Exposure to medical radiation during fetal life, childhood and adolescence and risk of brain tumor in young age: results from the MOBI-kids case-control study

Elisa Pasqual[1,2,3], Gemma Castaño-Vinyals[1,2,3,4*], Isabelle Thierry-Chef[1,2,3*], Noriko Kojimahara[5], Malcolm R Sim[6], Michael Kundi[7], Daniel Krewski[8,9], Franco Momoli[10], Brigitte Lacour[11,12,13], Thomas Remen[11,12,13], Katja Radon[14] Tobias Weinmann[14], Eleni Petridou[15, 16], Maria Moschovi[17], Rajesh Dikshit[18], Siegal Sadetski[19], Milena Maule[20], Mariangela Farinotti[21], Mina Ha[22], Andrea 't Mannetje[23], Juan Alguacil[24,25], Nuria Aragonés[3,26], Roel Vermeulen[27], Hans Kromhout[27], Elisabeth Cardis[1,2,3]

(1) Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain
(2) Universitat Pompeu Fabra (UPF), Barcelona, Spain
(3) CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
(4) IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
(5) Department of Public Health, School of Medicine, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan.
(6) Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia
(7) Department of Environmental Health, Center for Public Health, Medical University Vienna, Austria.
(8) McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, Ottawa, ON, Canada 18
(9) Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
(10) Ottawa Hospital Research Institute, Ottawa, ON, Canada; Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON, Canada
(11) French National Registry of Childhood Solid Tumors, CHRU, Nancy, France;
(12) Inserm U1153, Center of Research in Epidemiology and StatisticS (CRESS),
(13) Paris University, Epidemiology of childhood and adolescent cancers team (EPICEA), Paris, France.
(14) Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany.
(15) Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece.
(16) Unit of Clinical Epidemiology, Karolinska Institute, Stockholm, Sweden
(17) Haematology-Oncology Unit, First Department of Pediatrics, National and Kapodistrian University of Athens, Medical School, "Aghia Sophia" Children's Hospital, Athens, Greece
(18) Centre for Cancer Epidemiology, Tata Memorial Centre, Mumbai, India
(19) Cancer and Radiation Epidemiology Unit, Gertner Institute, Chaim Sheba Medical Center, Ramat Gan, Israel.
(20) Unit of Cancer Epidemiology, Department of Medical Sciences, University of Turin, Turin, Italy
(21) Unit of Neuroepidemiology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

(22) Department of Preventive Medicine, Dankook University College of Medicine, Cheonan, South Korea
(23) Centre for Public Health Research, Massey University, Wellington, New Zealand
(24) Centro de Investigación en Salud y Medio Ambiente (CYSMA), Universidad de Huelva, Huelva, Spain
(25) Ciber Epidemiología y Salud Pública (CIBERESP), Huelva, Spain
(26) Cancer Epidemiology Section, Public Health Division, Department of Health of Madrid, Spain
(27) Division Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, Netherlands
*GCV and ITC contributed equally to the work

Short Title: Diagnostic X-ray exposure and brain cancer in young people

*Corresponding Author

Dr. Elisabeth Cardis
ISGlobal, Radiation Programme
Barcelona Biomedical Research Park (PRBB)
Doctor Aiguader, 88 08003 Barcelona, Spain
Tel. +34 93 214 73 12; Fax: 932147320
elisabeth.cardis@isglobal.org

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Abstract

Background

We explored the association between ionizing radiation (IR) from pre-natal and post-natal radio-diagnostic procedures and brain cancer risk within the MOBI-kids study.

Methods

MOBI-kids is a international (Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, Japan, Korea, New Zealand, Spain, The Netherlands) case-control study including 899 brain tumor (645 neuroepithelial) cases aged 10 to 24 years and 1,910 sex, age, country matched controls. Medical radiological history was collected through personal interview.
We estimated brain IR dose for each procedure, building a look-up table by age and time period. Lifetime cumulative doses were calculated using 2 and 5 years lags from the diagnostic date. Risk was estimated using conditional logistic regression. Neurological, psychological and genetic conditions were evaluated as potential confounders. The main analyses focused on neuroepithelial tumors.

Results

Overall, doses were very low, with a skewed distribution (median 0.02 mGy, maximum 217 mGy). Odds Ratios (ORs) for post-natal exposure were generally below 1. ORs were increased in the highest dose categories both for post and pre-natal exposures: 1.63 (95% CI: 0.44; 6.00) and 1.55 (0.57, 4.23), respectively, based on very small numbers of cases. The change in risk estimates after adjustment for medical conditions was modest.

Conclusions

There was little evidence for an association between IR from radio-diagnostic procedures and brain tumor risk in children and adolescents. Though doses were very low, our results suggest a higher risk for pre-natal and early life exposure, in line with current evidence.

Abbreviation list

CI	Confidence Interval	SES	Socioeconomic Status
CT	Computed Tomography	IQR	Interquartile Range
IR	Ionizing radiation		
LRT	Likelihood Ratio Test		
OR	Odds Ratio		
MRI	Magnetic Resonance Imaging		

Introduction

The use of radio-diagnostic tools has drastically improved patient care and has become a fundamental part of clinical evaluation. However, this has resulted in an increase in the number of diagnostic procedures, and consequently, of ionizing radiation (IR) exposure [1–3]. This has become a public health and radiation protection concern [2], as there is growing evidence that IR may induce cancer even at low-to-moderate doses, such as those delivered in common diagnostic examinations [3]. Concern is particularly high in pediatric populations [4], as exposure in childhood is known to entail higher risk of radiation-induced cancer than exposure later in life [5]. It is well known that radiation can cause brain tumors in adults, particularly following exposure in early life [5,6].

Brain tumor is the second most frequent tumor in childhood and adolescence, after leukemia [7]. Previous studies have attempted to quantify brain tumor risk in young people from radio-diagnostic procedures. Case-control studies generally found a dose-related increased risk of brain tumors in offspring of mothers exposed to IR during pregnancy [8]; the effect of post-natal exposure is less conclusive [8–10]. Recent large-scale pediatric CT-scan cohort studies reported a dose-related increases in brain tumor risk that are higher (per unit radiation dose) [11–16], though statistically compatible, than those derived from the atomic bomb survivor study, which underpins much of radiological protection up to now.

The results of CT-scan studies published to date have been criticized because of potential for bias resulting from: confounding by indication due to underlying medical conditions related both to CT-scan exposure and brain cancer risk; reverse causation, which occurs when the CT-scan was in fact related to the symptoms or diagnosis of the tumors; as well as missing doses [17]. Analyses of data from the UK and French pediatric CT cohorts and simulation studies indicate that genetic predisposing conditions have little effects on radiation-risk estimates [11,16,18], but may act as effect modifiers [16,19]. Apart from genetic predisposing conditions, several

neurological and congenital conditions are associated with childhood brain cancer or higher CT-scan exposure [20–24], and could potentially confound estimates of brain cancer risk from medical radiation.

Here, we aimed to estimate the risk of brain tumor in children and young adults from exposure to pre- and post-natal medical diagnostic IR within one of the largest international case-control study on brain tumor in young people, the MOBI-Kids study. The analysis conducted here includes detailed cumulative brain dose estimation based on typical time-age radiographic protocols. In addition, the role of medical history, as a potential confounder of the relation between medical radiation dose and brain tumor risk is, for the first time, examined in detail.

Materials and Methods

Study design

We recruited 899 cases of brain tumors, aged 10 to 24 at diagnosis, from 14 countries (Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, Japan, Korea, New-Zeeland, Spain, The-Netherlands) between May 2010 and March 2016. For each case, two controls were selected among patients undergoing appendectomy in hospitals from the geographical area covered by the neurosurgery/oncology departments where cases were identified. Controls were matched by sex, age (1-year category up to age 19, 2 years thereafter), date of surgery/interview and region of residence. Controls with previous brain tumor diagnosis were not eligible. Participants with language difficulties or a known brain tumor predisposing syndrome (e.g. neurofibromatosis) were excluded. All histological brain tumor types were included. The main objective of MOBI-Kids was to study brain tumor risk from mobile phone use, thus midline tumors close to the sellar region were not included, because of the low radio-frequency exposure in these areas. Further methodological details have been published elsewhere [25].

Data collection

Data were collected through a personal interview conducted by trained personnel. Two questionnaires were used: the main questionnaire, administered to the participant (or a parent, depending on the age of the study subject and his/her health condition), captured information on demographic factors, use of mobile communication devices, medical and radiological history and other environmental exposures; the second, for parents, collected data on preconception, pre-natal and early life factors.

The medical radiation section of the main questionnaire included a screening question to identify subjects who had ever undergone a particular procedure (e.g. “Have you ever had X-rays of the head or neck?”). If the answer was positive, the interviewee was asked about the body part examined (head, neck, whole body), age and reason of examination. Procedures included: conventional X-ray, CT-scan, MRI, angiography and dental X-ray (bite-wing X-ray,

panoramic, full mouth and dental-CT). To help the interviewee identify the correct examination, pictures of the machine were shown. In the maternal questionnaire, the subject's mother was asked if she had radiation imaging/therapy during her pregnancy. If so, questions were asked, for each trimester of pregnancy, about the type of procedure, the body part, the number of examinations and whether the mother's abdomen was shielded during the procedures. The mother was also asked if her child underwent any radiological procedures during its first year of life. As subjects would typically be unable to report procedures early in life, we considered exposures in the first year of life only if it was reported by the parents (Online Supplement file 1)

Dose estimation

For the dose estimation, we had, for each subject, a list of procedures reported during the interview, with details on the time period where they were performed and the body part examined. We aimed to perform the risk analysis using as exposure metric the cumulative dose to the brain, expressed in mGy. Thus, for each examination, brain doses were estimated based on typical protocols by time period and age at exposure as follows [8,26]:

We searched the literature for publications reporting, for each examination type in a given time-age frame, either a distribution of technical parameters used by radiologists (i.e. X-ray tube voltage, X-ray beam energy, filtration, X-ray tube distance)[27] or an estimation of brain dose [28]. Technical parameters extracted from publications were used to estimate brain dose using the PCXMC software by entering the measures of central tendency (median or mean) of these technical parameters [29]. For each "examination x age x time period" frame, we obtained values of the brain absorbed dose simulated from a set of parameters which would have been the most representative of radiological practice at the time. Thus, we scored each publication with a "relevance score" (ranging from 0 to 5). To build the look-up table, we calculated the mean of the absorbed dose among the simulations coming from publications with the highest "relevance score" for each period of time and age range.

We obtained a look-up table where, for each examination, time period (1980-89; 1990-99; 2000-2010) and age category (fetal, 0-0.5, 0.5 to 2.5, 2.5 to 7.5, 7.5 to 12.5,12.5 to 18 years of age, and adults), a brain dose could be attributed (Online Supplement File 2).

The list of questions asked in the questionnaires, and all steps of the calculation of dose including the assumption made are reported in Online Supplement File 3. The dose estimation process implemented here and results for intraoral dental examination are published elsewhere [30].

Post-natal cumulative brain dose up two year before interview was calculated for each participant by summing the doses received for each examination the subject underwent. Fetal cumulative dose was calculated separately, using the approach described above, relying on a revision of typical fetal dose values during X-ray examination published in a doctoral thesis [31].

Definition of covariates

We identified the following a priori variables as being possibly associated with brain tumor risk: parental education, as a proxy of socio-economical status (SES) [32], presence of any neurological or psychological disease [20,21,23], genetic diseases [22].

Parental education was estimated as the highest of mother's or father's education level, categorized into low (primary education), medium (secondary education), and higher (university or more), along with a fourth category including missing or not classifiable.

The medical history section of the main questionnaire included a screening question formulated as: "Has a doctor ever told you that you have one of the following diseases?" with a list of conditions, including neurological, psychological and genetic diseases. For each condition reported, information was asked on the exact diagnosis and date. For the analysis of neurological diseases, we only considered diseases diagnosed at least two years before diagnosis, to avoid inclusion of neurological brain tumor symptoms. A full list of reported neurological, psychological and genetic conditions can be found in Online Supplement File 4.

As the presence of a brain tumor could influence the interview conditions, the interview quality score and identity of the interviewee (index, parent(s), and index with parent) were explored as

covariates. At the end of the main questionnaire, the interviewer evaluated two dimensions of interview quality: motivation ("was the interviewee responsive?") and memory ("how well did the interviewee remember the information about questions asked?"). We derived a single score by calculating the mean between the two scores. If the case interview was done with a parent present, the interviewer was also asked to evaluate the quality of the parents' answers. In this case, we considered the parental score rather than that of the index.

