WEB MATERIAL

Flexible Modeling of the Association Between Cumulative Exposure to Low-Dose Ionizing Radiation from Cardiac Procedures and Risk of Cancer in Adults with Congenital Heart Disease

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Web Appendix 1: Imputation of the total effective dose

Because procedure-specific delivered doses were not routinely collected in the Quebec Congenital Heart Disease Database, an effective dose for each low-dose ionizing radiation (LDIR) procedure had to be imputed, based on the typical effective dose (in milli-Sieverts (mSv)) reported in the literature[1-5], as reported previously[6]. However, it should be recognized that the actual LDIR dose may vary by sex, age, type of radiation, and exposed organ[7].

Web Appendix 2: Data manipulation

To avoid the immortal time bias issue, a data manipulation was carried out allowing all subjects to have an opportunity to have events observed at any time after January 1, 1995. Indeed, people born after 1977 (aged <18 years on January 1, 1995) have an immortal time bias period between January, 1, 1995, and the date of their 18th birthday, which corresponds to inclusion in the cohort (only adult subjects). To address this issue, their follow-up was shifted so that the "new" date of inclusion became January 1, 1995. The only drawback of this data manipulation is that, for this subgroup, some LDIR exposures at the beginning of the original follow-up may have been lost.

To illustrate this data manipulation, let's suppose that a patient was born in 1980 and, thus, turned 18 years old in 1998. The Quebec Congenital Heart Disease Database allows us to establish LDIR exposures from 1983 to 2009, and (as stated in the sub-section "Data Sources" in Methods section of the main article) the follow-up started in January 1995, but – for this patient – the potentially observed outcome is limited to cancer diagnosed in 1998 or later. Together, these facts imply that between 1995 and 1998, there is an immortal time bias for this patient, since he could not experience the event between these 2 dates. The data manipulation consisted in shifting all dates toward the past, by 3 years in this case, as if the patient turned 18 in 1995 and could start to be at risk at this time point. For example, if the patient developed a cancer in 2000, this data would be shifted to 1997 but his age at the cancer diagnosis would be also shifted by 3 years and, thus, would be correctly defined as 20 (2000 minus 1980). The LDIR exposures would be similarly manipulated, so that the true temporal relationship between exposures and the event would be unaffected. With this data manipulation, there is no more immortal time bias. However, exposures

that truly occurred between 1983 and 1986 were shifted to 1980-1983 and, therefore, disregarded in the analyses.

To account for the aforementioned data manipulation, the covariate *year of birth* was included in all analyses.

Web Appendix 3: Details of outcome ascertainment

Details of incident cancer ascertainment were reported in the work of Cohen et al.[6]

Incident cancer was defined as the first outpatient diagnosis of primary specified cancer confirmed by inpatient data occurring during the observation period from January 1, 1995, to December 31, 2009. Primary specified cancers were ascertained by ICD-9 codes before 2006 and by the corresponding ICD-10 codes thereafter, and categorized based on site of location as previously published. Confirmation of the cancer diagnosis and site by inpatient data was required to increase the accuracy of cancer identification. Moreover, defining cases using inpatient data as a diagnostic criterion is consistent with the Québec Cancer Registry, which used hospitalization and day surgery records to identify cases before 2011. To validate the outcomes, 2 congenital heart disease (CHD) specialists (S.C. and A.J.M.) conducted manual audits of life-long records from randomly generated patient samples (5% of all patients with at least one ICD code of cancer) to detect and correct potential discrepancies between the different data sources. As a result, 85% of cancer diagnoses identified using inpatient database were confirmed by outpatient database and were included in the study. Secondary cancers were excluded. To exclude prevalent cases, we excluded patients for whom there was evidence of prior diagnosis of cancer before entering the study. We defined such evidence as admission to hospital with a primary or secondary diagnosis of cancer, or any outpatient visit with a diagnosis of cancer. Since the Quebec CHD database contains medical records from 1983, we considered the years 1983-1994 as a washout period to exclude potential prevalent cases. Thus, any patients with a diagnosis of cancer before 1995 were excluded from the study.

