart in 21 persons who died of cardiovascular disease.

<sup>c</sup>cumulative mean dose to heart.

<sup>d</sup>equivalent dose to heart in 2 Gy fractions (EQD2).

<sup>e</sup>mean EQD2 dose to heart valves in controls.

<sup>f</sup>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* (Cutter et al. 2015): see Appendix A.

<sup>g</sup>mean EQD2 dose to heart in controls.

<sup>h</sup>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,  $\geq 31$  Gy mean heart dose groups given in Table 2 of van Nimwegen *et al* (van Nimwegen et al. 2017).

<sup>i</sup>based on 5-year lagged lung dose.

**Table S2. Estimated excess relative risks of circulatory disease in the Japanese atomic bomb survivors and in other groups with moderate- or low-dose radiation exposure, with mean dose generally < 0.5 Gy.** (Adapted from Little and Lipshultz (Little and Lipshultz 2015). All data are in relation to underlying cause of death, unless otherwise indicated.

Cohort/Study	Reference	Mean (range) heart/brain dose, Gy	Persons (person years of follow-up)	Endpoint (mortality unless otherwise indicated)	Excess relative risk Gy <sup>-1</sup> (95% CI)
<b>Japanese atomic bomb survivors</b>					
Japanese atomic bomb survivors 1950-2008	Takahashi <i>et al.</i> (Takahashi et al. 2017)	0.1 (0 - 4) <sup>a</sup>	86,600 (3,462,847)	Heart disease (ICD10 I05–I08, I09.1, I11, I13, I20–25, I34–I39, I50) overall	0.140 (0.060, 0.220)
				Ischemic heart disease (ICD10 I20-I25)	0.030 (-0.080, 0.150)
				Myocardial infarction (ICD10 I21-I23)	0.020 (-0.130, 0.200)
				Other ischemic heart disease (ICD10 I20, I24-I25)	0.040 (-0.120, 0.220)
				Valvular heart disease (ICD10 I05–I08, I09.1, I34–I39)	0.450 (0.130, 0.850)
				Rheumatic valvular heart disease (ICD10 I05–I08, I09.1)	0.960 (0.280, 1.920)
				Non-rheumatic valvular heart disease (I34–I39)	0.240 (-0.080, 0.680)
				Hypertensive organ damage (ICD10 I11-I13)	0.360 (0.100, 0.680)
Heart failure (ICD10 I50)	0.210 (0.070, 0.370)				
Japanese atomic bomb survivors	Yamada <i>et al.</i> (Yamada et al. 2004)	0.1 (0 - 4) <sup>b</sup>	10,339 (n.a.)	Hypertension incidence, 1958-1998 (ICD9 401)	0.05 (-0.01, 0.10) <sup>c</sup>
				Hypertensive heart disease incidence, 1958-1998 (ICD9 402, 404)	-0.01 (-0.09, 0.09) <sup>c</sup>
				Ischemic heart disease incidence, 1958-1998 (ICD9 410-414)	0.05 (-0.05, 0.16) <sup>c</sup>
				Myocardial infarction incidence, 1964-1998 (ICD9 410)	0.12 (-0.16, 0.60) <sup>c</sup>
				Occlusion incidence, 1958-1998 (ICD9 433, 434)	0.06 (-0.11, 0.30) <sup>c</sup>
				Aortic aneurysm incidence, 1958-1998 (ICD9 441, 442)	0.02 (-0.22, 0.41) <sup>c</sup>
				Stroke incidence, 1958-1998 (ICD9 430, 431, 433, 434, 436)	0.07 (-0.08, 0.24) <sup>c</sup>
<b>Occupational studies</b>					
Mayak workers	Moseeva <i>et al.</i> (Moseeva et al. 2014)	0.62 ± 0.80 (males) <sup>d</sup> 0.51 ± 0.68 (females) <sup>d</sup>	22,377 (447,281)	Ischemic heart disease morbidity (ICD9 410-414)	0.14 (0.08, 0.21) <sup>e</sup>
				Ischemic heart disease morbidity (ICD9 410-414)	0.14 (0.08, 0.21) <sup>f</sup>
	Azizova <i>et al.</i> (Azizova et al. 2015)	18,856 (341,663)	Ischemic heart disease morbidity (ICD9 410-414)	0.16 (0.10, 0.24) <sup>g</sup>	
			Ischemic heart disease mortality (ICD9 410-414)	0.05 (-0.01, 0.13) <sup>e</sup>	
			Ischemic heart disease mortality (ICD9 410-414)	0.05 (-0.01, 0.13) <sup>f</sup>	
			Ischemic heart disease mortality (ICD9 410-414)	0.05 (-0.01, 0.13) <sup>g</sup>	
			Cerebrovascular disease morbidity (ICD9 430-438)	0.497 (0.393, 0.601) <sup>e</sup>	
			Cerebrovascular disease morbidity (ICD9 430-438)	0.529 (0.415, 0.642) <sup>f</sup>	
	18,856 (272,525)	Cerebrovascular disease morbidity (ICD9 430-438)	0.572 (0.450, 0.695) <sup>g</sup>		
		Cerebrovascular disease mortality (ICD9 430-438)	0.057 (-0.046, 0.161) <sup>e</sup>		
	Cerebrovascular disease mortality (ICD9 430-438)	0.064 (-0.042, 0.170) <sup>f</sup>			
	Cerebrovascular disease mortality (ICD9 430-438)	0.076 (-0.033, 0.186) <sup>g</sup>			