Power calculation

We performed a *post-hoc* power calculation using the Power [33] software. Considering the number of cases we have and the estimated dose distribution in our study population, the estimated power to reject the hypothesis of no effect if the effect magnitude is as high as that reported in a recent CT- cohort study (RR of 3.3 for 100 mGy of dose - Pearce et al. [34]) is 85%, with an α of 0.05. The power is actually less than that because of possible exposure misclassification related to the actual technical parameters used in the radiological examination. If, instead, we hypothesize that the true risk (in absence of any dosimetric error) is closer to that seen in other populations such as the atomic bomb survivors (RR at 100 mGy of 2.5 or 2), the study power decreases considerably (to 60% and 40%, respectively).

Statistical analysis

We estimated the association between categories of estimated post-natal and pre-natal brain doses and risk of brain tumors using conditional logistic regression stratified by sex, attained age and country. Odds ratios (ORs) and Likelihood Ratio Test 95% confidence intervals (CIs) are shown throughout. The main analyses focused on risk of neuroepithelial tumors, which represent 75% of the tumors in the study. Embryonal tumors are the second largest group recruited, representing 14% of all tumors; the numbers of cases for each other subtype are very low, with only 45 cases of meningioma. Neuroepithelial tumors have a different age distribution than embryonal tumors and likely a different etiology. Thus we focused our analyses on the

more homogeneous group of neuroepithelial tumors. Supplementary analyses were also conducted for embryonal tumors and for all histological brain cancer types.

For post-natal exposure, cumulative dose was categorized into four groups using 20, 50 and 100 mGy as a priori cut-off points for consistency with previously published studies [13]; for pre-natal dose, only two categories were considered, using 5 mGy as the cut-off point, given the low levels of these doses. In the main analyses, doses were lagged by two years, whereas in a sensitivity analysis doses were lagged by five years, taking as a reference the date of diagnosis for cases and of appendectomy for controls.

The potential confounding effect of the covariates identified above were evaluated by testing for an association between each covariate and the lagged categorical cumulative dose (with 20 and 50 mGy cut-off points) using multinomial logistic regression. We used likelihood ratio tests to compare the null model which includes only sex, age, and country and the models where the covariate was added. Each covariate was tested separately.

Heterogeneity of risk by time since exposure was tested by including three dose variables (corresponding to the cumulative dose received in different windows of time before diagnosis: 2 to 5, 6 to 10, and over 10 years) in the model and comparing to the model with cumulative dose only. Heterogeneity of risk by age at exposure (0 to 5, 6 to 15 and more than 15 years of age) was evaluated in the same way.

Additional analyses were conducted to evaluate the sensitivity of the results to different assumptions. This included using 1) alternative exposure scenarios such as cumulative dose including procedures with missing date as performed before two years from diagnosis; cumulative fetal dose setting dose to 0 when the mother reported abdominal lead apron protection; using total number of head CTs instead of dose; and 2) alternative subsets, such as only participants with high interview quality score; only participants for whom the interview was conducted with parents present; excluding subjects with any reported genetic condition;

excluding subjects reporting any neurological condition diagnosed 5 year before cancer/appendicitis; adjusting for parental education. Risk of neuroepithelial tumors was also estimated in relation to number of MRIs as a “negative control” (MRI does not emit IR).

Statistical analysis was conducted with the R software [35].

Results

A total of 899 cases and 1,910 controls were recruited. Participation rate was 72% in cases and 54% in controls. Details of reason for non-participation are described elsewhere [36]. We excluded nine cases and five controls reporting a previous cancer and four controls whose age at appendectomy was missing. With stratification by attained age, sex and country, 859 cases (645 neuroepithelial, 124 embryonal) and 1730 controls (1700 for neuroepithelial and 865 for embryonal cases) were included in the analysis; 31 cases and 171 controls were excluded as they belonged to a stratum lacking of at least one control or case. Countries with the highest number of neuroepithelial cases were Spain (143), Italy (122), France (74), Israel (74), and Germany (68).

Characteristics of the participants are reported in Table 1, by case/control status and tumor morphology (neuroepithelial, embryonal and all brain tumors). There were slightly more males than females. Parents of controls tended to have slightly higher education level then cases parents. Prevalence of neurological, psychological and genetic disease was similar between cases and controls. The index was interviewed alone more often in controls, however, no difference in quality of interview was found between cases and controls.

Overall cumulative brain dose was very low and the dose distribution was skewed (Figure 1) with two peaks: the first, including 75% of participants, is below 1 mGy; the second, less prominent, is around 30 mGy and includes subjects who underwent at least 1 CT-scan.

Table 2 describes the distribution of doses. Median post-natal dose was similar (0.02 mGy) in cases and controls for all three tumor groupings when doses were lagged by either two or five years. The percentage of controls with at least one CT-scan was higher than in cases (6.5% versus 3.7% in the neuroepithelial sample). Only a small proportion of subjects received pre-natal doses. Median pre-natal dose was higher among cases than controls (Table 2).

Concerning potential confounders, statistically significant associations with doses were found for neurological disease, psychological disease and quality of interview, but not for parental

education, genetic diseases or identity (subject, parent, other) of the interviewee (Online Supplement 5).

Table 3 reports ORs and 95% CI by post-natal and pre-natal by dose level based on categorical and continuous analyses for neuroepithelial, embryonal, and brain tumors overall. For post-natal dose, there was no evidence of a trend with dose; ORs were below 1 in all but the highest dose category, where they were systematically above 1, based on small numbers of cases. Continuous analyses showed no evidence of a dose-response relationship. Adjustment for neurological, psychological and genetic conditions modified the risk estimates only slightly. Analyses with a 5-year lag showed similar results, though risk estimates in the highest dose category were lower and confidence intervals wider.

For fetal exposure above 5 mGy, unadjusted ORs of 1.52 (95% CI 0.56; 4.14 CI), 2.04 (0.22; 18.63), 1.34 (0.52; 3.48) were found for neuroepithelial, embryonal and all brain cancer cases, respectively. Results did not change substantially after adjustment.

Table 4 shows results of analyses of the potential modifying effect of time since exposure and age at exposure in neuroepithelial cases. For doses received in the first five years of life, the OR in the above 50 mGy category was 1.29 (0.49; 3.40) based on a very small number of cases. The ORs were above 1 (with large CIs) for doses above 50 mGy cumulated in the 2 to 5 and 6 to 10 years before diagnosis windows. For doses above 50 mGy received more than 10 years before diagnosis, the OR was below 1 but not statistically significantly (Table 4).

Results of sensitivity analyses for neuroepithelial tumors are shown in Online Supplement file 6. Risk estimates were generally statistically compatible with those of the main analyses. Assigning 0 dose for pre-natal procedures with a lead apron protection resulted in an OR of 2.1 (0.45; 6.04) for doses above 5 mGy category. The OR was 0.53 (0.26; 1.05) for exposure to one CT-scan compared to none and 0.72 (0.45; 1.15) for one MRI scan.

Discussion

We explored the association between categories of cumulative brain IR dose from medical diagnostic exposures during pre-natal and post-natal life and brain cancer risk among young people in one of the largest population based case-control studies of this disease to date [10,37,38]. Cumulative brain dose derived from common medical diagnostic examinations was generally low, with 90% of subjects having cumulative lifetime doses below or equal to 1 mGy. In comparison, the average annual per capita dose in the world is 1-2 mGy from natural and human made sources [39], excluding radon, which does not contribute to brain dose.

Overall, no statistically significant differences were found across categories of exposure and continuous analyses showed no evidence of a dose-response relationship. The OR was systematically above 1 for cumulative doses above 100 mGy, with very large confidence intervals, based on small numbers. The sensitivity analyses did not substantially modify the results.

These findings are in line with previous case-control studies on childhood/adolescent brain tumor risk following medical diagnostic radiation exposure, which generally reported non-statically significant increased risks [10,37]. Compared to those studies, we included a much larger number of cases and we performed an analysis based on category of absorbed dose to the brain instead of using number of examinations. In addition, we took into account medical history variables as potential confounders of the association.

We also found reduced ORs, statistically significant in some analyses, for the 20 to 50 mGy categories, and for having had one head CT-scan. The findings were generally consistent across the sensitivity analyses and remained after excluding interviews with poor quality. This observation likely reflects a difference in the percentage of controls undergoing one CT-scan (6.4%), compared to cases (3.8%), possibly due to chance, selection bias or unmeasured confounding. Indeed, selection bias was observed in an adult brain cancer case-control

study [40], where controls who had experienced previous head injury (and consequently underwent head and neck examination) were more likely to participate than those who had not. It is conceivable that a similar phenomenon might at least partly explain our results, where potential controls with a history of head injury or other neurological diseases may be more interested in participating in a brain cancer case-control study.

SES may confound the association between radiation dose and brain tumor risk in this study as parents of controls tended to have higher education levels (thus, likely, higher level of SES) compared to parents of cases. However, recent reports, show no consistent association between SES and CT-scan exposure [18,41–44]. We tested if parental education was related to cumulative dose, and found no association. Adjustment for parental education did not substantially change the results.

Regarding time since exposure, the risk of brain tumors for subjects with doses of 50 mGy or more appears to decrease with increasing time since exposure; the small numbers and very large confidence intervals preclude any clear conclusions. We detected a non-statistically significant increased risk for exposure above 50 mGy cumulated up to 5 year of age, in line with current evidence suggesting increased sensitivity from exposures early in life [5].

Though only a low percentage (about 2%) of parents reported pre-natal radiation exposure, an OR of 1.55 (0.57; 4.23) was found for subjects with the highest pre-natal doses (>5mGy) for all outcomes considered. This result, based on very small numbers of subjects appeared to be robust to sensitivity analyses.

Evidence of an association between pre-natal diagnostic X-rays exposure and subsequent cancer risk in the offspring mainly come from the Oxford Survey of Childhood Cancer study, the findings of which [45], based on generally higher doses than observed here, have resulted in a drastic reduction of the use of diagnostic IR procedures in pregnant women [46]. While this reduction

is clearly beneficial for patients, it limits the power of more recent studies, including ours, to detect an increased risk for pre-natal exposures [8–10,37].

Strengths and limitations

Our work is subject to certain limitations. This study, one of the largest population based case-control study of brain tumors in young people, had low statistical power to detect an association with diagnostic IR exposure, due to the very low dose levels received [47]. Our dose distribution likely reflects current and recent past childhood/adolescent population exposure levels, where the majority of subjects received very low levels of dose from common X-ray examinations (including dental) and only a small proportion underwent CT-scans.

Our estimated doses are subject to error and we identified two main sources of uncertainty. First, using self-reported information may have induced recall errors (systematic and random). If these are non-differential with respect to case-control status, this would likely bias risk estimates towards the null. Second, the estimated dose accounted only for a *time x age* variability, but not for the full range of variability (related to patient characteristics, country variability in radiographer practice, or actual technical parameters used in the specific patients examinations) and are thus subject to Berkson error – which is unlikely to affect the risk estimates in a linear dose-response model, though it may affect the width of the confidence intervals.

CT-scan cohort studies have been criticized for not taking into account medical conditions that could predispose to cancer and prompt to radiological examination (confounding by indication) and because of the possibility of reverse causation [12,17,34].

Confounding by indication due to a genetic syndrome known to predispose to brain cancer (e.g.. neurofibromatosis) is unlikely in the present study, because participants with these conditions were excluded by design. In addition, we adjusted the analysis for the presence of other medical conditions.

Regarding the issue of reverse causation, in the main analysis, we have lagged doses for a period of two years before diagnosis (and for five years in a sensitivity analysis). Most symptoms for brain tumors tend to appear only a few months before the diagnosis [51,52] and this was also seen in the MOBI-kids population [53]. Therefore, reverse causation seems unlikely here, particularly in analyses with a 5-year lag. However, the decreased OR with increasing time since exposure may suggest a certain degree of reverse causation. We conducted a sensitivity analysis by excluding subjects who reported a neurological disease diagnosed 5 year before cancer/appendicitis, assuming that these diseases could potentially represent early cancer symptoms. Results of the sensitivity analysis were comparable to those of the main analysis. Thus, the finding of decreasing ORs with increasing time since exposure is difficult to interpret as it is based on small numbers of subjects; however it could also reflect a poorer recall of the procedures back in time.

Recall error

Both cases and controls may be already familiar with medical history questions, because they have been recruited in hospitals, and, when hospitalized, it is common to be asked by a doctor to report previous diseases. For the same reason, participants may all be familiar with radiological history questions. It is true that cases may tend to distinguish better MRI from CT-scans, because both procedures may be required for cancer diagnosis; however, this would introduce lower response accuracy in controls, rather than explaining differential over or under-reporting in one of the two groups.

The accuracy of reporting medical radiological history may also be affected by interview conditions. For medical radiological history, particularly in early life, the parents' answers are likely to be more accurate than the participant's. Indeed, recalling examinations during childhood might be problematic for the participants. Interviews of subjects aged less than 18 years of age were generally conducted in the presence of a parent (80%) (or with the parent(s) alone) while only 25% of young adults were interviewed with parents. In addition, older cases

tended to be interviewed in the presence of parents more often than controls, because of their poorer health conditions, and thus information collected for cases would tend to be more accurate than for controls, in particular for young adults. We conducted two sensitivity analyses: one restricted to interviews with parents and the other restricted to high quality interview. Results were similar to those of the main analysis.