Web Appendix 4: Estimation of the hazard ratio for different exposure patterns

The (separate) weight functions $\widehat{w}(u-t)$for each of the 2 events, defined in equation 1 in the main article, are estimated, together with the effects of all covariates, by fitting our multivariable competing risks weighted cumulative exposure (WCE) model defined in text equation 2[8].

The shape of the estimated weight function describes how the relative impact of past exposures (e.g. logarithms of LDIR doses) on the current hazard of the event of interest, at time *u* during follow-up, changes depending on the time elapsed since exposure (*u*-*t*), with higher values indicating higher impact.

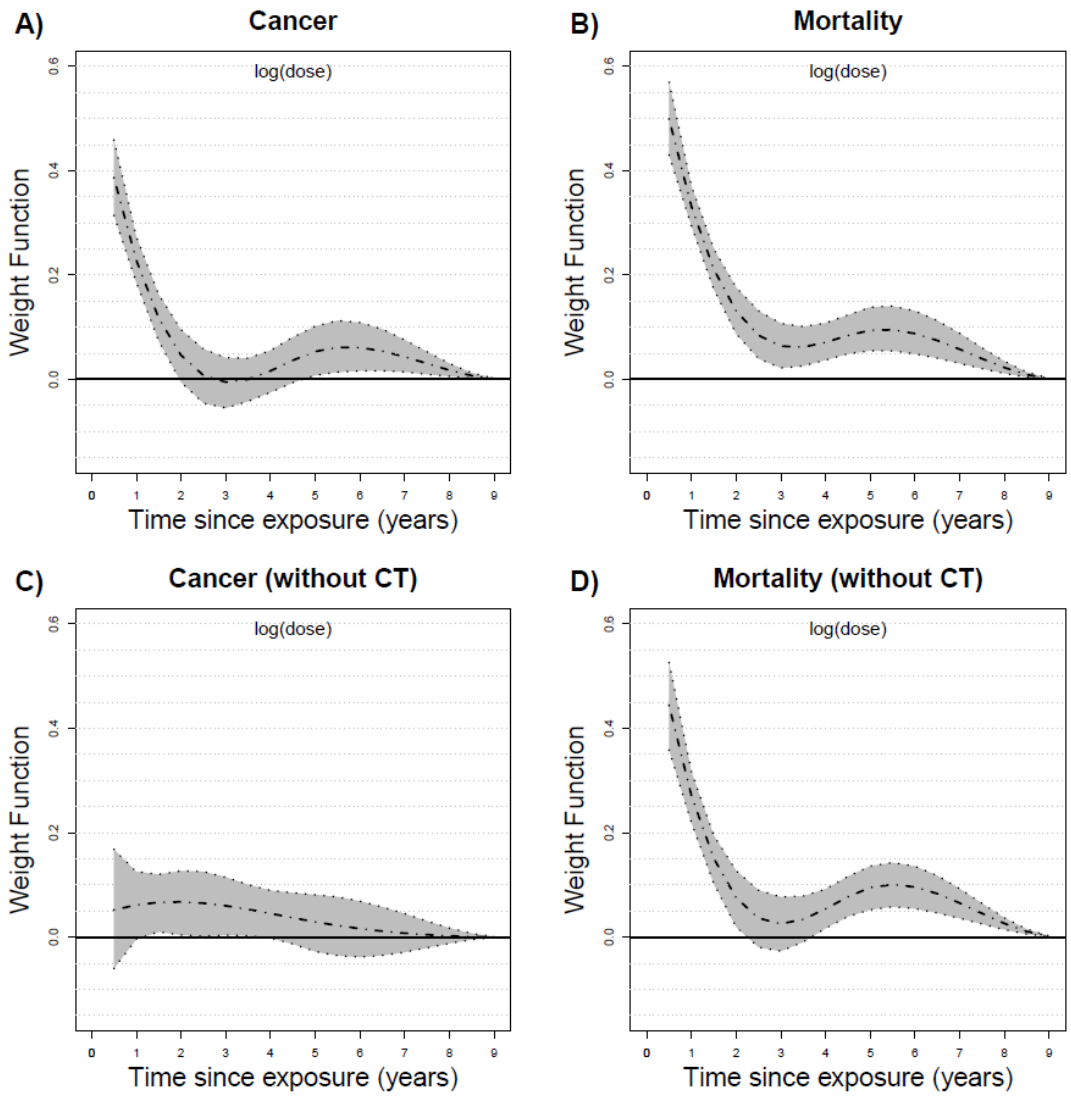
Equation 2 in the main article implies that the adjusted log hazard ratio (log HR) for the cumulative effect of past exposures/doses varies depending on both the intensity (e.g. dose *X(t)*) and timing (*u*-*t*) of past exposures. Calculations necessary to reconstruct the log HR corresponding to a specific exposure history involve 2 steps:

1. First, for each time *t* in the relevant time window $u\text{-}a < t \leq u$, the value of exposure received at that time, *X(t)*, is multiplied by the corresponding value of the estimated weight function $\widehat{w}(u-t)$.
2. Then, the resulting products are summed up across all times $u\text{-}a < t \leq u$ to calculate the value of the resulting log HR for the cumulative exposure effect[8].

Web Appendix 5: Results of preliminary unlagged analyses

Preliminary analyses did not include the exposure lag, which was applied to minimize the risk of reverse causality bias, i.e. that these analyses accounted for all past exposures, including the most recent ones. The main goal was to illustrate how flexible WCE modeling may help detect reverse causality bias. Bold dot-dashed curves in Web Figures 1A and 1B show the right-constrained 9-year weight functions respectively for cancer incidence and all-cause mortality, with their 95% confidence intervals (CIs). The high positive values in the left tails of both curves suggest important increases of the hazards of both events associated with LDIR exposures (represented by the logarithm of dose, as in the final analyses reported in the main article) from the past 2 years. However, the seemingly harmful effect of recent LDIR exposures on the cancer

risk (positive weights) may largely reflect the reverse causality bias where some diagnostic radiation procedures, especially computed tomography (CT) scans of the chest, were administered *because* of early cancer symptoms[9-10]. Indeed, excluding CT scans from the count of LDIR procedures eliminated this acute association of cancer incidence with most recent LDIR exposures (Web Figure 1C). However, LDIR exposures, other than CT scans, from about 1 to 4 years ago, unlikely to be related to early cancer symptoms, were still associated with increased cancer incidence (Web Figure 1C). In contrast, the exclusion of CT scans barely changed the results for all-cause mortality (Web Figure 1D vs. Web Figure 1B), which was expected, as CT scans of the chest are unlikely to be ordered because of symptoms of most life-threatening conditions other than cancers. However, the associations of recent LDIR exposures with all-cause mortality is probably almost entirely due to reverse causality bias reflecting the trend for sicker patients, with more severe CHD and/or serious comorbidities, to (i) require more diagnostic procedures, especially in the last phase of their life, and (ii) have a higher risk of mortality.



Web Figure 1. Results of preliminary unlagged analyses that accounted for all LDIR exposures (log doses, as in our final model) received in the past 9 years, including those from the last 2 years. It presents the estimated weight functions (bold dot-dashed lines) and pointwise 95% bootstrap confidence intervals (doted lines) for the associations between LDIR exposures and, respectively, A) cancer incidence and B) all-cause mortality, when CT scans were included in the calculation of LDIR doses, and C) cancer incidence and D) all-cause mortality when CT scans were excluded. CT, computed tomography; LDIR, low-dose ionizing radiation.

Web Appendix 6: Comparison of the 3 alternative ways of measuring time-varying LDIR exposure

We compared 3 alternative ways of measuring time-varying LDIR exposure $X(t)$ in consecutive 6-month intervals: 1) the total number of LDIR procedures, ignoring their doses; 2) the total dose of all corresponding procedures; and 3) the logarithm of the total dose.

