Ecological association between residential natural background radiation exposure and the incidence rate of childhood central nervous system tumors in France, 2000–2012

Justine Berlivet, Denis Hemon, Enora Clero, Geraldine Ielsch, Dominique Laurier, Sandra Guissou, Brigitte Lacour, Jacqueline Clavel, Stéphanie Goujon

Manuscript Details

Manuscript number	JENVRAD_2019_293
Title	Association between childhood central nervous system tumors and residential exposure to natural background radiation in France, 2000-2012
Article type	Research Paper

Abstract

High-dose ionizing radiation is an established risk factor for childhood central nervous system tumors (CNST) but the role of low doses remains debated. In particular, there are few studies of natural background radiation (NBR, gamma radiation and radon) and childhood CNST, and their results are inconclusive. This study aimed to investigate the association between NBR exposure and childhood CNST in France, over the period 2000-2012, based on data from the French national registry of childhood cancers. 5,471 childhood CNST cases, and their municipality of residence at diagnosis, were recorded, and municipality NBR exposures were estimated by cockriging models, using NBR measurements and additional geographic data. The standardized incidence ratios (SIR) per unit variation of exposure were estimated with Poisson log-linear regression models. NBR exposures were considered at the time of diagnosis, and cumulatively from birth to diagnosis. In an exploratory analysis, the cumulative brain dose due to NBR was used. Overall, there was no significant association between NBR exposure and childhood CNST, but an association was suggested for pilocytic astrocytomas with NBR levels at diagnosis: SIR = 1.12 (1.00,1.25) per 50 nSv/h for gamma radiation, and SIR = 1.15 (1.01,1.32) per 100 Bq/m3 for radon). Upward trends for this subtype were also suggested with the cumulative exposures to gamma radiation and radon separately. The results for the total brain dose were similar to those for the cumulative exposure to gamma radiation. Adjustment for socio-demographic factors did not change the findings. Conclusions: Our study was based on high quality incidence data, large numbers of CNST cases, and validated models of assessment of NBR exposures. However, we could not disentangle the possible role of each type of radiation in the association with pilocytic astrocytomas, even though gamma radiation may be more implicated than radon, given its physical properties.

Keywords	childhood cancer; central nervous system tumors; natural background radiation; radon
Taxonomy	Environmental Radioactivity, Environmental Issues

Corresponding Author	Justine Berlivet
Order of Authors	Justine Berlivet, Denis HÉMON, Enora Cléro, Géraldine Ielsch, dominique laurier, Sandra Guissou, Brigitte Lacour, Jacqueline Clavel, Stéphanie Goujon

Suggested reviewers	Atte Nikkilä, Ole Raaschou-Nielsen, Claudia Spix, Ben Spycher, Gerald Kendall

Submission Files Included in this PDF

File Name [File Type]

HIGHLIGHTS-JER.docx [Highlights]

Abstract-JER.docx [Abstract]

Title page JER.docx [Title Page (with Author Details)]

Manuscript-JER.docx [Manuscript (without Author Details)]

Figure 1 JER.pdf [Figure]

Figure 2 JER.pdf [Figure]

Figure 3 JER.pdf [Figure]

Table 1.docx [Table]

Table 2.docx [Table]

Table 3.docx [Table]

Table 4.docx [Table]

Table 5.docx [Table]

Table 6.docx [Table]

Table 7.docx [Table]

Table 8.docx [Table]

Figure caption JER.docx [Supporting File]

Supplemental Material-JER.docx [Supporting File]

Coverletter_JER.docx [Supporting File]

To view all the submission files, including those not included in the PDF, click on the manuscript title on your EVISE Homepage, then click 'Download zip file'.

Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
The data that has been used is confidential

Highlights :

- 5,471 childhood central nervous system tumor cases recorded nationwide for 13 years
- Natural background radiation estimated on a fine scale (36,280 units)
- Overall, no association with gamma radiation or radon concentration
- Positive association between radiation exposure and pilocytic astrocytomas
- Greater support for a role of gamma radiation rather than radon

Abstract

Background: High-dose ionizing radiation is an established risk factor for childhood central nervous system tumors (CNST) but the role of low doses remains debated. In particular, there are few studies of natural background radiation (NBR, gamma radiation and radon) and childhood CNST, and their results are inconclusive.

Objectives: This study aimed to investigate the association between NBR exposure and childhood CNST in France, over the period 2000-2012, based on data from the French national registry of childhood cancers.

Methods: 5,471 childhood CNST cases, and their municipality of residence at diagnosis, were recorded, and municipality NBR exposures were estimated by cockriging models, using NBR measurements and additional geographic data. The standardized incidence ratios (SIR) per unit variation of exposure were estimated with Poisson log-linear regression models. NBR exposures were considered at the time of diagnosis, and cumulatively from birth to diagnosis. In an exploratory analysis, the cumulative brain dose due to NBR was used.

Results: Overall, there was no significant association between NBR exposure and childhood CNST, but an association was suggested for pilocytic astrocytomas with NBR levels at diagnosis: SIR = 1.12 (1.00,1.25) per 50 nSv/h for gamma radiation, and SIR = 1.15 (1.01,1.32) per 100 Bq/m^3 for radon). Upward trends for this subtype were also suggested with the cumulative exposures to gamma radiation and radon separately. The results for the total brain dose were similar to those for the cumulative exposure to gamma radiation. Adjustment for socio-demographic factors did not change the findings.

Conclusions: Our study was based on high quality incidence data, large numbers of CNST cases, and validated models of assessment of NBR exposures. However, we could not disentangle the possible role of each type of radiation in the association with pilocytic astrocytomas, even though gamma radiation may be more implicated than radon, given its physical properties.

Association between childhood central nervous system tumors and residential exposure to natural background radiation in France, 2000-2012

Justine Berlivet[a], Denis Hémon[a], Énora Cléro[b], Géraldine Ielsch[c], Dominique Laurier[b], Sandra Guissou[a,d], Brigitte Lacour[a,d], Jacqueline Clavel[a,e], Stéphanie Goujon[a,e]

[a] Inserm, UMR 1153 Epidemiology and Biostatistics Sorbonne Paris Cité Research Center (CRESS), Epidémiologie des cancers de l'enfant et de l'adolescent Team (EPICEA), Villejuif, F-94807, France; Paris Descartes University, Sorbonne Paris Cité, France.
[b] Institut de Radioprotection et de Sûreté Nucléaire, IRSN, PSE-SANTE/SESANE, Fontenay aux Roses, F-92262, France
[c] Institut de Radioprotection et de Sûreté Nucléaire, IRSN, PSE-ENV/SEREN, Fontenay aux Roses, F-92262, France
[d] CHU Nancy, French National Registry of Childhood Solid Tumors (RNTSE), Faculté de médecine, Vandoeuvre-lès-Nancy, F-54500, France
[e] French National Registry of Childhood Hematological Malignancies (RNHE), Villejuif, F-94807, France

Corresponding author : Justine Berlivet
Epidémiologie des Cancers de l'Enfant et de l'Adolescent
UMRS-1153 Equipe 7 (EPICEA), INSERM
16 avenue Paul Vaillant Couturier - Bat 15/16
94807 Villejuif Cedex France
Tel.: +33 (01) 45 59 52 53
Email: justine.berlivet@inserm.fr

Declarations of interest : None

Acknowledgments: The authors are grateful to Didier Gay, Christophe Debayle, Olivier Laurent and Jérôme Guillevic of the IRSN for providing the data and discussing the methodology on natural background radiation exposure assessment. The authors are also grateful to the staff of the French national registry of childhood cancer, who contributed to the active search for information in clinical departments. We thank François Doz of the 'Institut Curie' for fruitful discussions about CNST classification. The study was supported by the 'Institut National du Cancer', 'Santé Publique France', 'Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du travail' (ANSES), 'Agence Nationale de la Recherche, Investment for the future' (ANR-10-COHO-0009 grant for HOPE-EPI). Justine Berlivet's PhD was supported by Paris Descartes University.