Dose estimation

Variability of doses by country has not been taken into account, due to the scarcity of literature relevant for our dose estimation methodology. However, a recent study showed that, for head CT-scans, dose variation across country is limited, suggesting that protocols for head CTs are standardized across countries [48]. We based our head-CT dose estimation on the work published by Lee and colleagues and doses are comparable to those from ongoing work in Australia and Europe [49,50].

Another issue for consideration is that we could not capture eventual retakes of the same image. Retakes are done when using contrast technique or because of the poor image quality. This is unlikely to cause substantial misclassification for non-CT images (doubling the dose of a head X-ray will not lead to a subject changing dose category), but it is important for CT-scans, where doubling the dose can shift participants into higher dose categories. As a result, we could have underestimated the dose for some participants, albeit non-differentially between cases and controls.

Despite the limitations discussed, our work, presents two important original aspects. It is the first brain tumor case-control study of medical IR diagnostic exposure to use time-period based dose estimation; even if it comes with some uncertainty, this is a valid alternative to using merely number of examinations [8,26]. Indeed, using number of examinations leads to exposure misclassification due to the wide range of doses for each procedure. The other important aspect of our study is the collection of detailed medical history, including the list of diseases diagnosed

in each subject. This allowed previous medical history to be taken into account, which could confound the association between IR dose and brain tumor risk.

Role of medical conditions

Some neurological and psychological conditions have been suggested to increase brain tumor risk [20,21,23,54]. These may be early signs/symptoms of the tumor; however, a causal association has not been excluded. Neurological and psychological conditions have never been taken into account in diagnostic radiation studies of brain tumors. We found that these diseases were related to higher IR exposure from medical procedures, with a stronger association for neurological diseases. Thus, we adjusted our analyses for the presence of these diseases to overcome possible bias due to confounding by indication (in the case that the association between neurological disease and brain cancer is interpreted as causal) or reverse causation bias (if the presence of neurological/psychological conditions represents early signs/symptoms) (Figure 2). We also adjusted for the presence of any genetic/congenital disease because these may be associated with brain cancer or with exposure to CT-scans [22,24]. After adjustment, there was a slight decrease in point estimates in all categories, suggesting possible confounding, however, the change in risk estimates was modest.

Conclusion

In this large multi-center case-control study, with very low average doses, we found little evidence of an increased risk of pre-natal and post-natal exposure to external IR dose from diagnostic medical procedures.

Statements

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Statement of Ethics

Ethical approval was obtained from all the relevant ethics committees in the participating countries. The study protocol followed was in accordance with the ethical standards of the responsible committees on human experimentation and with the Helsinki Declaration. Written consent was obtained from all participants (or their parents) for each part of the study, including the interview, whose data has been used for the present publication.

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The authors have no conflicts of interest to declare.

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Author Contributions

- Substantial contributions to the design of the study and the acquisition of data: Gemma Castaño-Vinyals, Noriko Kojimahara, Malcolm R Sim, Michael Kundi, Daniel Krewski, Franco Momoli, Brigitte Lacour, Thomas Remen, Katja Radon, Tobias Weinmann, Eleni Petridou, Maria Moschovi, Rajesh Dikshit, Siegal Sadetski, Milena Maule, Mariangela Farinotti, Mina Ha, Andrea ’t Mannetje, Juan Alguacil, Nuria Aragonés, Roel Vermeulen, Hans Kromhout, Elisabeth Cardis

- Manuscript conception: Elisa Pasqual, Gemma Castaño-Vinyals, Isabelle Thierry-Chef, Noriko Kojimahara, Elisabeth Cardis

- Statistical Analysis: Elisa Pasqual

- Exposure assessment: Elisa Pasqual, Isabelle Thierry-Chef

- Interpretation of data for the work: Elisa Pasqual, Gemma Castaño-Vinyals, Isabelle Thierry-Chef, Noriko Kojimahara, Elisabeth Cardis

- Drafting the work: Elisa Pasqual

- Revising it critically for important intellectual content: Elisa Pasqual, Gemma Castaño-Vinyals, Isabelle Thierry-Chef, Elisabeth Cardis, Brigitte Lacour, Thomas Remen, Katja Radon, Tobias Weinmann, Eleni Petridou, Nuria Aragonés, Andrea ’t Mannetje, Michael Kundi

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Tables

Table1: Characteristics of the study population

	Neuroepithelial		Embryonal		All brain tumours[a]	
Variable	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
n	**645**	**1700**	**124**	**865**	**859[2]**	**1730**
Sex (Male) N (%)	352 (54.6)	969 (57.0)	88 (71.0)	535 (61.8)	487 (56.7)	991 (57.3)
Age at diagnosis (median [IQR])	15.7 [12.7, 20.0]	15.8 [12.9, 20.3]	14.6 [11.6, 17.7]	15.1 [12.3, 19.7]	15.7 [12.7, 20.1]	15.7 [12.9, 20.9]
Parental education N (%)						
Low	216 (33.5)	483 (28.4)	53 (42.7)	252 (29.1)	300 (34.9)	493 (28.5)
Medium	189 (29.3)	400 (23.5)	26 (21.0)	218 (25.2)	242 (28.2)	405 (23.4)
High	196 (30.4)	630 (37.1)	39 (31.5)	292 (33.8)	262 (30.5)	643 (37.2)
Other/don't know	44 (6.8)	187 (11.0)	6 (4.8)	103 (11.9)	55 (6.4)	189 (10.9)
Any neurological disease N(%)	69 (10.7)	147 (8.6)	7 (5.6)	75 (8.7)	88 (10.2)	149 (8.6)
Missing	0 (0.0)	12 (0.7)	1 (0.8)	6 (0.7)	1 (0.1)	12 (0.7)
Difference in years between age at diagnosis of the cancer/appendicitis and the neurological disease (median [IQR])	6.4 [3.5, 10.0]	8.0 [4.6, 11.7]	11.3 [5.8, 16.8]	7.1 [4.6, 10.4]	6.4 [3.6, 10.5]	8.0 [4.7, 11.7]
Any psychological disease N (%)	23 (3.6)	69 (4.1)	7 (5.6)	31 (3.6)	33 (3.8)	70 (4.0)
Missing	2 (0.3)	16 (0.9)	1 (0.8)	7 (0.8)	3 (0.3)	16 (0.9)
Any genetic disease N(%)	12 (1.9)	28 (1.6)	4 (3.2)	12 (1.4)	16 (1.9)	28 (1.6)
Missing	6 (0.9)	18 (1.1)	2 (1.6)	8 (0.9)	9 (1.0)	18 (1.0)
Identity of the interviewee N (%)						

Index only	176 (27.3)	773 (45.5)	22 (17.7)	326 (37.7)	237 (27.6)	791 (45.7)
Index with proxy/ proxy only	468 (72.6)	916 (53.9)	102 (82.3)	533 (61.6)	621 (72.3)	928 (53.6)
Missing	1 (0.2)	11 (0.6)	0 (0.0)	6 (0.7)	1 (0.1)	11 (0.6)
Interview quality score 1 (poor)-6 (very good) (median [IQR])	5.00 [4.00, 6.00]	5.00 [4.00, 6.00]	5.00 [4.00, 6.00]	5.00 [4.00, 6.00]	5.00 [4.00, 6.00]	5.00 [4.00, 6.00]

[a] All brain cancer includes all histological tumor type: 645 Neuroepithelial, 124 embryonal, 45 meningiomas, 45 Other Non-neuroepithelial

Table 2: Distribution of dose and number of radiological examinations by brain tumor morphology among cases and controls

Embryonal		All brain cancer	
Cases	**Controls**	**Cases**	**Controls**
124	865	859	1730
74 (59.7)	570 (65.9)	564 (65.7)	1173 (67.8)
Distribution of dose in the exposed			
0.02 [0.01, 0.05]	0.02 [0.01, 0.66]	0.02 [0.01, 0.17]	0.02 [0.01, 0.66]
0.02 [0.01, 0.05]	0.02 [0.01, 0.07]	0.02 [0.01, 0.06]	0.02 [0.01, 0.07]
Prenatal exposure			
2 (0.2)	20 (2.3)	20 (2.3)	49 (2.8)
6.38 [3.21, 9.54]	0.33 [0.01, 3.15]	0.73 [0.01, 12.70]	0.05 [0.00, 12.70]

Table 3: OR and 95% CI for neuroepithelial, embryonal and all brain tumors by cumulative dose for post-natal and pre-natal exposure.

		Crude[a]					Adjusted[b]				
		Cases	Controls	OR	95% CI	p	Cases	Controls	OR	95% CI	p
Neuroepithelial tumors											
Postnatal 2 year lag	*Categorical analysis*										
	[0: 20) mGy	607	1552	1			597	1529	1		
	[20; 50) mGy	25	113	0.61	0.38 0.96		24	112	0.56	0.35 0.9	
	[50;100) mGy	9	28	0.79	0.36 1.73		9	28	0.73	0.33 1.6	
	≥100 mGy	4	7	1.93	0.53 7.07		4	7	1.64	0.45 6.06	
	Continuous (per mGy)	645	1700	1.00	0.99 1.00	0.32	634	1676	0.99	0.99 1,00	0.17
Postnatal 5 year lag	*Categorical analysis*										
	[0: 20) mGy	618	1608	1			607	1585	1		
	[20; 50) mGy	17	62	0.84	0.48 1.49		17	61	0.82	0.46 1.45	
	[50;100) mGy	8	25	0.84	0.37 1.91		8	25	0.77	0.33 1.78	
	≥100 mGy	2	5	1.35	0.24 7.62		2	5	1.16	0.2 6.63	

Table 3: OR and 95% CI for neuroepithelial, embryonal and all brain tumors by cumulative dose for post-natal and pre-natal exposure.

		Crude[a]						Adjusted[b]					
		Cases	**Controls**	**OR**	**95% CI**		**p**	**Cases**	**Controls**	**OR**	**95% CI**		**p**
	Continuous (per mGy)	645	1700	1.00	0.99	1.01	0.57	634	1676	1.00	0.99	1.01	0.41
Fetal	*Categorical analysis*												
	[0;5) mGy	639	1686	1				628	1662	1			
	≥ 5 mGy	6	14	1.52	0.56	4.14		6	14	1.55	0.57	4.23	
Embryonal tumors													
Postnatal 2 year lag	*Categorical analysis*												
	[0: 20) mGy	120	801	1				117	788	1			
	[20; 50) mGy	2	54	0.31	0.07	1.3		2	52	0.35	0.08	1.48	
	≥ 50 mGy	2	10	1.37	0.26	7.23		2	10	1.49	0.26	8.56	
	Continuous (per mGy)	124	865	1.00	0.99	1.02	0.91	121	850	1.00	0.99	1.02	0.75
Fetal	*Categorical analysis*												
	[0;5) mGy	123	860	1				120	845	1			

Table 3: OR and 95% CI for neuroepithelial, embryonal and all brain tumors by cumulative dose for post-natal and pre-natal exposure.

		Crude[a]						Adjusted[b]					
		Cases	**Controls**	**OR**	**95% CI**		**p**	**Cases**	**Controls**	**OR**	**95% CI**		**p**
	≥ 5 mGy	1	5	2.04	0.22	18.63		1	5	1.5	0.14	16.28	
All brain tumors													
Postnatal 2 year lag	*Categorical analysis*												
	[0: 20) mGy	806	1580	1				792	1559	1			
	[20; 50) mGy	35	114	0.66	0.44	0.99		34	113	0.63	0.41	0.95	
	[50;100) mGy	11	29	0.72	0.35	1.47		11	29	0.68	0.33	1.4	
	≥100 mGy	7	7	2.98	0.96	9.29		7	7	2.58	0.82	8.13	
	Continuous (per mGy)	859	1730	1.00	1.00	1.01	0.75	844	1708	1.00	1.00	1.01	0.52
Fetal	*Categorical analysis*												
	[0;5) mGy	852	1716	1				837	1694	1			
	≥ 5 mGy	7	14	1.34	0.52	3.48		7	14	1.35	0.52	3.51	

[1] Conditional logistic regression. Matching was done by country, sex and age (1 year group until 19 age, then by two years)
[2] Models adjusted for presence of neurologic, mental and genetic disease

Table 4: Effect modification by time since exposure and age at exposure for neuroepithelial

		Cases	Controls	OR	LCI	UCI
ORs and 95% CI for dose cumulated in different windows of age at exposure						
0-5 ages	[0; 50) mGy	627	1663	1		
	≥ 50 mGy	7	13	1.29	0.49	3.4
6-15 ages	[0; 50) mGy	631	1657	1		
	>50 mGy	3	19	0.39	0.11	1.37
>15 ages	[0; 50) mGy	633	1673	1		
	≥ 50 mGy	1	3	1.09	0.09	13.33
	LRT results			**0.80**		
ORs and 95% CI for dose cumulated in different time windows before diagnosis						
2-5 years	[0; 50) mGy	632	1674	1		
	≥ 50 mGy	2	2	3.4	0.44	26.53
6-10 years	[0; 50) mGy	631	1671	1		
	≥ 50 mGy	3	5	2.7	0.58	12.63
>10 years	[0; 50) mGy	627	1652	1		
	≥ 50 mGy	7	24	0.68	0.28	1.65
	LRT results			**0.60**		

[1] Conditional logistic regression
[2] Model adjusted for presence of neurologic, mental and genetic disease
[3] LRT results refers to the p value of the Likelihood Ratio test between the null model (with the lifetime cumulative exposure) and the model with the cumulative exposure in different windows periods

Figure Legends

Fig. 1. Distribution of cumulative brain dose (two year lag period) in cases and controls. 759 subjects with dose=0 are excluded.