Web Table 1 shows the corresponding Akaike information criterion (AIC) values for the WCE models accounting for the competing risk of mortality, with the 9-year time window (selected time window, Web Appendix 7), using the alternative exposure definitions. Lower AIC values indicate a better fit of the model to the data, with differences of 10 or more AIC points considered important[11]. Because using the log-transformed dose systematically improved the WCE model's fit to data relative to the other 2 exposure measures (Web Table 1), all results presented in the main article rely on the log-dose. For example, for the right-constrained WCE model in the lagged analyses (model 2 in Web Table 1, corresponding to the final model in the main article), the log-dose model yielded a AIC lower by about 16 and 23 points than the equivalent models with exposure defined as, respectively, the untransformed dose and the number of procedures.

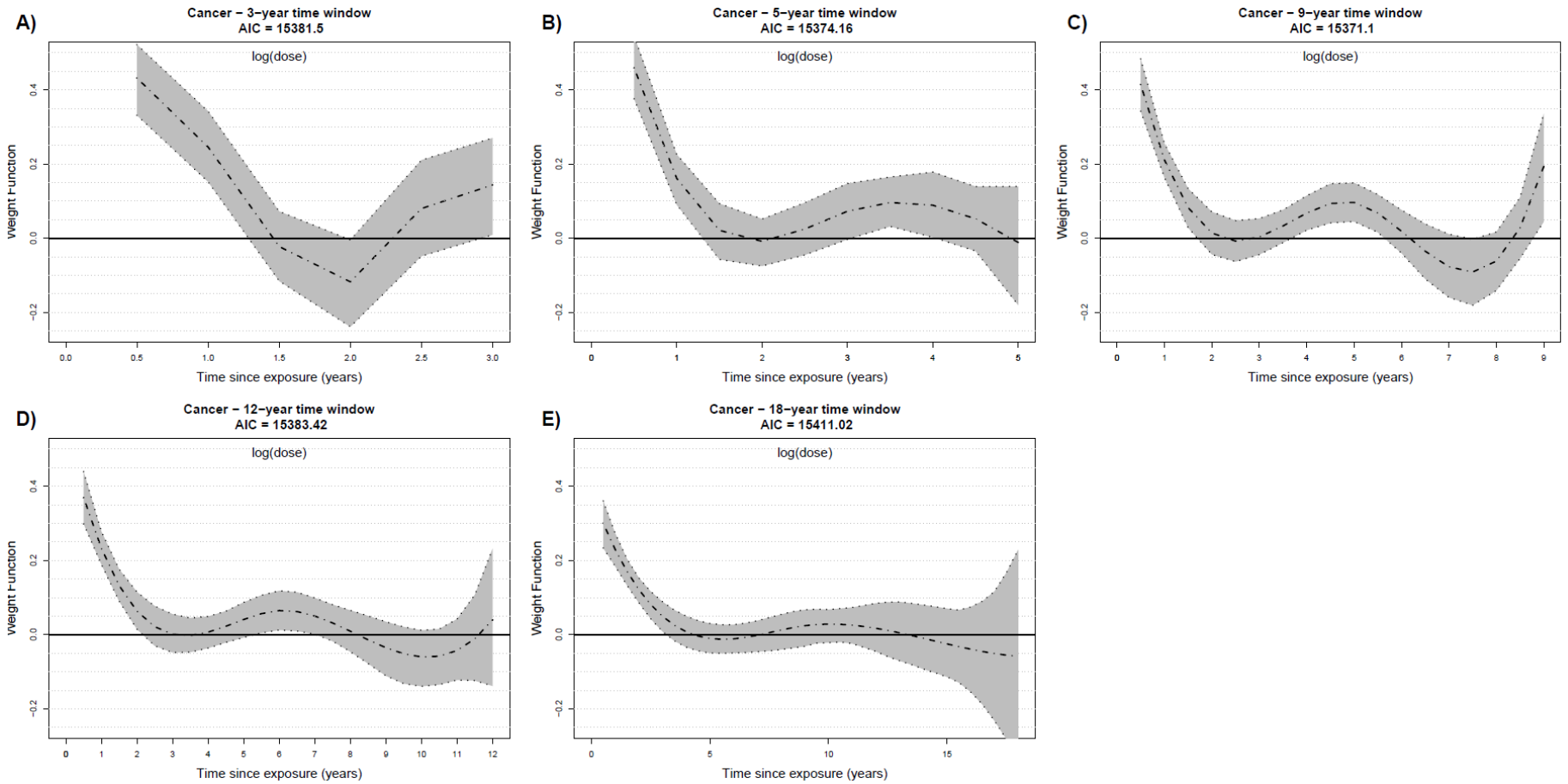
Web Table 1. Comparison of the performance of the WCE model with 9-year time window using different exposure definitions (Quebec Congenital Heart Disease Database, 1995-2010). The last column indicates the corresponding AIC values for the 4 alternative models (1-4) for each of the 3 exposure definitions. Results for the model 2 (lagged analyses with the right-constrained weight function), corresponding to our final model, are highlighted.