Funding sources: The study was supported by the 'Institut National du Cancer', 'Santé Publique France', 'Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du travail' (ANSES), 'Agence Nationale de la Recherche, Investment for the future' (ANR-10-COHO-0009 grant for HOPE-EPI). Justine Berlivet's PhD was supported by Paris Descartes University.

Association between childhood central nervous system tumors and residential exposure to natural background radiation in France, 2000-2012

Declarations of interest : None

Keywords: childhood cancer, central nervous system tumors, natural background radiation, radon

1. Introduction[1]

Central nervous system tumors (CNST) are the second most common cancer worldwide in children aged 0-14 years, after leukemia. On average, 400 cases per year are diagnosed in mainland France. The etiology of childhood CNST is still largely unknown, and only a few rare genetic syndromes (neurofibromatosis, tuberous sclerosis, Li-Fraumeni syndrome, Gorlin's syndrome and Turcot's syndrome) and high-dose ionizing radiation (IR) exposure are known risk factors (Baldwin and Preston-Martin 2004; Johnson et al. 2014; McKinney 2005).

IR is classified as carcinogenic for humans by the International Agency for Research on Cancer (IARC 2000). The main results for the effects of IR on human health derive from studies of atomic bomb survivors, who received acute high levels of external IR. A positive association with various types of cancers was evidenced, several years or decades after IR exposure, in particular for CNST, but not childhood CNST specifically. With regard to medical irradiation during childhood (therapeutic or diagnostic), which may result in exposure to high doses of IR, a long latency period has been suggested, with the cancers mainly occurring during adulthood. However, with a high level of evidence, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has suggested a greater sensitivity of children compared to adults with regard to IR-induced tumors. Moreover, the younger children are, the greater the risk may be (UNSCEAR 2013).

A linear relationship between IR and solid cancers (including CNST) is generally considered, with no threshold. This assumption appears consistent with recent epidemiological findings, even though the effects of low dose radiation exposure on health are still under debate (NCRP 2018). In particular, the role of natural background radiation (NBR, i.e. gamma rays and the IR associated with radon gas and its decay products) in childhood CNST is under discussion. NBR gives rise to chronic low levels of exposure, and the general population is continuously

[1] **Abbreviations :**
CI : Confidence Interval; CNST : Central Nervous System Tumors; CT-scan : Computerized Tomography scan; DNA : Deoxyribonucleic Acid; ERR : Excess Relative Risk; FDep : French Deprivation Index ; HR : Hazard Ratio; IARC : International Agency for Research on Cancer ; ICCC : International Classification of Childhood Cancer; INSEE : French National Institute for Statistics and Economic Studies; IR : Ionizing Radiation; IRSN : French Institute for Radiological Protection and Nuclear Safety; LET : Linear Energy Transfer; NBR : Natural Background Radiation; RR : Risk Ratio; RNCE : French National Registry of Childhood Cancer; RPL : Radiophotoluminescent; SIR : Standardized Incidence Ratio; UNSCEAR : United Nations Scientific Committee on the Effects of Atomic Radiation

exposed to NBR, externally and internally by inhalation and ingestion. Natural gamma radiation exposure is the result of two components: the cosmic rays that enter the atmosphere, and the terrestrial rays emitted by the disintegration of radioactive elements present in the ground (uranium-238, potassium-40 and thorium-232). Gamma radiation is also classified in the first IARC group of carcinogens for several cancer sites, and especially the brain and central nervous system (IARC 2000). Radon gas also derives from the disintegration of uranium-238 present in the ground. Radon gas diffuses in the air and may be concentrated indoor, where it may be inhaled. Radon gas and its decay products emit alpha particles that may irradiate the lungs, and, to a lesser extent, other parts of the body, including the brain. Radon is classified by the IARC as carcinogenic to humans, for its association with lung cancer (occupational and indoor-residential exposure).