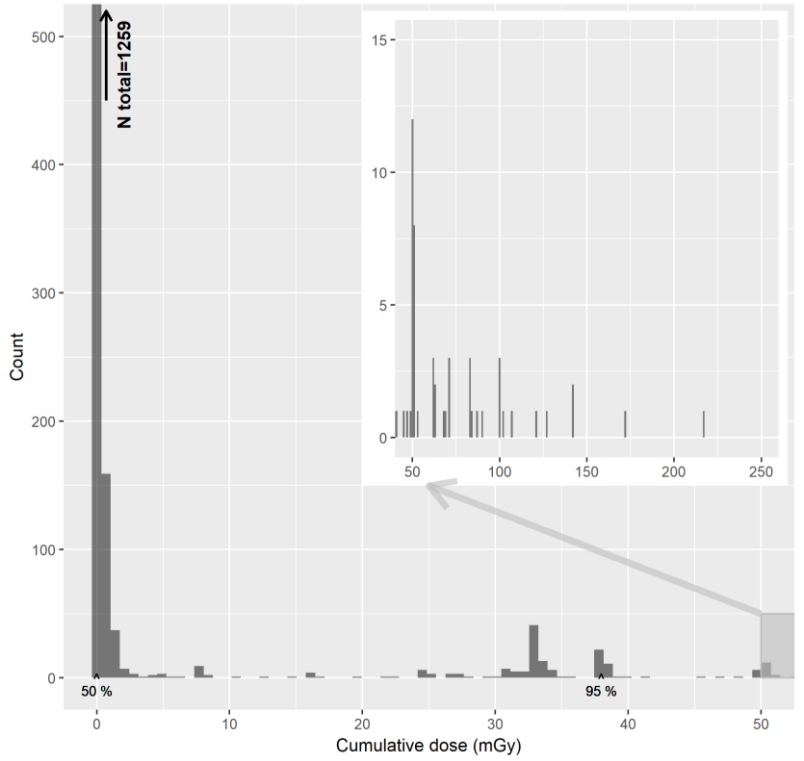
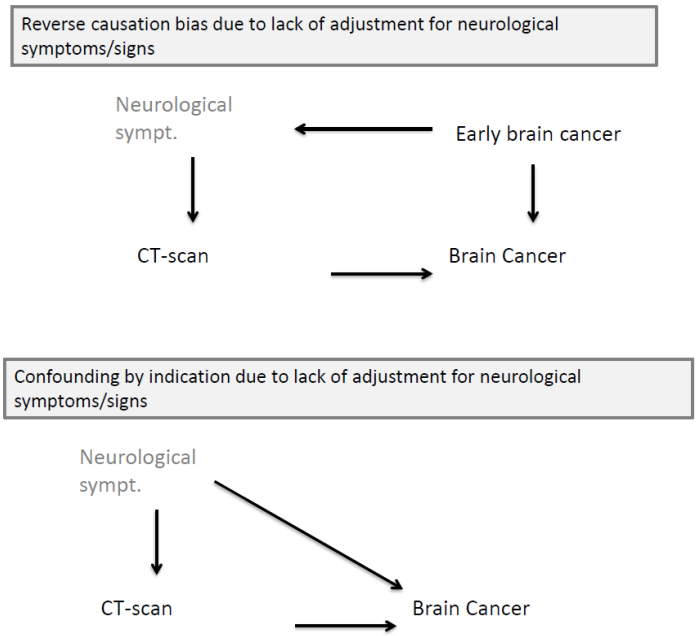


Fig. 2. Direct Acyclic Graphs showing issue of confounding by indication and reverse causality



Online Supplement File 1:
Details concerning newborn examination

As examinations during the first year of life of the subject were collected both in the maternal and in the main questionnaire we proceeded as following:

As subjects would typically be unable to report procedures early in life, we considered exposures in the first year of life only if it was "confirmed" by the parents: that is, reported both in the maternal and main questionnaires, or reported only in the maternal questionnaire, or reported only in the main questionnaire when the interview was conducted with parents.

In total we excluded 6 examinations that were not "confirmed" by parents (Last row of the table below).

Questionnaire of origin	**Coincidence between maternal and main questionnaire**	**Interviewee**	**count**	**Final decision (kept: YES/NO)**
main	Complete: also reported in the maternal questionnaire	Participant toghether with parent(s)	15	YES
main	Only in Main*	Participant toghether with parent(s)	16	YES
maternal	Only in maternal questionnaire	No matter the identity of the interviewee	31	YES
main	Only in Main	Participant alone	6	NO

*Only in Main can also be due to missing of the maternal questionnaire

Online Supplement File 2:
Look- up tables

Contents

Look up table: Head conventional x-ray

Exam type	Body part	Decade	Age	Representative Score	Mean dose per exam #	Minimum dose per exam #	Maximum dose per exam #	Number of projection*	Number of observation$	References
Conventional	Skull	1980-1989	0	3	2.43	1.50	3.36	4	6	Ruiz 1991
Conventional	Skull	1980-1989	1	4	1.53	1.23	1.94	4	12	Gallini 1992
Conventional	Skull	1980-1989	5	4	1.15	0.89	1.51	4	12	Gallini 1992
Conventional	Skull	1980-1989	10	4	1.06	0.81	1.41	4	12	Gallini 1992
Conventional	Skull	1980-1989	15	4	0.97	0.73	1.33	4	12	Gallini 1992
Conventional	Skull	1980-1989	Adult	4	3.40	3.40	3.40	5	1	Melo 2016
Conventional	Skull	1990-1999	0	3	0.43	0.41	0.46	4	6	McDonald 1996
Conventional	Skull	1990-1999	1	3	0.93	0.52	1.37	4	12	McDonald 1996, Martin 1994
Conventional	Skull	1990-1999	10	3	0.68	0.33	1.21	4	18	McDonald 1996, Martin 1994
Conventional	Skull	1990-1999	15	3	0.74	0.25	1.27	4	12	McDonald 1996, Martin 1994
Conventional	Skull	1990-1999	5	3	0.70	0.38	1.04	4	18	McDonald 1996, Martin 1994
Conventional	Skull	1990-1999	Adult	4	1.50	1.50	1.50	3	1	Melo 2016
Conventional	Skull	2000-2010	0	5	0.57	0.55	0.58	4	2	Kiljunen 2009
Conventional	Skull	2000-2010	1	5	0.42	0.34	0.50	4	2	Kiljunen 2009
Conventional	Skull	2000-2010	10	5	0.79	0.76	0.82	4	2	Kiljunen 2009
Conventional	Skull	2000-2010	15	5	0.67	0.34	1.18	4	3	Kiljunen 2009
Conventional	Skull	2000-2010	5	5	0.65	0.60	0.69	4	3	Kiljunen 2009
Conventional	Skull	2000-2010	Adult	2	0.60	0.55	0.65	4	2	Knight 2014
Conventional	Skull	2000-2010	Adult	4	1.50	1.50	1.50	4	1	Melo 2016
Conventional	Sinus	1980-1989	Adult	4	0.63	0.63	0.63	5	1	Melo 2016
Conventional	Sinus	1990-1999	Adult	4	0.48	0.48	0.48	3	1	Melo 2016
Conventional	Sinus	2000-2010	10	5	0.21	0.21	0.21	2	1	Kiljunen 2009

Conventional	Sinus	2000-2010	15	5	0.35	0.35	0.35	2	1	Kiljunen 2009
Conventional	Sinus	2000-2010	5	5	0.15	0.15	0.15	2	1	Kiljunen 2009
Conventional	Sinus	2000-2010	Adult	4	0.48	0.48	0.48	3	1	Melo 2016

(#) mean, minimum and maximum reflect the distribution across the different simulations that were performed for each procedure x age x time period frame. For the analysis we used the mean dose.
(*) To obtain the dose for a single projection, divide the mean dose per exam by the number of projection
($) The mean, minimum and maximum reported is calculate across the number of values reported in this column

Look up table: Neck conventional x-ray

Exam type	Body part	Decade	Age	Representative Score	Mean dose per exam #	Minimum dose per exam #	Maximum dose per exam #	Number of projection*	Number of observation$	References
Conventional	Neck soft	1980-1989	Adult	4	0.02	0.02	0.02	2	1	Melo 2017
Conventional	Neck soft	1990-1999	Adult	4	0.01	0.01	0.01	2	1	Melo 2017
Conventional	Neck soft	2000-2010	0	2	0.01	0.00	0.02	2	2	Knight 2013
Conventional	Neck soft	2000-2010	1	2	0.01	0.00	0.02	2	2	Knight 2013
Conventional	Neck soft	2000-2010	10	2	0.01	0.00	0.02	2	2	Knight 2013
Conventional	Neck soft	2000-2010	15	2	0.01	0.00	0.01	2	2	Knight 2013
Conventional	Neck soft	2000-2010	5	2	0.00	0.00	0.01	2	2	Knight 2013
Conventional	Neck soft	2000-2010	Adult	2	0.00	0.00	0.01	2	2	Knight 2013
Conventional	Neck soft	2000-2010	Adult	4	0.01	0.01	0.01	2	1	Melo 2017
Conventional	Full spine	1980-1989	10	3	0.27	0.05	0.53	3	6	Ruiz 1990
Conventional	Full spine	1980-1989	15	3	0.22	0.08	0.33	3	4	Ruiz 1990
Conventional	Full spine	1980-1989	5	3	0.10	0.04	0.16	3	2	Ruiz 1990
Conventional	Cervical spine	1980-1989	Adult	4	0.04	0.04	0.04	4	1	Melo 2017
Conventional	Cervical spine	1990-1999	Adult	4	0.03	0.03	0.03	5	1	Melo 2017
Conventional	Cervical spine	2000-2010	0	2	0.02	0.00	0.03	2	4	Knight 2013
Conventional	Cervical spine	2000-2010	1	2	0.01	0.00	0.03	2	4	Knight 2013
Conventional	Cervical spine	2000-2010	10	2	0.02	0.00	0.04	3	4	Knight 2013
Conventional	Full spine	2000-2010	10	3	0.00	0.00	0.00	3	10	Gogos 2003
Conventional	Cervical spine	2000-2010	15	2	0.02	0.00	0.04	3	4	Knight 2013
Conventional	Full spine	2000-2010	15	3	0.00	0.00	0.00	3	10	Gogos 2003
Conventional	Cervical spine	2000-2010	5	2	0.01	0.00	0.01	2	4	Knight 2013
Conventional	Cervical spine	2000-2010	Adult	2	0.03	0.00	0.06	5	4	Knight 2013
Conventional	Cervical spine	2000-2010	Adult	4	0.03	0.03	0.03	5	1	Melo 2017

(#) mean, minimum and maximum reflect the distribution across the different simulations that were performed for each procedure x age x time period frame. For the analysis we used the mean dose.