Mayak nuclear workers lower extremity arterial disease	Azizova <i>et al.</i> (Azizova et al. 2016)	0.51 ± 0.72	22,377 (512,801)	Lower extremity arterial disease morbidity (ICD9 440.2)	0.27 (0.11, 0.48)
Mayak part of combined nuclear worker study	Azizova <i>et al.</i> (Azizova et al. 2018)	0.52 (0, 8.4)	22,734 (842,538)	Circulatory disease (ICD10 I00-I99)	0.04 (-0.00, 0.09)
				Ischemic heart disease (ICD10 I20-I25)	0.06 (0.01, 0.13)
Sellafield part of combined nuclear worker study	Azizova <i>et al.</i> (Azizova et al. 2018)	0.07 (0, 1.88)	23,443 (602,311)	Circulatory disease (ICD10 I00-I99)	0.42 (0.12, 0.78)
				Ischemic heart disease (ICD10 I20-I25)	0.53 (0.14, 1.00)
				Cerebrovascular disease (ICD10 I60-I69)	0.05 (-0.46, 0.79)
3 <sup>rd</sup> Analysis of UK National Registry for Radiation Workers	Muirhead <i>et al.</i> (Muirhead et al. 2009)	0.0249 (<0.01 - >0.4)	174,541 (3.9 x 10 <sup>6</sup> )	All circulatory disease (ICD9 390-459)	0.251 (-0.01, 0.54) <sup>f</sup>
				Circulatory disease not strongly related to smoking (ICD9 390-409, 415-440, 442-459)	0.280 (-0.19, 0.85) <sup>f</sup>
				Aortic aneurysm (ICD9 441)	-0.132 (-1.29, 1.92) <sup>f</sup>
				Ischemic heart disease (ICD9 410-414)	0.259 (-0.05, 0.61) <sup>f</sup>
				Cerebrovascular disease (ICD9 430-438)	0.161 (-0.42, 0.91) <sup>f</sup>
French nuclear workers	Leuraud <i>et al.</i> (Leuraud et al. 2017)	0.0184 ± 0.0407	59,004 (1,469,949)	Circulatory disease (ICD10 G45, I00-I99)	0.31 (-0.71, 1.52)
				Ischemic heart disease (ICD10 I20-I25)	1.06 (-0.62, 3.23)
				Cerebrovascular disease (G45.0–G45.2, G45.8–G45.9, I60-I69)	0.65 (-1.65, 4.01)
French nuclear fuel cycle workers	Zhivin <i>et al.</i> (Zhivin et al. 2018)	0.002 (0, <0.027)	102 cases and 416 controls	Circulatory disease (ICD10 I00-I99)	10 (-20, 40)
			44 cases	Ischemic heart disease (ICD10 I20-I25)	0 (-50, 40)
			31 cases	Cerebrovascular disease (ICD10 I60-I69)	-10 (-50, 30)
				Cerebrovascular disease (ICD10 I60-I69)	0.00 (-0.06, 0.08)
French uranium miners case-control study	Drubay <i>et al.</i> (Drubay et al. 2015)	0.0434 (0 - 0.471)	76 cases, 237 counter-matched controls	All circulatory disease (ICD10 I00-I99)	0.4 (-1.6, 2.9) <sup>h</sup>
				Ischemic heart disease (ICD10 I20-I25)	-1.0 (-3.9, 3.3) <sup>h</sup>
				Cerebrovascular disease (ICD10 I60-I69)	2.4 (-0.6, 11.4) <sup>h</sup>
German uranium miner study	Kreuzer <i>et al.</i> (Kreuzer et al. 2013)	0.047 (0.0002 – 0.909)	58,982 (2,180,639)	All circulatory disease (ICD10 I00-I99)	-0.13 (-0.38, 0.12) <sup>f</sup>
				Ischemic heart disease (ICD10 I20-I25)	-0.03 (-0.38, 0.32) <sup>f</sup>
				Cerebrovascular disease (ICD10 I60-I69)	0.44 (-0.16, 1.04) <sup>f</sup>
US nuclear workers	Schubauer-Berigan <i>et al.</i> (Schubauer-Berigan et al. 2015)	0.0202 (0 - >0.6)	119,195 (2,664,782)	Cardiovascular disease (ICD9 390-398, 402, 404, 410-414, 420-429)	2.6 (-25, 32) <sup>f</sup>
Chernobyl emergency workers	Kashcheev <i>et al.</i> (Kashcheev et al.)	0.161 (0.0001 - 1.24)	53,772 (958,540.5)	Cerebrovascular disease (ICD10 I60-I69) morbidity after no diabetes	0.35 (0.18, 0.53)