Before 2002, three studies reported a positive association between radon and childhood CNST (Collman et al. 1991; Henshaw et al. 1990; Kaletsch et al. 1999), and one study did not find any significant association with radon exposure or gamma radiation (UKCCS Investigators 2002). However, those studies suffer from serious limitations in terms of the measurement of exposure for the ecological studies (Collman et al. 1991; Henshaw et al. 1990) and participation rates for the case-control studies involving indoor measurements of exposure (Kaletsch et al. 1999; UKCCS Investigators 2002).

More recently, six large record-linkage studies were conducted in European countries, linking national registries of childhood cancer data and national modeling of radiation exposure levels on a fine scale (Del Risco Kollerud et al. 2014; Hauri et al. 2013; Kendall et al. 2013; Raaschou-Nielsen et al. 2008; Spix et al. 2017; Spycher et al. 2015) (Table 1). Radiation exposure levels were estimated using predictive models based on large national samples of geolocated measurements, and, in three studies (Kendall et al. 2013; Raaschou-Nielsen et al. 2008; Spycher et al. 2015), information on soil composition and structure. Positive associations between gamma radiation and childhood CNST were reported in Switzerland and Germany (Spix et al. 2017; Spycher et al. 2015), while no significant association was observed in a large British study (Kendall et al. 2013). Four studies investigated the link between radon exposure and childhood CNST (Del Risco Kollerud et al. 2014; Hauri et al. 2013; Kendall et al. 2013; Raaschou-Nielsen et al. 2008), and three of them reported positive but not statistically significant associations (Del Risco Kollerud et al. 2014; Hauri et al. 2013; Kendall et al. 2013). Radon levels were not associated with childhood CNST in Denmark either (RR = 0.92 (0.69,1.22) per 100 Bq/m^3 (Raaschou-Nielsen et al. 2008)).

Several childhood CNST subgroups were considered only in the Danish study (ependymomas, astrocytomas, medulloblastomas), which reported non-significant results for radon exposure (Raaschou-Nielsen et al. 2008).

In this context, the aim of our ecological study was to investigate, for the first time in mainland France, the association between NBR and childhood CNST, over the period 2000-2012. We used a large dataset from the French national registry of childhood cancer (RNCE), including 5,471 cases of childhood CNST, together with local information on the levels of NBR on the fine scale of 36,280 French municipalities. The large number of cases and the wide range of exposure levels ensured high statistical power with respect to childhood CNST overall and by subtype.

2. Methods

2.1. Geographic units

Mainland France is divided into 95 *départements* and more than 36,000 municipalities, the smallest administrative units. In 2006 the French population was 61,399,719, with 11,249,984 children less than 15 years old. Seventy-five percent of the population lived in municipalities with less than 1,000 inhabitants (Table S1).

A few municipalities were grouped together to take into account the variation in their perimeter over the study period. We thus considered 36,280 spatial units with a stable definition over 2000-2012 (referred to as municipalities hereafter).

2.2. Population estimates on the municipality scale

Population data were provided by the French National Institute for Statistics and Economic Studies (INSEE). Annual population data were available for each *département* over the whole study period and, for each municipality for 1999 and each year from 2006 (census years). For years between 2000 and 2005, the age-specific populations in a given municipality were estimated using a linear interpolation of the annual proportion of population in the municipality relative to its *département* population between 1999 and 2006. The estimated proportions were applied to the annual *département* population estimates.