(*) To obtain the dose for a single projection, divide the mean dose per exam by the number of projection

($) The mean, minimum and maximum reported is calculate across the number of values reported in this column

Look up table: Head CT scan

Exam type	Body part	Decade	Age exam	Representative score	Mean exam	references
Scan	Head	1980-1989	0 to 14	5	Table 4, Brain dose from head CT (Mean value) before 1990; in Lee 2016	Lee 2016
Scan	Head	1990-1999	0 to 19	5	Table 4, Brain dose from head CT (Mean value) 1990-1999; in Lee 2016	Lee 2016
Scan	Head	2000-2010	0 to 4	5	Table 4, Brain dose from head CT (Mean value); in Lee 2016	Lee 2016
Scan	Head	2000-2010	5 to 9	5	Table 4, Brain dose from head CT (Mean value); in Lee 2016	Lee 2016
Scan	Head	2000-2010	10 to 14	5	Table 4, Brain dose from head CT (Mean value); in Lee 2016	Lee 2016
Scan	Head	2000-2010	15 to 19	5	Table 4, Brain dose from head CT (Mean value); in Lee 2016	Lee 2016

Look up table: dental x-ray

Exam type	Decade	Age	Mean dose per exam	References
Intraoral x-ray	1980-1989	Adult	Table 5, Mean value 1980-1989; in Fontana 2019	Fontana 2019
Intraoral x-ray	1990-1999	Adult	Table 5, Mean value 1990-1999; in Fontana 2019	Fontana 2019
Intraoral x-ray	2000-2009	Adult	Table 5, Mean value 2000-2009; in Fontana 2019	Fontana 2019
Full Mouth x-ray	1980-1989	Adult	We took the correspondent value for the Intraoral x-ray and multiplied it for 20, as the number of intraoral x-ray required to cover the full mouth	Fontana 2019
Full Mouth x-ray	1990-1999	Adult	We took the correspondent value for the Intraoral x-ray and multiplied it for 20, as the number of intraoral x-ray required to cover the full mouth	Fontana 2019
Full Mouth x-ray	2000-2009	Adult	We took the correspondent value for the Intraoral x-ray and multiplied it for 20, as the number of intraoral x-ray required to cover the full mouth	Fontana 2019
Panoramic x-ray	1980-1989	Adult	0.049	Gibbs 1988 (Mean across 3 measurement)
Panoramic x-ray	2000-2010	Adult	0.008	Lecomber 2000, Hayakawa 2001 (mean a cross 9 measurement)

Look up table: fetal dose from common x-ray examinations

Exam type	Body part	Representative score	Mean dose per exam*	Minimum dose per exam*	Maximum dose per exam*	Number of observation$	references
Conventional	Dental	2	0.00	0.00	0.00	3	Fenig 2001, Toppenberg 1999, Wagner 1997
Conventional	Extremities	2	0.01	0.01	0.18	3	Fenig 2001, Toppenberg 1999, Wagner 1997
Conventional	Thorax	5	0.05	Not found	0.01	3	Chahed 2000, Sharp 1998, Tung and Tsai 1999
Scan	Thorax	5	0.06	Not found	0.96	1	Sharp 1998
Conventional	Mammography	5	0.16	Not found	Not found	1	Chahed 2000
Conventional	Abdomen	5	1.40	Not found	4.20	2	Sharp 1998, Tung and Tsai 1999
Conventional	Barium enema	5	6.80	Not found	24.00	1	Sharp 1998
Scan	Abdomen	5	8.00	Not found	49.00	1	Sharp 1998
Conventional	Pelvimetry	2	12.70	Not found	Not found	2	Fenig 2001, Fergurson 1996
Conventional	Skull	5	Not found	Not found	0.01	1	Sharp 1998
Scan	Head	5	Not found	Not found	0.01	1	Sharp 1998

(*) Mean, minimum and maximum reflect the distribution across the different simulations that were performed for each procedure x age x time period frame. For the analysis we used the mean dose.

The values reported here are values of mean (minimum or maximum) of fetal dose. Time period was not taken into account for this table because of the paucity of data

($) The mean, minimum and maximum reported is calculate across the number of values reported in this column

Look up table: newborn dose from common x-ray examination

Exam type	Body part	Decade*	Mean dose #	Minimum dose #	Maximum dose #	References
Conventional	abdomen	1980-1989	Mean between minimum and maximum	0.00	0.00	Kettunen 2004 (babygram)
Conventional	abdomen	1990-1999	Mean between minimum and maximum	0.00	0.00	Kettunen 2004 (babygram)
Conventional	abdomen	2000-2010	Mean between minimum and maximum	0.00	0.00	Kettunen 2004 (babygram)
Conventional	extremities	1980-1989	0.00	0.00	0.00	Kettunen 2004 (babygram). For the mean dose (the one that we will use in the main analysis), we will use the minimum of the babygram) as the dose will be actually virtually 0.
Conventional	extremities	1990-1999	0.00	0.00	0.00	Kettunen 2004 (babygram)
Conventional	extremities	2000-2010	0.00	0.00	0.00	Kettunen 2004 (babygram)
Conventional	head	1980-1989	2.43	1.50	3.36	Ruiz 1991
Conventional	head	1990-1999	0.43	0.41	0.46	Mcdonald 1996, Martin 1994
Conventional	head	2000-2010	0.57	0.55	0.58	Kilujenen 2009
Conventional	sinus	1980-1989	2.43	1.50	3.36	We do not have sinus in in 1980-89. We used the dose for skull in the same time period
Conventional	skull	1990-1999	0.43	0.41	0.46	Mcdonald 1996, Martin 1994
Conventional	skull	2000-2010	0.57	0.55	0.58	Kiljunen 2009
Conventional	thorax	1980-1989	Mean between minimum and maximum	0.00	0.00	Kettunen 2004 (chest proyection)
Conventional	thorax	1990-1999	Mean between minimum and maximum	0.00	0.00	Kettunen 2004 (chest proyection)
Conventional	thorax	1990-1999	Mean between minimum and maximum	0.00	0.00	Kettunen 2004 (babygram)
Conventional	thorax	2000-2010	Mean between minimum and maximum	0.00	0.00	Kettunen 2004 (chest proyection)
Conventional	whole body	1990-1999	Mean between minimum and maximum	0.00	0.00	Kettunen 2004 (babygram)
Conventional	whole body	2000-2010	Mean between minimum and maximum	0.00	0.00	Kettunen 2004 (babygram)

Exam type	Body part	Decade*	Mean dose #	Minimum dose #	Maximum dose #	References
Nuclear	abdomen	1990-1999	0.00	0.00	0.00	Treves 2010 said that the dose from nuclear medicine procedure is comparable with common imaging procedure. Thus we will just imputing the dose from common x-ray procedures of the same body part
Nuclear	abdomen	2000-2010	0.00	0.00	0.00	Treves 2010 said that the dose from nuclear medicine procedure is comparable with common imaging procedure. Thus we will just imputing the dose from common x-ray procedures of the same body part
Nuclear	head	1990-1999	0.43	0.41	0.46	Treves 2010 said that the dose from nuclear medicine procedure is comparable with common imaging procedure. Thus we will just imputing the dose from common x-ray procedures of the same body part
Nuclear	head	2000-2010	0.57	0.55	0.58	Treves 2010 said that the dose from nuclear medicine procedure is comparable with common imaging procedure. Thus we will just imputing the dose from common x-ray procedures of the same body part
Nuclear	thorax	1980-1989	0.00	0.00	0.00	Treves 2010 said that the dose from nuclear medicine procedure is comparable with common imaging procedure. Thus we will just imputing the dose from common x-ray procedures of the same body part
Nuclear	thorax	1990-1999	0.00	0.00	0.00	Treves 2010 said that the dose from nuclear medicine procedure is comparable with common imaging procedure. Thus we will just imputing the dose from common x-ray procedures of the same body part

Exam type	Body part	Decade*	Mean dose #	Minimum dose #	Maximum dose #	References
Nuclear	thorax	2000-2010	0.00	0.00	0.00	Treves 2010 said that the dose from nuclear medicine procedure is comparable with common imaging procedure. Thus we will just imputing the dose from common x-ray procedures of the same body part
Nuclear	whole body	1990-1999	0.00	0.00	0.00	Treves 2010 said that the dose from nuclear medicine procedure is comparable with common imaging procedure. Thus we will just imputing the dose from common x-ray procedures of the same body part
Scan	abdomen	1990-1999	0.54	0.08	1.05	Thierry-Chef 2019 (1990-95)
Scan	abdomen	2000-2010	0.36	0.02	2.33	Thierry-Chef 2019 (2000-05)
Scan	extremities	2000-2010	0.06	0.00	0.26	Thierry-Chef 2019 (limb, 2000-05)
Scan	head	1990-1999	Table 4, Brain dose from head CT (Mean value) 1990-1999 for age range 0 to 14; in Lee 2016	see same table	see same table	Lee 2016
Scan	head	2000-2010	Table 4, Brain dose from head CT (Mean value) 2000-2010 for age range 0 to 14; in Lee 2016	see same table	see same table	Lee 2016
Scan	thorax	1990-1999	3.03	1.61	4.73	Thierry-Chef 2019 (chest, 1990-95)
Scan	thorax	2000-2010	1.51	0.31	12.58	Thierry-Chef 2019 (chest, 1990-95)
Scan	whole body	1990-1999	23.87	5.58	40.46	Thierry-Chef 2019
Scan	whole body	2000-2010	27.42	4.49	38.64	Thierry-Chef 2019

(#) Mean, minimum and maximum reflect the distribution across the different simulations that were performed for each procedure x age x time period frame. For the analysis we used the mean dose.

(*) Age is not reported here as in this table we reported values for newborns (that is children age 0 to 1 year)

Look up table: How we treated missing values in the previous look-up tables

After having matched the previous look up tables with the data from MOBI-kids we had some of the reported examination remaining without an assigned dose, because the dose was not reported in the look up table. Here we summarized what we assumed for each specific case in assigning the dose

Exam type	Body part	Decade	Age	n observations in the dataset	Assumed dose (mean)	Reference	Rational for assumption
Conventional	sinus	1980-1989	0	1	0.15	Sinus, 5 years of age, 2000-2010 (Kiljunen 2009)	Closest age and closest period
Conventional	sinus	1990-1999	1	3	0.15	Sinus, 5 years of age, 2000-2010 (Kiljunen 2009)	Closest age and closest period
Conventional	sinus	1990-1999	5	7	0.15	Sinus, 5 years of age, 2000-2010 (Kiljunen 2009)	Closest age and closest period
Conventional	sinus	1990-1999	10	1	0.21	Sinus, 10 years of age, 2000-2010 (Kiljunen 2009)	Closest age and closest period
Conventional	sinus	2000-2010	1	1	0.15	Sinus, 5 years of age, 2000-2010 (Kiljunen 2009)	Closest age and closest period
Conventional	neck	1990-1999	0	1	0.1	Full spine, 5 years of age, 1980-89 (Ruiz 1991)	Full spine does include the neck and likely the dose to the brain in mainly deriving from the scatter radiation when examining the cervical spine
Conventional	neck	1990-1999	1	2	0.1	Full spine, 5 years of age, 1980-89 (Ruiz 1991)	Full spine does include the neck and likely the dose to the brain in mainly deriving from the scatter radiation when examining the cervical spine
Conventional	neck	1990-1999	5	3	0.1	Full spine, 5 years of age, 1980-89 (Ruiz 1991)	Full spine does include the neck and likely the dose to the brain in mainly deriving from the scatter radiation when examining the cervical spine
Conventional	neck	1990-1999	10	2	0.27	Full spine, 10 years of age, 1980-89 (Ruiz 1991)	Full spine does include the neck and likely the dose to the brain in mainly deriving from the scatter radiation when examining the cervical spine

Conventional	neck	1990-1999	15	1	0.22	Full spine, 15 years of age, 1980-89 (Ruiz 1991)	Full spine does include the neck and likely the dose to the brain in mainly deriving from the scatter radiation when examining the cervical spine
Conventional	breast		fetal	1	0.16	Mammography (Chaled 2000)	Similar type of examination
Conventional	lumbar spine		fetal	2	12.7	Pelvimetry (Sharp 1998)	Very similar examinations in term of fetal exposure
Conventional	whole body		fetal	1	12.7	Pelvimetry (Sharp 1998)	Image of the whole body, does include the pelvis
Conventional	lumbar spine		fetal		8.41	Linet 2009 (sum of AP and lat projection)	
Scan	head		fetal		0.5	Toppenberg 1999	
conventional	head		fetal		0.01	Kettunen 2004	
Scan	dental		fetal	2	0.001	Fenig 2001, Toppenberg 1999, Wagner 1997	Max of dental conventional as in Fenig 2001, Toppenberg 1999 and Wagner 1995 (head scan max is 0.005)
Scan	abdomen	2000-2010	5 to 9	1	0.14	Thierry-Chef 2019	
Scan	abdomen	2000-2010	10 to 14	8	0.09	Thierry-Chef 2019	
Scan	abdomen	2000-2010	15 to 19	11	0.05	Thierry-Chef 2019	
Scan	abdomen	2000-2010	>19	10	0.03	Thierry-Chef 2019	
Scan	head	2000-2010	>19	146	33	Lee 2016	Closest age (15 to 19 age) for the same decade
Scan	neck	1990-1999	0 to 4	1	18.95	Thierry-Chef 2019	
Scan	neck	2000-2010	5 to 9	1	16.74	Thierry-Chef 2019	
Scan	neck	2000-2010	10 to 14	11	16.41	Thierry-Chef 2019	
Scan	neck	2000-2010	15 to 19	9	10.20	Thierry-Chef 2019	