Exposure Definition	Model	AIC
No. of procedures	1. Constrained – no lag	15,601.9
	2. Constrained – lag	15,793.2
	3. Unconstrained – no lag	15,600.6
	4. Unconstrained – lag	15,796.7
Dose	1. Constrained – no lag	15,531.2
	2. Constrained – lag	15,785.9
	3. Unconstrained – no lag	15,530.4
	4. Unconstrained – lag	15,789.6
log(Dose)	1. Constrained – no lag	15,375.8
	2. Constrained – lag	15,769.3
	3. Unconstrained – no lag	15,371.1
	4. Unconstrained – lag	15,771.9

Abbreviations: AIC, Akaike information criterion; WCE, weighted cumulative exposure.

Web Appendix 7: Comparison of weight function estimates and AIC values between models with alternative time windows

Because of the uncertainty regarding how long past LDIR exposures may affect the current hazard of cancer incidence[12], we estimated alternative unlagged 1-knot WCE models, with log dose, for time windows [0, *a*] with *a* = 3, 5, 9, 12 and 18 years (because we considered very short time windows, these analyses did not consider the 2-year lag). In these sensitivity analyses, we fit unconstrained WCE models. This approach allowed us to assess the behavior of weight estimates close to the end of the corresponding exposure time window (*a* years ago). If the estimated weights in this region were systematically much higher than 0, this could suggest that the exposures that occurred more than *a* years ago could still affect the current hazard. However, the unconstrained cubic spline estimates in the upper tail are notoriously unstable[13], so interpretation of this visual assessment of the estimates had to take also into account the comparison of AIC values of the models with different time windows (shown in the headings of each panel of Web Figure 2). Web Figure 2 shows that the 9-year model yielded the lowest AIC. Furthermore, the estimates based on shorter windows suggest that the effect of past doses lasted at least 5 years since exposure (Web Figures 2A and 2B), whereas the 12- and 18-year estimates did not show any risk increases associated with LDIR doses received more than 7-8 years ago (Web Figures 2D and 2E). Based on these results, all our final analyses, reported in the main article, relied on the 9-year time window.



Web Figure 2. Comparison of results obtained with different exposure time windows, for lagged analyses with exposure defined as log dose and unconstrained WCE models. It presents the estimated weight functions and pointwise 95% bootstrap confidence intervals for the associations between LDIR exposures and cancer incidence for the A) 3-year time window, B) 5-year time window, C) 9-year time window, D) 12-year time window, and E) 18-year time window. Corresponding AIC values are shown in the heading of each graph, with a lower AIC indicating a better fit to data. Best AIC is yielded by the 9-year window (panel C), and is lower by at least 3 points than AICs for any of the 4 other models. AIC, Akaike information criterion; LDIR, low-dose ionizing radiation.