The CNST cases were identified by the RNCE, which has included all malignant and non-malignant CNS neoplasms diagnosed since 2000 in children under the age of 15 living in mainland France at the time of diagnosis. Thus, 5,471 childhood CNST cases diagnosed over the period 2000-2012 were included in the study. CNST were coded using the International Classification for Disease in Oncology and classified in line with the recommendations of the International Classification of Childhood Cancer, third edition (ICCC-3). Analyses were

performed for all childhood CNST, and for various subtypes: ependymomas and plexus choroid tumors (IIIa. in ICCC-3), referred to as "ependymomas" hereafter, embryonal tumors (IIIc. in ICCC-3) and gliomas (IIIb, IIId. and IIIe4. in ICCC-3). We also analyzed pilocytic astrocytomas (36.7 % of all gliomas) separately from other gliomas.

The national childhood CNST incidence rates were estimated over the whole study period and were used as reference rates. They were estimated by age group (<1 year,1-4 years, 5-9 years, 10-14 years) for the analyses of NBR exposure at diagnosis, or year of age (0 to 14) for the analyses based on cumulative NBR exposure. The number of cases expected in each municipality under the hypothesis of homogeneous age-specific incidence rates over mainland France was obtained by multiplying the age-specific at-risk populations by the reference incidence rates.

2.3. Exposure assessment

The methodology used to estimate NBR exposure has been described in detail in two recent papers (IRSN 2012; Warnery et al. 2015).

During a national campaign conducted in 2011 and 2012, the French Institute for Radiological Protection and Nuclear Safety (IRSN) performed 97,595 measurements of indoor gamma radiation in 17,404 locations using radiophotoluminescent (RPL) dosimeters exposed to natural sources of radiation for several months. Multi-collocated cokriging was performed on a 1x1 km^2 grid combining gamma ray dose-rate measurements and the uranium potential of the French geological formations, classified as four qualitative categories (Warnery et al. 2015).

Between 1982 and 2003, a national campaign of indoor radon concentration measurements was also conducted by the IRSN, using Kodalpha LR 115 track-etch detectors. In all, 10,843 measurements of indoor radon concentration were available. As for gamma radiation, cokriging based on those measurements and complementary information from a map of the geogenic radon potential (Ielsch et al. 2010) was performed in order to estimate radon concentration on a 5x5 km^2 grid (IRSN 2012).

Gamma radiation and radon concentration (expressed in nSv/h and Bq/m^3, respectively) were estimated at the town hall of each French municipality.

2.4. Statistical analyses

Analyses were conducted using SAS V9.4 software (SAS Institute Inc. Cary, North Carolina, USA).

Taking into account the scarcity of childhood cancer, the 36,280 municipalities were grouped into ten categories of exposure to avoid over- or under-dispersion in Poisson regression models. Each category contained ten percent of the total number of expected cases. Standardized incidence ratios (SIR) were calculated as the ratio of the observed (Oi) to the expected (Ei) numbers of cases in each group of exposure 'i' and Byar's approximation was used for the 95% confidence intervals (95% CI) (Breslow and Day 1987). Chi-square tests were used to test the hypothesis of a statistical heterogeneity of SIRs between categories.

To explore the possibility of a continuous exposure-response relationship, a linear Poisson-regression model was fitted using ln(Ei) as an offset: $\ln\left(\mathrm{E}(\mathrm{O_i})\right) = \ln\left(\mathrm{E_i}\right) + \beta_0 + \beta_1 \mathrm{X_i}$ in which $\mathrm{X_i}$ is the population-weighted average of exposure (to gamma radiation or radon) in the i^{th} category (I = 1 to 10), β_0 is the intercept and β_1 is the slope of the log-linear trend. The exponential of β_1 represents the SIR or excess relative risk (ERR) of childhood CNST per unit variation of radiation exposure $\mathrm{X_i}$.

We systematically checked that there was no statistically significant departure from linearity in the Poisson regression models with the log-likelihood ratio test.