Scan	neck	2000-2010	>19	1	13.72	Thierry-Chef 2019	
Scan	spine	2000-2010	10 to 14	1	16.41	Thierry-Chef 2019	
Scan	whole body	1990-1999	0 to 4	4	27.56	Thierry-Chef 2019	
Scan	whole body	1990-1999	5 to 9	2	22.07	Thierry-Chef 2019	
Scan	whole body	2000-2010	0 to 4	2	24.29	Thierry-Chef 2019	
Scan	whole body	2000-2010	5 to 9	11	26.61	Thierry-Chef 2019	
Scan	whole body	2000-2010	10 to 14	41	24.49	Thierry-Chef 2019	
Scan	whole body	2000-2010	15 to 19	35	19.93	Thierry-Chef 2019	
Scan	whole body	2000-2010	>19	24	19.93	Thierry-Chef 2019	
Scan	Dental	2000-2010	10 to 14	27	7.48	Thierry-Chef 2019	
Scan	Dental	2000-2010	15 to 19	11	5.05	Thierry-Chef 2019	
Scan	Dental	2000-2010	20 to 24	13	8.69	Thierry-Chef 2019	
Scan	Dental	2000-2010	Before 10	8	15.97	Thierry-Chef 2019	
Nuclear	abdomen	1990-1999	fetal		0.00	Treves 2011	
Nuclear	abdomen	2000-2010	fetal		0.00	Treves 2011	
Nuclear	head	1990-1999	fetal		0.43	Treves 2011	In Treves 2011 it is reported that the dose from a nuclear x-ray examination, thus we imputed the dose from the equivalent conventional examination
Nuclear	head	2000-2010	fetal		0.57	Treves 2011	
Nuclear	thorax	1980-1989	fetal		0.00	Treves 2011	
Nuclear	thorax	1990-1999	fetal		0.00	Treves 2011	
Nuclear	thorax	2000-2010	fetal		0.00	Treves 2011	
Nuclear	whole body	1990-1999	fetal		0.00	Treves 2011	

Look up table: decision that we took when we had a missing values in the MOBI-kids dataset

We also had missing in the information collected. Here we have a summary of the type of information that were missing and the decision we took in each specific case

Exam type	Body part	Decade	Age	n observations in the dataset	Comments
Conventional	skull	**NA**	**NA**	24	Not included in the main analysis. In a sensitivity analysis they were included as done before the two year window period
Conventional	**NA**		fetal	1	Not included
NA	**NA**		fetal	1	Not included
Scan	**NA**	1990-1999	0 to 4	2	We assumed it was a head procedure. Head procedure is the most common in the dataset and in general is the most common procedures in children
Scan	**NA**	2000-2010	5 to 9	8	We assumed it was a head procedure. Head procedure is the most common in the dataset and in general is the most common procedures in children
Scan	**NA**	2000-2010	10 to 14	10	We assumed it was a head procedure. Head procedure is the most common in the dataset and in general is the most common procedures in children
Scan	**NA**	2000-2010	15 to 19	12	We assumed it was a head procedure. Head procedure is the most common in the dataset and in general is the most common procedures in children
Scan	**NA**	2000-2010	>19	11	We assumed it was a head procedure. Head procedure is the most common in the dataset and in general is the most common procedures in children
Scan	head	**NA**	**NA**	9	Not included in the main analysis. In a sensitivity analysis they were included as done before the two year window period
Nuclear	**NA**	1980-1989	Newborn	1	Mean across all the nuclear medicine procedures
Scan	**NA**	1980-1989	Newborn	1	We assumed it was a head procedure. Head procedure is the most common in the dataset and in general is the most common procedures in children

NA= Missing

Bibliography for Supplementary File 2

Reference lists for the look up tables

Table	Reference
Head conventional table	(1–6)
Neck conventional table	(1,3,7,8)
Head CT	(9)
Dental	(10–13)
Fetal	(14–21)
Newborn	(1,4–6,9,14)
Missing values	(1,6,9,22–24)

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Online Supplement File 3:
MOBI-kids dose estimation from medical diagnostic examinations: Details of the procedures

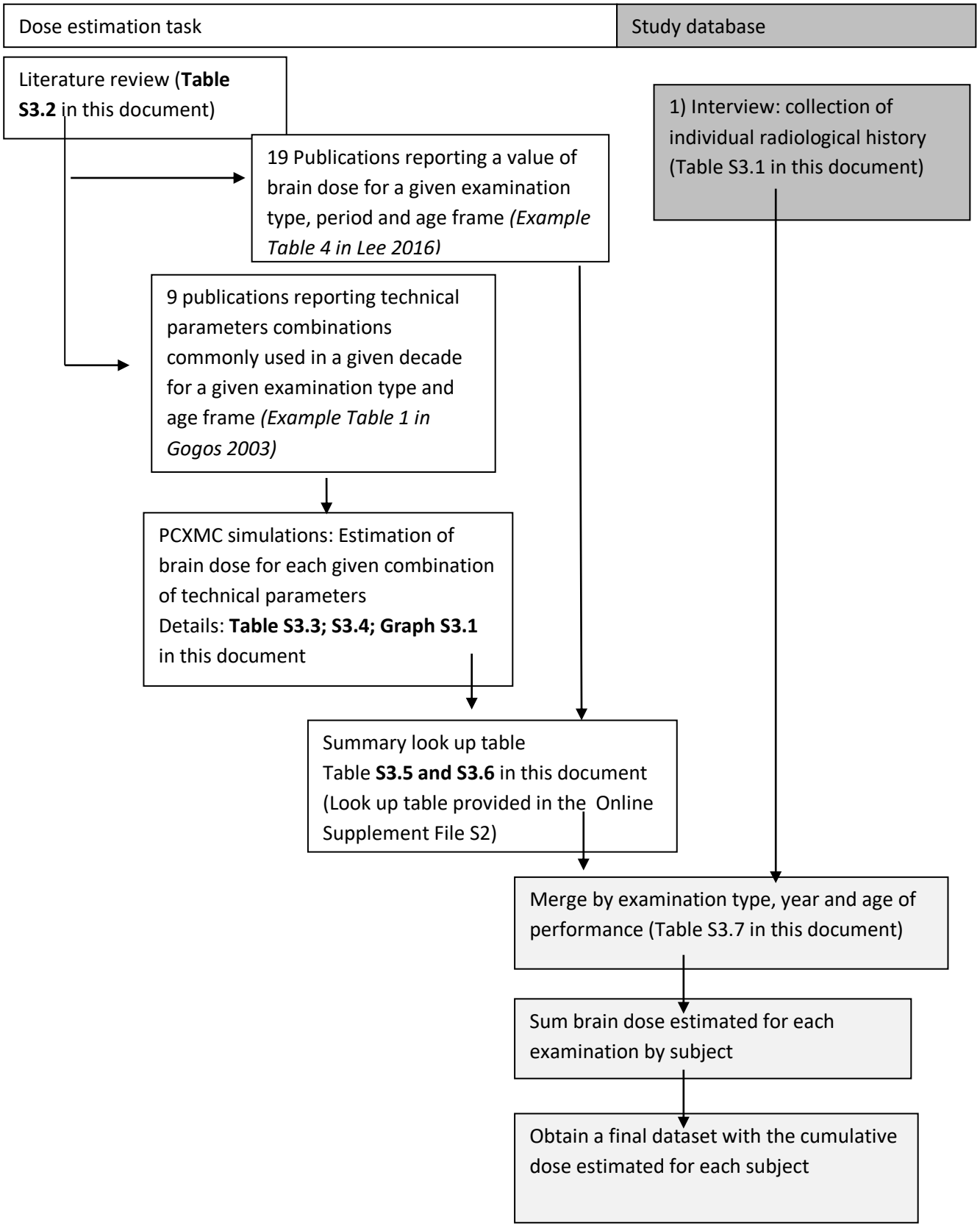
The aim of this work was to calculate for each participants of MOBI-kids study the cumulative absorbed dose to the brain from medical exposure. This was achieved with the following steps:

1) Determine the absorbed dose to the brain from each procedure. Due to the lack of availability of individual specific data for individual dose reconstruction, organ doses were estimated for each reported examination based on typical dose values by time period and age at exposure.
2) For each subject, the cumulative lifetime brain dose was obtained as the sum of the organ doses attributed to each examination, as reported in the personal interview.

The present document contains:

Figure S3.1: Visual summary of the process

Overall process has been described in the methods section of the Manuscript. Details and assumptions made in each step may be found in the present document.



Information collected in the MOBI-kids study

Within the MOBI-kids study, detailed information on medical radiological history has been collected via personal interview. Information consists in a list of potential medical diagnostic procedures that the subject could have had during his life. In addition, interviewers had images of each examination type to avoid confusion between procedures. The table below detailed how questions to collected radiological history were formulated in the two questionnaires (Main questionnaire to the participants, Parental questionnaire to the mother of participant).

Table S3.1 List of questions of the questionnaire's medical radiation section that were used in the analysis.

Type of radiological examination	Question formulation	If "Yes" detailed collected
Main questionnaire		
Conventional head and neck x ray	Have you ever had x-rays of the head or neck?	How many of these types of x-rays did you have in your lifetime? For each one: How old were you? Body Part in X-Ray Reason for X-Ray
CT-scan	In your lifetime, have you ever had a CT or PET CT scan of the head, neck or whole body (including the head)?	How many of these types of tests did you have in your lifetime? For each one: How old were you? Body Part in CT Reason for CT
Intraoral x-ray	In your lifetime, have you ever had a bite-wing x-ray?	Please tell me how frequently you had bite-wing x-rays at different stages in your life: <10; 10-14, 15-19, 20-24 age
Full mouth x-ray	In your lifetime, have you ever had a full mouth x-ray?	Please tell me how frequently you had full mouth x-ray at different stages in your life: <10; 10-14, 15-19, 20-24 age
Panorex x-ray	In your lifetime, have you ever had a panorex x-ray?	Please tell me how frequently you had panorex x-ray at different stages in your life: <10; 10-14, 15-19, 20-24 age
Dental CT	In your lifetime, have you ever had a dental CT?	Please tell me how frequently you had dental CT at different stages in your life: <10; 10-14, 15-19, 20-24 age
Maternal questionnaire		
Any examination	During the pregnancy with the	For each one:

during pregnancy	index, were any X-rays (including dental X-rays), CT scans or MRI examinations or any radiation treatments carried out?	**Type of exam** (X-ray; dental bite wing; dental full mouth; dental panoramic; dental CT; angiography; isotope scanning; fluoroscopy; CT; MRI; therapeutic radiation; other **Part of the Body** (head & neck, teeth, thorax, abdomen, extremities,| whole body, other **Reason** **Trimester during pregnancy** **Was the abdomen protected from X-rays by lead shielding?**
Any examination of the child during the first year of life	Was the infant subjected to any X ray or nuclear medicine during the birth hospitalization and/or during the first year of life?	**Body parts that were imaged**: head & neck, thorax, abdomen, extremities, whole body **Type of exam** (x-ray, CT, MRI, Nuclear medicine) **Number of exams**

Notes regarding the cleaning of this database:

1) **CT scan**: There were reported 28 head CT with reason “appendicitis”. In such cases, we changed the body part to the abdomen.

Table S3.2 List of publication retrieved with the literature review

Ref	Country	Exam	Body part #	Information extracted	Number of rows(*) extracted	Age covered	Period covered	Study type	Relevance score $
Fontana 2019 (1)	Level I countries	Conventional	Dental, Full mouth	Brain dose	6	Adult	1980-1989, 1990-1999, 2000-2010	Estimation of organ doses from collection of technical parameters in a literature review	4
Gogos 2003 (2)	Greece	Conventional	Skull , Full spine	Technical parameters	59	1, 5, 10, 15	2000-2010	Measurement of Entrance Surface Dose and collection of parameters in a large pediatric hospital	3
Ruiz 1991 (3)	Spain	Conventional	Full spine, Skull	Technical parameters	52	5, 10, 15	1980-1989	Measurement of entrance surface dose and collection of parameters in an hospital	3
Mazonakis 2004 (4)	Crete	Conventional	Skull	Technical parameters	12	5, 10	2000-2010	Measurement of dose and collection of parameters	3
Martin 1994 (5)	UK	Conventional	Skull	Technical parameters	40	1, 5, 10, 15	1990-1999	Measurement of entrance surface dose and dose-area product in an hospital	3
McDonald 1996 (6)	UK	Conventional	Skull	Technical parameters	42	0, 1, 5, 10, 15	1990-1999	Measurement of entrance surface dose and dose-area product in an hospital	3
Gallini 1992 (7)	Italy	Conventional	Skull	Technical parameters	72	1, 5, 10, 15	1980-1989	Measurement of dose and collection of parameters in 7 hospital belonging to the same region	4
Sonawane 2011 (8)	India	Conventional	Skull	Technical parameters	91	0, 1, 5, 10, 15	2000-2010	DRL publication: Collection of parameters for the definition of DRL levels (2240 measurement in 22 public and private hospitals	4