Web Appendix 8: Estimated hazard ratios associated with selected dose histories observed in our CHD cohort

The WCE model implies that, among the exposed subjects, the (adjusted) hazard ratio (HR) varies depending on both (i) the LDIR doses received in the past and (ii) their timing, in terms of time elapsed since exposure. Figure 3 in the main article presents sex-specific HRs associated with arbitrarily selected *hypothetical* exposure patterns. To further assess the strength of the estimated associations, corresponding to exposure patterns relevant for our study population, separately for each sex, we first constructed the entire distribution of HRs estimated, based on the final sex-stratified 9-year lagged WCE models for log dose, across all exposed subjects, compared to a subject who was not exposed to LDIR in the time window. We then identified HR values corresponding to the 50^{th} (median), 75^{th} (3^{rd} quartile), 90^{th} and 95^{th} percentile of the distribution of HRs for each sex, and sampled a single exposure pattern corresponding to a given HR. The results are summarized in Web Table 2. The leftmost column of Web Table 2 shows, for each row, the percentile and the corresponding HR. Then, the other columns in the same row show the actual LDIR dose(s), in milliSieverts (mSv), received by the selected subject in each of the 6-month intervals in the past 2 to 9 years that contributed to this HR value. (Blanks indicate that the subject had no LDIR procedures in the corresponding 6-month period, and exposures received less than 2 years ago are excluded, to reflect the 2-year lag). For example, the 1^{st} row of Web Table 2 shows that, for men, the median HR = 1.17 and corresponds, for example, to a single LDIR exposure of 7.0 mSv received about 5.5 years ago. Similarly, the 4^{th} row shows that a man who received 3 doses, about 4, 5.5 and 7.5 years ago, has an adjusted HR = 1.64, which corresponds to the 95^{th} percentile of all HRs estimated for men in our cohort.

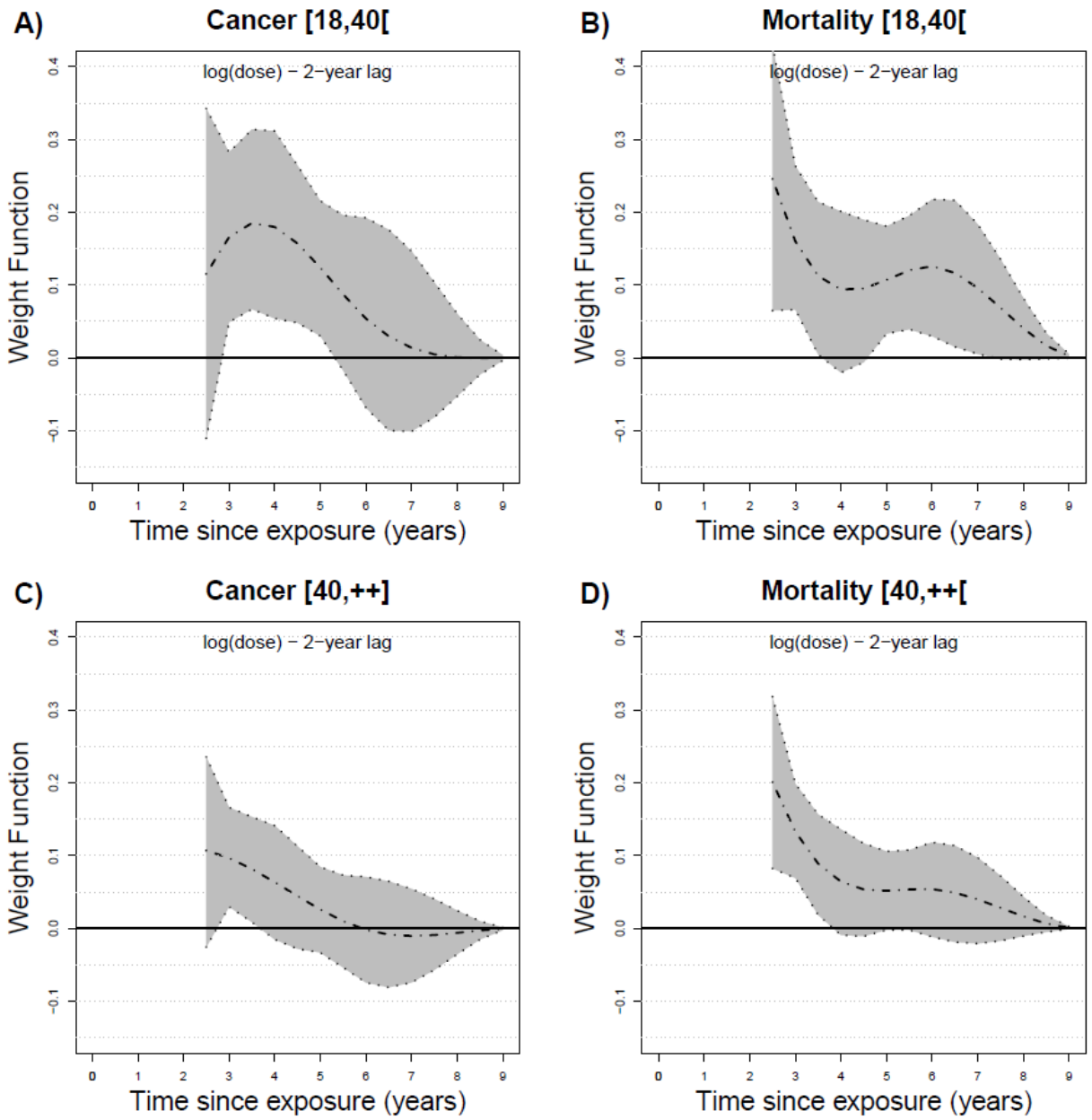
Web Table 2. Estimated adjusted sex-specific HRs associated with selected dose histories observed in the cohort, relative to patients with the same values of all covariates and who were not exposed to LDIR in the past 9 years.