Cumulative exposures to gamma radiation (mSv) and radon ($Bq/m^3 \times y$) were derived, for each year of age, from the exposure level of the municipality of residence at diagnosis, assuming that exposure levels were constant from birth to diagnosis. We introduced an age-dependent intercept, β_{0a}, in the regression model for cumulative exposure:

$$\ln\left(\mathrm{E}(\mathrm{O_i})\right) = \ln\left(\mathrm{E_i}\right) + \beta_{0a} + \beta_2 \mathrm{X}_{ia}^{cum} \qquad [1]$$

in which X_{ia}^{cum} is the cumulative exposure level (due to gamma rays or radon) estimated for a child aged 'a' who had been living in municipality 'i' since birth ($\mathrm{X}_{ia}^{cum} = \mathrm{X_i} \times (a + 0.5)$).

A multivariate model including both exposure variables was considered to evaluate the joint effects of gamma radiation and radon exposure. We compared this model with the null model using the likelihood ratio test.

2.5. Supplementary analyses

We divided the study period into halves (2000-2005, 2006-2012) to evaluate the temporal stability of the main results. We also conducted sensitivity analyses considering 20 groups of radiation exposure (instead of 10 in the main analysis), with $1/20^{th}$ of the pediatric population in each group.

A higher incidence rate of childhood gliomas, possibly due to differences in clinical practices or registration, has recently been evidenced in the south of France, mainly in the Occitanie region (Goujon et al. 2018) . Sensitivity analyses excluding that region (i.e. 8% of the pediatric population) were conducted.

We performed separate analyses for children younger than 7 years (*vs.* older children), because of a potentially higher sensitivity of the youngest children to IR (UNSCEAR 2013).

Gamma radiation and radon concentration are spatially correlated. We tried to separate the effects of gamma radiation and radon on childhood CNST by excluding the municipalities with the highest levels of radon concentration (i.e. in the 9th and 10th deciles) in a sensitivity analysis on gamma radiation.

We also considered an index of socio-economic disparities on the municipality scale (the French deprivation index, FDep) (Rey et al. 2009), and an indicator of urbanization (the size of urban unit of the municipality) as potential confounders in the association between NBR and childhood CNST.

In an exploratory analysis, we estimated the cumulative brain dose due to NBR exposures. Only intracranial CNST localized in skull bone were considered. For the dose due to radon and its decay products, we used conversion coefficients estimated with gas diffusion models from air to different organs in a child-body (Kendall and Smith 2005). The coefficients for the brain were 0.09 mSv and 0.08 mSv for a 200 Bq/m^3 exposure for one year, for children aged 1 year and 10 years, respectively. We considered that all gamma-rays pass through skull bone and thus used a conversion coefficient of 1 between the gamma dose rate in air and the equivalent dose to the brain.

2.6. Statistical power

The study included 5,471 cases of childhood CNST diagnosed over the period 2000-2012. Under the hypothesis that only 10% of the pediatric population had a higher risk of CNST due to their exposure to NBR, using a two-sided test with an error rate of 5%, we were able to detect a minimum SIR of 1.09 with a statistical power of 80% considering CNST overall. The minimum detectable SIR was about 1.44 for ependymomas, 1.27 for embryonal CNST, and 1.16 for all gliomas (1.28 for pilocytic astrocytomas, 1.20 for other gliomas).

We also evaluated the statistical power of the study under the hypothesis of a linear association between childhood CNST incidence rate (overall and by diagnostic group) and NBR using a simulation procedure. The alternative hypotheses were based on Poisson regression models with the following hypothetical values of ERR: 5%, 10%, 15%, 20%, 25% and 30% per

50 nSv/h and per 100 Bq/m^3 for gamma radiation exposure and radon concentration at diagnosis, respectively. Five thousand simulations were run for each hypothetical value of the ERR. In each simulation, the total number of observed cases was distributed in the municipalities using a multinomial distribution with probabilities proportional to the numbers of 0-14 year old cases expected under the various alternative hypotheses.