Begum 2001 (9)	Bangladesh	Conventional	Skull	Technical parameters	6	Adult	2000-2010		NA
Knight 2014 (10)	Australia	Conventional	Skull, Neck soft, Cspine	Technical parameters	50	0, 1, 5, 10, 15, Adult	2000-2010	Suggested optimal value (review of optimization strategy)	2
Melo 2016 (11)	US	Conventional	Skull, Paranasal sinus, Neck soft, Cervical spine	Brain dose	12	Adult	1980-1989, 1990-1999, 2000-2010	Estimation of organ doses from collection of technical parameters in a literature review	4
Kiljunen 2008 (12)	Finland	Conventional	Skull, Sinus, abdomen, thorax	Brain dose	20	0, 1, 5, 10, 15	2000-2010	Collection of examination parameters in 24 Finnish hospitals	5
Hayakawa (13)	Japan	Panoramic	Dental	Brain dose	8	Adult, NA	2000-2010	Phantom measurement using lowest exposure (but still enough to take image) and highest exposure scenario	4
Gibbs 1988 (14)	worldwide	Panoramic, Conventional	Dental, Full mouth	Brain dose	5	Adult	1980-1989	Phantom measurement using standard protocol	4
Lecomber 2001 (15)	worldwide	Panoramic, Scan	Dental	Brain dose	2	Adult	2000-2010	Phantom measurement using standard protocol	4
Lee 2016 (16)	UK	Scan	Head	Brain dose	18	NA	1980-1989, 1990-1999, 2000-2010	Estimation of doses from parameters as collected form a sample of 1073 CT-scans from 36 hospitals.	5
Fenig 2001 (17)	US	Conventional	Abdomen, Barium enema, Dental, Extremities, Mammography, Pelvimetry, Skull, Thorax	Brain dose	8	Fetal	2000-2010	Review reporting organ dose estimation	2

Wagner 1995 (18)	US	Conventional	Abdomen, Barium enema, Dental, Extremities, Mammography, Skull, Thorax	Brain dose	15	Fetal	1990-1999	Review reporting organ dose estimation	2
Tung and Tsai 1999 (19)	china	Conventional	Abdomen, Thorax	Brain dose	2	Fetal	1990-1999	National survey	5
Chahed 2000 (20)	tunisia	Conventional	Mammography, Thorax	Brain dose	2	Fetal	1990-1999	Dose estimation in a cohort of pregnant women	5
Fergurson 1996 (21)	US	Conventional	Pelvimetry	Brain dose	1	Fetal	1990-1999	Phantom measurement using standard protocol	2
Toppenberg 1999 (22)	US	Conventional, Scan	Abdomen, Barium enema, Dental, Extremities, Skull, Thorax, Head	Brain dose	9	Fetal	1990-1999	Review reporting organ dose estimation	2
Osei 1999 (23)	UK	Conventional, Scan	Abdomen, Barium enema, Skull, Thorax	Brain dose	14	Fetal	1990-1999, 2000-2010	Dose estimation from parameter collection in a cohort of 50 pregnant women	4
Sharp 1998 (24)	UK	Conventional, Scan	Abdomen, Barium enema, Skull, Thorax, Head	Brain dose	11	Fetal	1990-1999	NRPB national survey	5
Parry 1999 (25)	US	Conventional, Scan	Abdomen, Barium enema, Thorax	Brain dose	4	Fetal	1990-1999	Radiological textbook	2
Helmrot 2003 (26)	Sweeden	Conventional, Scan	Abdomen, Barium enema, Thorax	Brain dose	6	Fetal	2000-2010	Estimation of organ doses based on data registered in the Radiological Information System/Picture Archive and	3

								Communication System of one hospital	
Linet 2009 (27)	worldwide	conventional	various	Brain dose	1	Fetal	Not reported	Not reported	2
Kettunen 2004 (28)	Finland	conventional	thorax, thorax and abdominal	Brain dose	9	0	1990-1999	Nationwide survey	5

* as row we identify here: a) The number of different parameters combination (each combination is resulting in a dose estimation with the PCXMC software; or b) The number of different value of the brain doses reported

(#) For neck procedures, manuscript reporting full spine or scoliosis projection was considered as projection for cervical spine. Justification: Cervical spine is included in full spine projection and scoliosis projection. Some of the reported reason for a neck x-ray was “scoliosis”.

$ Relevance score: To each of the publication found we gave a relevance score. Relevance refer to the specific aim of this work, which is to obtain the dose which could be taken as most representative of the practice of a given age and time period. Thus, if parameters/estimation comes from a collection of parameters/measurement at national level a high score is given. For more details around this score see Fontana 2019 (1)

PCXMC simulation details

Table S3.3: Details on the age categories used for simulation on the PCXMC software

PCXMC use the following age group (in years of age) 0 (0 to 0.5); 1 (0.5 to 2.5); 5 (2.5 to 7.5); 10 (7.5 to 12.5); 15 (12.5 to 17) and adult. Age reported in the publication may not match with these categories. Here we report first the age category as reported in the publication, and after the age categories that were used for the simulation

Reference	Age categories reported in the manuscript	Age categories used in the simulations
Sonawane 2011	<1y	0 (0 to 0.5) years of age
Sonawane 2011	1-4 y	1 (0.5 to 2.5) AND 5 (2.5 to 7.5) years of age
Sonawane 2011	5-9y	5 (2.5 to 7.5) AND 10 (7.5 to 12.5) years of age
Sonawane 2011	10-15 y	10 (7.5 to 12.5) AND 15 (12.5 to 17) years of age
Knight 2014	0-6 months	0 (0 to 0.5) years of age
Knight 2014	6-18 months	1 (0.5 to 2.5) years of age
Knight 2014	18-36 months	1 (0.5 to 2.5) years of age
Knight 2014	3-7 years	5 (2.5 to 7.5) years of age
Knight 2014	8-12 years	10 (7.5 to 12.5) years of age
Knight 2014	13-17 years	15 (12.5 to 17) years of age
Ruiz 1991	0-1y	0 (0 to 0.5) years of age
Ruiz 1991	1-5y	1 (0.5 to 2.5) AND 5 (2.5 to 7.5) years of age
Ruiz 1991	5-10y	5 (2.5 to 7.5) AND 10 (7.5 to 12.5) years of age
Ruiz 1991	10-14y	10 (7.5 to 12.5) AND 15 (12.5 to 17) years of age
Gallini 1992	1-14 y (Mean 5.8 y; SD 4.1)	0 (0 to 0.5) AND 1 (0.5 to 2.5) AND 5 (2.5 to 7.5) AND 10 (7.5 to 12.5) AND 15 (12.5 to 17) years of age
Gogos 2003	0.5-2	1 (0.5 to 2.5) years of age
Gogos 2003	3-7y	5 (2.5 to 7.5) years of age
Gogos 2003	8-12y	10 (7.5 to 12.5) years of age
Gogos 2003	13-18 y	15 (12.5 to 17) years of age
McDonald 1996	infant	0 (0 to 0.5) years of age
McDonald 1996	1-5 y	1 (0.5 to 2.5) AND 5 (2.5 to 7.5) years of age
McDonald 1996	5-10 y	5 (2.5 to 7.5) AND 10 (7.5 to 12.5) years of age
McDonald 1996	10-15 y	10 (7.5 to 12.5) AND 15 (12.5 to 17) years of age
Martin 1994	1-5 y	1 (0.5 to 2.5) AND 5 (2.5 to 7.5) years of age
Martin 1994	6-10 y	10 (7.5 to 12.5) years of age
Martin 1994	11-15 y	12.5 to 17) years of age

Table S3.4: Details on the location of the x-ray beam used for simulation on the PCXMC software

PCXMC required to specify the location of the x-ray beam with respect to the phantom by imputing the coordinates (x,y,z) of the point inside the phantom, through which the central axis of the x-ray beam passes. The following values were inserted:

- Skull xray

Age	ref point x	y	z
adult	0	0	89
15	0	0	79
10	0	0	65
5	0	0	53
1	0	0	40
0	0	0	17

- Neck x-ray

Age	ref point x	y	z
Neck			
adult	0	0	75
15	0	0	69
10	0	0	53
5	0	0	43
1	0	0	33
0	0	0	20
Full spine			
adult	0	0	67
15	0	0	57
10	0	0	43
5	0	0	33
1	0	0	23
0	0	0	15

Graph S3.1: Details on the use of information on HVL when lacking of information on filtration on the PCXMC simulations

In some publication Half Value Layer (HVL) were reported instead of total filtration. The half value layer is the amount of absorbing material (i.e. the thickness of a standard material), which is needed to reduce the intensity of the x-ray beam by 50%. We used the following graph to derive the total mmAl filtration (Consider that CDA is HVL in French)

de faisceaux. L'influence de la tension d'accélération sur la CDA a tout d'abord été étudiée. Les résultats sont présentés :

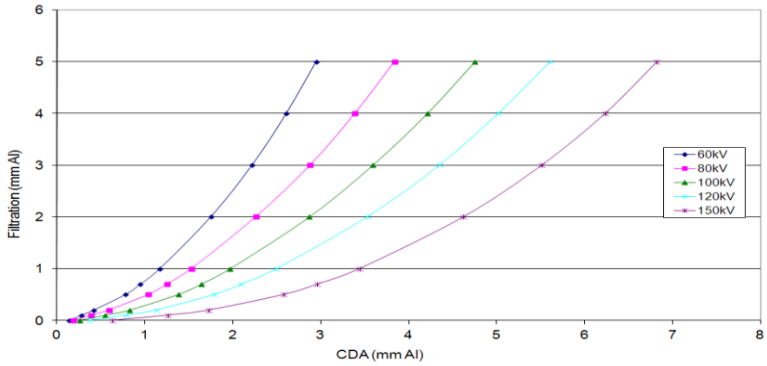


Figure 5 : Evolution de la CDA avec la filtration pour différentes valeurs de tension d'accélération du tube RX.

On constate que pour une valeur de filtration donnée, la variation relative de la CDA est égale à la variation relative de la tension d'accélération.

Reference of the graph personal communication Carlo Maccia

Table S3.5: Details on the steps conducted to build the look up table

Step Number	Identification of the step	Details
1	Combination of technical parameters (dose quantity and Kv)	We used the mean, minimum and maximum of the dose quantity (either air kerma, mAs…) combined with the reported mean kV. We further refer to these combinations as combinations with central values, minimum values and maximum values, respectively.
2	Creation of a dose database	Putting together values coming from different simulations and the values of brain dose as found in the literature, we obtain a database. For each examination, period, and age frame (example for conventional head x-ray in 2000-2010 for a child age 5 to 10) we complied several values (depending on the number of publications found).
3	Creation of a look up table	To obtain a look up table with one entry per each examination, period, and time frame we proceeded as follows: We grouped observation by time period, age, type examination and relevance score. For each group we calculated a summary of measures: Arithmetic mean, minimum, maximum, Geometric mean, Standard deviation. For dose values coming from simulations with PCXMC, as a first choice we selected values coming from

		"combinations of central values", thus we didn't considered dose resulted from combination of a minimum/maximum dose value (Air kerma, mAs) with the mean kV values. It is important to note that the difference between values estimated from combination with extreme parameters in comparison with values estimated from central parameters were in the order of few decimals. This indicates that, even considering a large variation in the parameters used by radiologists (which is very likely and represented by the maximum and minimum values), the resulting estimation is in good agreement with the one selected for imputation (i.e "combinations of central values").
4	Calculation of dose for each single examination (Combination of dose per projection)	Another important issue when summarizing information is the difference between projection and examination. A single exam (for example a skull x-ray) is the result of various projections. Here we list the most common number of projections for conventional x-ray by time period. Therefore, when we report a value of organ dose for a single projection (i.e. skull Anterior-Posterior), the value of brain dose for the full examination is obtained by multiplying according to the number of projection usually required to perform the given examination (see table S3.6)

Table S3.6: Common number of projection for a single radiographic procedure

Body part	Period range	Age	Number of projections	Reference
Neck	1980-1989	adult	2	Melo 2016 (11)
Neck	1980-1989	children	2	Kirks 1998 (29)
Neck	1990-1999	adult	2	Melo 2016 (11)
Neck	1990-1999	children	2	Kirks 1998 (29)
Neck	2000-2010	adult	2	Melo 2016 (11)
Neck	2000-2010	children	2	Coley 2013 (Caffey's Paediatric diagnostic imaging) (30)
sinus	1980-1989	adult	5	Melo 2016 (11)
sinus	1980-1989	children	2	Swischuk 1982 (31)
sinus	1990-1999	adult	3	Melo 2016 (11)
sinus	1990-1999	children	3	Diament 1992 and Kirks 1998 (32)
sinus	2000-2010	adult	3	Melo 2016 (11)
sinus	2000-2010	children	2	Clark 2005 (33)
skull	1980-1989	adult	5	Melo 2016 (11)
skull	1980-1989	children	4	Kirks 1998 (29)
skull	1990-1999	adult	3	Melo 2016 (11)
skull	1990-1999	children	4	Kirks 1998 (29)
skull	2000-2010	adult	4	Melo 2016 (11)
skull	2000-2010	children	4	Glass 2004 (34)
spine	1980-1989	adult	4	Melo 2016 (11)
spine	1980-1989	children	3	Kirks 1998 (29)
spine	1990-1999	adult	5	Melo 2016 (11)
spine	1990-1999	children	3	Kirks 1998 (29)
spine	2000-2010	adult	5	Melo 2016 (11)
spine	2000-2010	children	2-3	Lustrin 2003 (35)

Merge the dose with the MK database

Table S3.7: List of assumptions made when merging the look up table with the information collected in the MOBI-kids study

We matched the look up tables with the database containing the list of reported radiological examination by type of examination, body part, decade and age. In doing so some assumptions has been made.