Percentile of HR Distribution - HR	**Dose History (mSv) According to Time Since Exposure (years)**																		
Men	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**5.5**	**6**	**6.5**	**7**	**7.5**	**8**	**8.5**	**9**
50% - HR = 1.17												7.0							
75% - HR = 1.27											15.0								
90% - HR = 1.46								15.6				7.8							
95% - HR = 1.64									22.0			7.8				7.8			
Women	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**5.5**	**6**	**6.5**	**7**	**7.5**	**8**	**8.5**	**9**
50% - HR = 1.06								15.0					22.6			15.6		15.6	
75% - HR = 1.47							7.0												
90% - HR = 1.70							15.0				30.0								
95% - HR = 1.92						22.0													

Abbreviations: HRs, hazard ratios; LDIR, low-dose ionizing radiation; mSv: milliSieverts.

Web Appendix 9: Results of age-stratified analyses

The extended competing risks WCE model that estimated separate weight functions for younger adults, aged <40 years at cohort entry versus ≥40 years, did not fit the data significantly better than the simpler model that assumed the LDIR effects do not differ by age class ($P = 0.13$ for the likelihood ratio statistic with 6 degrees of freedom). For both age groups, LDIR exposures (log doses) from 2 to about 5 years ago are associated with increased cancer incidence (Web Figures 3A and 3C), but the shapes of the estimated weight functions are somewhat different, and the association seems stronger for younger adults, as reflected by higher values of the corresponding weights (Web Figure 3A vs. Web Figure 3C). On the other hand, for both age groups, all-cause mortality hazard is strongly associated with recent LDIR exposures from the last 3-4 years (Web Figures 3B and 3D), which most likely reflects the reverse causality bias discussed in Web Appendix 5 above.



Web Figure 3. Results of age-stratified WCE models, for the lagged analyses with exposure defined as log dose and 9-year window. It presents the estimated weight functions, with pointwise 95% bootstrap confidence intervals, for the associations between LDIR exposures and, respectively, i) cancer incidence and ii) all-cause mortality, for patients aged between 18 and 39 years at cohort entry (panels A and B), and patients aged 40 years old or over at cohort entry (panels C and D). LDIR, low-dose ionizing radiation; WCE, weighted cumulative exposure.

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