	2016)			Cerebrovascular disease (ICD10 I60-I69) morbidity after diabetes	1.29 (0.63, 1.94)
				Cerebrovascular disease (ICD10 I60-I69) morbidity after no atherosclerosis	0.43 (0.25, 0.62)
				Cerebrovascular disease (ICD10 I60-I69) morbidity after atherosclerosis	0.50 (0.09, 0.90)
				Cerebrovascular disease (ICD10 I60-I69) morbidity after no hypertensive disease	0.38 (0.08, 0.68)
				Cerebrovascular disease (ICD10 I60-I69) morbidity after hypertensive disease	0.48 (0.27, 0.68)
				Cerebrovascular disease (ICD10 I60-I69) morbidity after no IHD	0.41 (0.14, 0.68)
				Cerebrovascular disease (ICD10 I60-I69) morbidity after IHD	0.47 (0.25, 0.69)
				Cerebrovascular disease (ICD10 I60-I69) morbidity after no concomitant disease	0.19 (-0.99, 1.37)
				Cerebrovascular disease (ICD10 I60-I69) morbidity	0.45 (0.28, 0.62)
Chernobyl emergency workers	Kashcheev <i>et al</i> (Kashcheev et al. 2017)	0.161 (0.0001, 1.42)	53,772 (940,204.5)	Circulatory disease (ICD10 I00-I99)	0.44 (0.16, 0.74)
International Nuclear Workers Study (INWORKS)	Gillies <i>et al</i> (Gillies et al. 2017)	0.0252 (0, 1.932)	308,297 (8.2 x 10 <sup>6</sup> )	Circulatory disease (ICD10 I00-I99)	0.22 (0.08, 0.37) <sup>i</sup>
				Ischemic heart disease (I20-I25)	0.18 (0.004, 0.36) <sup>i</sup>
				Acute myocardial infarction (I21)	0.26 (0.03, 0.51) <sup>i</sup>
				Chronic ischemic heart disease (I25)	0.07 (-0.19, 0.36) <sup>i</sup>
				Cerebrovascular disease (I60-I69)	0.50 (0.12, 0.94) <sup>i</sup>
<b>Environmental studies</b>					
Techa River study	Krestinina <i>et al.</i> (Krestinina et al. 2013)	0.035 (0-0.51) <sup>k</sup>	29,735 (901,563)	All circulatory disease mortality (ICD9 390-459)	0.18 (-0.13, 0.52) <sup>j, e</sup>
				All circulatory disease mortality (ICD9 390-459)	0.24 (-0.08, 0.59) <sup>j, f</sup>
				All circulatory disease mortality (ICD9 390-459)	0.36 (0.02, 0.75) <sup>j, g</sup>
				Ischemic heart disease mortality (ICD9 410-414)	0.26 (-0.22, 0.81) <sup>j, e</sup>
				Ischemic heart disease mortality (ICD9 410-414)	0.40 (-0.11, 0.99) <sup>j, f</sup>
				Ischemic heart disease mortality (ICD9 410-414)	0.56 (0.01, 1.19) <sup>j, g</sup>
Semipalatinsk nuclear test study	Grosche <i>et al.</i> (Grosche et al. 2011)	0.09 (0-0.63)	19,545 (582,656)	Heart disease (ICD9 410-429): all settlements	3.22 (2.33, 4.10) <sup>f</sup>
				Heart disease (ICD9 410-429): exposed settlements	0.06 (-0.39, 0.52) <sup>f</sup>
				Stroke (ICD9 430-438): all settlements	2.96 (1.77, 4.14) <sup>f</sup>
				Stroke (ICD9 430-438): exposed settlements	-0.06 (-0.65, 0.54) <sup>f</sup>
				Cardiovascular disease (ICD9 390-459): all settlements	3.15 (2.48, 3.81) <sup>f</sup>
				Cardiovascular disease (ICD9 390-459): exposed settlements	0.02 (-0.32, 0.37) <sup>f</sup>

CI, Confidence Interval; ICD, International Classification of Diseases

<sup>a</sup> Analysis based on colon dose.

<sup>b</sup> Analysis using underlying or contributing cause of death.

<sup>c</sup> Analysis based on stomach dose, derived from Table 3 of Yamada *et al.* (Yamada et al. 2004) with smoking and drinking in the stratification.

<sup>d</sup> Risk estimates in relation to cumulative whole body external gamma dose; doses given here are from Moseeva *et al.* (Moseeva et al. 2014).

<sup>e</sup> Assuming a lag period of 5 years.

<sup>f</sup> Assuming a lag period of 10 years.

<sup>g</sup> Assuming a lag period of 15 years.

<sup>h</sup> Assuming a lag period of 0 years.

<sup>i</sup> 90% CI

<sup>j</sup> Analysis based on dose to muscle.

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