We also estimated the statistical power of the analysis based on cumulative NBR exposure, considering ERR values of 5%, 10%, 15%, 20%, 25% and 30% per 5 mSv and per 1000 Bq/m^3 $\times$ y, for cumulative gamma exposure and cumulative radon exposure, respectively. A multinomial distribution was considered separately for each year of age.

For gamma radiation exposure, the power to detect an ERR greater than 10% per 50 nSv/h was greater than 80% for all childhood CNST and all gliomas (Table S2). For ependymomas and embryonal tumors, ERRs of 25% and 20% per 50 nSv/h, respectively, were detected with similar statistical power. For cumulative gamma radiation exposure, the log-linear Poisson regression analysis had a statistical power greater than 80 % to detect an ERR greater than 15% per 5 mSv for all childhood CNST and gliomas, and greater than 30% per 5 mSv for embryonal tumors. The statistical power was weaker for ependymomas.

Overall, with the same values of hypothetical ERR (per 100 Bq/m^3 and 1000 Bq/m^3 $\times$ y), the statistical power estimates were of the same order of magnitude for radon concentration and cumulative radon exposure, as for gamma radiation and cumulative gamma radiation exposure (Table S2).

3. Results

Over 2000-2012, 5,471 cases of CNST were diagnosed in children under the age of 15 years, in mainland France, of which 532 ependymomas (9.7%), 1,079 embryonal CNST (19.7%), and 3,340 gliomas (61%). The glioma group included 1,215 pilocytic astrocytomas and 2,125 other gliomas.

3.1. NBR exposure at diagnosis and childhood CNST

The population-weighted gamma radiation exposure in mainland France was 92.2 nSv/h on average on the municipality scale, with first and third quartile values of 72.0 and 106.2 nSv/h, respectively (Table 2). With regard to radon, the annual indoor concentration was 67.8 Bq/m^3 on average with an interquartile range of 41.0 Bq/m^3 (41.0 Bq/m^3-82.0 Bq/m^3). Both exposures were correlated on the municipality scale (Spearman correlation coefficient = 0.61, $p < 0.0001$, Figure 1).

Tables 3 and 4 show the results for qualitative and linear Poisson regression analyses considering gamma radiation and radon exposures at diagnosis separately. For gamma radiation, we did not find any significant association with all CNST (SIR = 1.04 (0.98,1.09), p = 0.19 for a 50 nSv/h increase in exposure), ependymomas or embryonal tumors. A positive trend was observed for gliomas (SIR = 1.06 (0.99,1.14), p = 0.07 for a 50 nSv/h increase in exposure), in particular for pilocytic astrocytomas (SIR = 1.12 (1.00,1.25), p = 0.04 for a 50 nSv/h increase in exposure, Table 3, Figure 2).

With regard to radon exposure, there was no significant association with all childhood CNST (SIR = 1.04 (0.97,1.11), p = 0.26 for a 100 Bq/m^3 increase in exposure, Table 4), or with the main CNST groups, but a significant positive trend was found for pilocytic astrocytomas (SIR = 1.15 (1.01,1.32), p = 0.03 for a 100 Bq/m^3 increase in exposure, Table 4, Figure 3).

Overall, the results were similar when we considered two time periods (Table S3) and when municipalities were grouped into 20 exposure categories (Table S4, Figures S1 and S2).

NBR exposure levels in the Occitanie region were slightly higher than in all mainland France, with a population-weighted average of 108.7 nSv/h (*vs.* 92.2 nSv/h) for gamma radiation and 79.5 Bq/m^3 (*vs.* 67.8 Bq/m^3) for radon concentration, on the municipality scale. Thus, about 99% of the pediatric population in Occitanie lived in a municipality with a gamma radiation exposure level higher than the median French level while 93% of the same population had a radon exposure level higher than the median French level. Overall, the results were unchanged when the Occitanie region was excluded from the main analyses (Table S3).