Identification of assumption	**Description**
Identifying the correct examination type	The level of details on the information collected does not distinguished between the different types of head (or neck x-rays, as such type of details would have been impossible to capture in a self-reported questionnaire. For example a head conventional x-ray could be different examination types (i.e. skull x-ray or sinus x-ray) and a neck conventional x-ray could be a soft neck tissue x-ray or a cervical spine examination. We proceeded as following: ➢ Head conventional: if the specified reason was "sinusitis" >> the examination was considered as a sinus x-ray, otherwise a skull. ➢ Neck conventional: the mean between spine and neck was calculated for each period and age group. When, for a given period/age, either dose for spine or neck examination was missing, the only available value was considered. The two examinations were almost comparable in terms of brain absorbed dose, spine being slightly higher (few decimals of mGy).
Missing information on the dose	For some of the reported radiological examinations, the brain dose value was missing, with main reasons being: - Type A: Missing info in the MOBI-kids database when reported data was of poor quality (missing type of exam, and age at examination). Decisions taken in each case are reported in Online Supplement File S2 (Missing table). - Type B: Dose for the type of examination was not available, for a given period and age group. Decisions taken in each case are reported in Online Supplement File S2 ("Unmatched table").

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Online Supplement File 4:
List of reported neurological, psychological and genetic diseases

List of reported neurological diseases

Neurologic diseases

ICD10 Name	ICD10 code	Count
Agenesis of corpus callosum	Q040	1
Arteriovenous malformation of brain NOS	Q282	1
Benign childhood epilepsy with centrotemporal EEG spikes	G400	2
Benign intracranial hypertension	G932	2
brain tumor	C719	8
Cerebrovascular disease, unspecified	I679	1
Degenerative disease of nervous system, unspecified	G319	1
Degenerative disease of nervous system, unspecified	G43	1
Depression NOS	F329	1
Dizziness and giddiness	R42	1
Dyslexia and alexia	R480	2
Dystonia, unspecified	G249	1
Encephalitis, myelitis and encephalomyelitis	G04	1
Epilepsy, unspecified	G409	106
Febrile convulsions	R560	10
Generalized idiopathic epilepsy and epileptic syndromes	G403	1
Grand mal seizures, unspecified (with or without petit mal)	G406	1
Headache	R51	1
Hearing loss, unspecified	H919	1
Hydrocephalus	G91	9
Intracerebral haemorrhage, intraventricular	I615	1
Localization-related (focal)(partial) symptomatic epilepsy	G401	2
Medulloblastoma	C716	1
Meningitis, unspecified	G039	1
Migraine	G43	187
Moyamoya disease	I675	1
Obsessive-compulsive disorder, unspecified	F429	1
Ophthalmoplegic migraine	G438	3
Other and unspecified symptoms and signs involving cognitive functions and awareness	R418	1
Other and unspecified symptoms and signs involving the nervous and musculoskeletal systems	R298	1
Other epilepsy	G408	1
Other specified headache syndromes	G448	2
Personal history of medical treatment, unspecified	Z929	1
Pervasive developmental disorder, unspecified	F849	1

Petit Mal seizure	G407	1
Petit mal, unspecified	G407	1
Plagiocephaly	Q673	2
Sinusitis (chronic) NOS	J329	1
Tension headache NOS	G442	20
Tremor, unspecified	R251	1
Unspecified headache	R51	4
unspecified neurological condition	G	1
Missing	NA	2

List of reported psychological/behavioral diseases

ICD10 Name	ICD10 code	Count
Agoraphobia	F40.0	1
Anorexia nervosa	F50.0	7
Anxiety disorder, unspecified	F41.9	37
Aspergers Syndrome	F84.5	2
Bipolar affective disorder, unspecified	F31.9	2
Bulimia nervosa	F50.3	3
Childhood autism	F84.0	1
Childhood disorder of social functioning, unspecified	F94.9	1
Childhood emotional disorder, unspecified	F93.9	1
Depressive episode, unspecified	F32.9	37
Disorder of autonomic nervous system, unspecified	G90.9	1
Eating disorder, unspecified	F50.9	1
Mental disorder, not otherwise specified	F99.9	3
Mild depressive episode	F32.0	2
Mixed anxiety and depressive disorder	F41.2	9
Nightmares	F51.5	1
Obsessive-compulsive disorder, unspecified	F42.9	1
Panic disorder [episodic paroxysmal anxiety]	F41.0	1
Personal history of self-harm	Z91.5	1
Personality disorder, unspecified	F60.9	3
Phobic anxiety disorder, unspecified	F40.9	1
Post-traumatic stress disorder	F43.1	2
Specific disorder of arithmetical skills	F81.2	1
Trichotillomania	F63.3	1
Unspecified disorder of psychological development	F89	1
Unspecified nonorganic psychosis	F29	1
Missings	*NA*	*2*

List of reported genetic disease

Genetic conditions

ICD10 Name	ICD10 code	Count
Activated protein C resistance [factor V Leiden mutation]	D685	1
amelogenesis imperfecta	K005	1
Atresia and stenosis of ureter	Q621	1
Bradycardia, unspecified	R001	1
Cardiac murmur, unspecified	R011	3
Cardio-facio-cutaneous syndrome	Q87.8	1
Chromosomal abnormality, unspecified	Q99.9	2
Chromosomal abnormality, unspecified	Q999	1
Cleft lip	Q36	1
Coeliac disease	K900	1
Congenital deformity of feet, unspecified	Q669	2
congenital hypothyroidism NOS	E032	1
Congenital malformation of cardiac chambers and connections, unspecified	Q209	1
Congenital malformation of heart, unspecified	Q249	1
Congenital subluxation of hip, unspecified	Q655	3
Congenital vesico-uretero-renal reflux	Q627	1
Crohn disease, unspecified	K509	1
Degenerative disease of nervous system, unspecified	G319	1
Disorder of bone, unspecified	M899	1
Down syndrome, unspecified	Q909	2
Fetus and newborn affected by other abnormalities of membranes	P028	1
G6PD deficiency anaemia	D550	3
Gilbert syndrome	E804	1
Hyperlipidaemia, unspecified	E785	1
Hypospadias	Q54	2
Iron deficiency anaemia, unspecified	D509	1
Lupus erythematosus	L93	1
Muscular dystrophy	G710	1
Non-follicular (diffuse) lymphoma, unspecified	C839	1
Noonan syndrome	Q871	1
Other congenital malformations of musculoskeletal system	Q798	1
Polyposis (hereditary) of colon	D126	1
Preauricular sinus and cyst	Q181	1

Pulmonary valve atresia	Q220	1
Renal agenesis, unilateral	Q600	1
Scoliosis, unspecified	M419	1
Small kidney, unilateral	N270	1
Spastic cerebral palsy NOS	G801	1
Strabismus, unspecified	H509	1
Von Willebrand disease	D680	1
Missings	NA	2

Online Supplement File 5:
Association between the exposure (categorized using 20 and 50 mGy as cut-off points) and selected covariates using a multinomial logistic regression models.

Supplementary table S5.1: OR and 95% CI for different category of cumulative dose by potential confounder variables (Only in Controls)

	Variables	[20; 50) mGy	95% CI		≥50 mGy	95% CI	
Sex	Female	1			1		
	Male	1.32	0.89	1.97	**0.44**	**0.23**	**0.87**
Age category	<14 years	1			1		
	[14,18) years	**2.20**	**1.24**	**3.91**	**2.54**	**0.77**	**8.39**
	≥18 years	**2.72**	**1.57**	**4.70**	**5.97**	**2.01**	**17.78**
Country	Spain	1			1		
	Italy	0.71	0.38	1.34	1.28	0.37	4.39
	Israel	0.65	0.29	1.47	1.67	0.41	6.83
	France	0.77	0.37	1.60	1.93	0.50	7.48
	Japan	1.52	0.79	2.91	5.53	1.61	18.97
	Germany&Austria	0.84	0.38	1.82	0.65	0.11	3.69
	AU,CA,IN,GR,NL,NZ,KR	0.73	0.38	1.39	2.50	0.75	8.35
SES	Low	1			1		
	Medium	0.78	0.45	1.35	1.79	0.71	4.52
	High	0.70	0.43	1.16	1.48	0.63	3.45
	other/don't know	0.99	0.52	1.87	0.83	0.21	3.30
Neurological disease	None	1					
	Yes	**2.90**	**1.73**	**4.85**	**11.71**	**5.81**	**23.59**
Psychological disease	None						
	Yes	**2.23**	**1.09**	**4.55**	0.97	0.25	3.71
Quality of interview (Continous)	Quality score	0.90	0.76	1.06	0.99	0.73	1.33

Supplementary table S5.1: OR and 95% CI for different category of cumulative dose by potential confounder variables (Only in Controls)

Variables	[20; 50) mGy	95% CI	≥50 mGy	95% CI

Supplementary table S5.1:

We present the p value of the LRT of the comparison between the null model (exposure= sex + age + country) and the model where the covariate was added (exposure= COVARIATE + sex + age + country)

Null model: exposure= sex + age + country	p of LRT (in the whole study sample)	p of LRT (only in controls)
Covariate tested		
+ Parental education	0.6102	0.6789
+ Neurological disease	**< 0.001**	**< 0.001**
+Pyschological disease	**0.0361**	0.1059
+ Genetic disease	0.1153	0.1518
+ Congenital disease	0.1583	NA
+ Interviewee	0.2253	0.6667
+ Interview quality	**0.0431**	0.2264

Online Supplement File 6:

Sensitivity analyses of exposure to ionizing radiation in association with brain tumor risk for neuroepithelial brain tumors and their controls

				Adjusted		
Analysis	**Dose**	**Cases**	**Controls**	**OR**	**LCI**	**UCI**
Alternative dose estimation assumption						
Including procedures with missing date as before 2 years from diagnosis	[0: 20) mGy	595	1527	1		
	[20; 50) mGy	25	113	0.58	0.36	0.93
	[50;100) mGy	10	29	0.78	0.36	1.67
	≥100 mGy	4	7	1.66	0.45	6.1
Fetal exposure considered null if mother reported lead apron protection	[0-5) mGy	624	1643	1		
	≥5 mGy	6	11	2.1	0.73	6.04
Neuroepithelial, number of CT-scan	None	605	1555	1		
	One CT	23	110	0.52	0.32	0.84
	Two or more	6	11	1.07	0.38	3
Neuroepithelial, number of MRI	No MRI	600	1563	1		
	One MRI	27	93	0.72	0.45	1.15
	Two or more	7	20	0.65	0.26	1.65
Interview conditions						
Interview conducted with parents	[0: 20) mGy	405	799	1		
	[20; 50) mGy	13	50	0.48	0.25	0.92
	[50;100) mGy	7	12	0.79	0.3	2.12
	≥100 mGy	2	1	1.49	0.11	20.73
Excluding poor quality interview (quality score <=3)	[0: 20) mGy	490	1259	1		
	[20; 50) mGy	16	86	0.5	0.28	0.88
	[50;100) mGy	9	24	0.8	0.36	1.79
	≥100 mGy	3	2	3.79	0.61	23.42
Medical conditions						
Excluding genetic condition	[0: 20) mGy	585	1505	1		
	[20; 50) mGy	24	110	0.58	0.36	0.93
	[50;100) mGy	8	27	0.66	0.29	1.51
	≥100 mGy	4	6	1.85	0.48	7.16

Sensitivity analyses of exposure to ionizing radiation in association with brain tumor risk for neuroepithelial brain tumors and their controls

				Adjusted		
Analysis	**Dose**	**Cases**	**Controls**	**OR**	**LCI**	**UCI**
Excluding those with a diagnosis of neurological disease 5 year before cancer/appendicitis	[0: 20) mGy	541	1389	1		
	[20; 50) mGy	17	85	0.51	0.29	0.89
	[50;100) mGy	6	17	0.95	0.36	2.53
	≥100 mGy	3	3	2.86	0.53	15.52
Socioeconomic status						
Adjusted for parental education	[0: 20) mGy	597	1529	1		
	[20; 50) mGy	24	112	0.56	0.35	0.91
	[50;100) mGy	9	28	0.68	0.31	1.51
	≥100 mGy	4	7	1.78	0.48	6.69