The association between childhood pilocytic astrocytomas and radon seemed to be slightly higher for children aged less than 7 years than for older children (SIR = 1.22 (1.02,1.45), p = 0.03, vs. 1.09 (0.89,1.32), p = 0.41 for a 100 Bq/m^3 increase, Table S3). However, no statistically significant interaction with age was evidenced for either radon or gamma radiation.

Overall, we did not find any significant association between childhood CNST and the socio-economic and urbanization indexes we considered (Table S5). The degree of urbanization was slightly associated with NBR, with lower levels in the Paris urban unit than in the other urbanization categories (Figure S3). The NBR levels were also lower in the least deprived FDep category (Figure S3), which consists of several municipalities in the Paris urban unit (48% of the population of that FDep category). The results for the association between NBR and childhood CNST were mostly unchanged when adjusted for the socio-economic and demographic indicators (Table S6 and S7).

We investigated the joint effects of gamma radiation and radon exposures on childhood CNST incidence (Table 5). Both exposures, taken together, were slightly associated with pilocytic astrocytoma incidence ($p_{LR\ test}$=0.10). The slope parameter associated with each type of radiation was lower than when gamma radiation and radon exposures were considered separately, and far from being statistically significant (SIR = 1.07 (0.90,1.26) for a 50 nSv/h increase, p = 0.44, and SIR = 1.08 (0.89,1.31) for a 100 Bq/m^3 increase, p = 0.45, for gamma radiation and radon, respectively). When we excluded the municipalities of the two highest deciles of radon exposure, 23,273 municipalities remained with a radon concentration lower than 90 Bq/m^3 and a large range of gamma radiation exposure (population-weighted average: 85 nSv/h, range: 54.4 nSv/h to 173.5 nSv/h). The residual Spearman correlation coefficient between radon and gamma exposures was 0.43. In those municipalities, 946 cases of pilocytic astrocytoma were diagnosed. A positive association of the same order of magnitude as in the main analysis was observed with gamma radiation exposure (SIR = 1.13 (0.96,1.33) for 50 nSv/h, p = 0.14, not shown).

3.2. Association between cumulative exposure to NBR and CNST

The population-weighted cumulative exposures resulting from the environmental levels of NBR were on average 6.1 mSv and 508.7 Bq/m^3 × y for 0-14 year-old children, for gamma radiation and radon, respectively (Table 2). As expected, the average levels and ranges of exposure were strongly dependent on age. For 90% of children aged 14 years, the cumulative exposure was in the range of 8.0-18.3 mSv for natural gamma radiation, and in the range of 326.8-2,111.4 Bq/m^3 × y for radon (Table S8, S9).

No statistically significant associations were observed between all CNST and cumulative exposure to gamma radiation or radon separately (SIR = 1.07 (0.99,1.16) for 5 mSv, p = 0.09, and SIR = 1.05 (0.96,1.14) for 1000 Bq/m^3 × y, p = 0.29, respectively, Table 6). However, positive associations were observed for cumulative exposure to gamma radiation and gliomas, and especially pilocytic astrocytomas (SIR = 1.18 (1.00,1.40) for 5 mSv, p = 0.05). The association between cumulative radon exposure and pilocytic astrocytomas was also positive but not statistically significant (SIR = 1.14 (0.96,1.36), p = 0.15 for a 1000 Bq/m^3 × y increase).

As expected, the range of cumulative exposures was larger in the 7-14 year-old group than in the youngest group (from 3.6 to 32.4 mSv *vs.* 0.2 to 14.5 mSv for gamma radiation, Table S8; from 93.5 to 11,998.2 Bq/m^3 × y *vs.* 6.2 to 5,378.5 Bq/m^3 × y for radon, Table S9). For 7-14 year-old children, the associations with pilocytic astrocytomas were of the same order of magnitude as in the main analysis (SIR = 1.15 (0.96,1.39) for 5 mSv and SIR = 1.12 (0.92,1.36) for 1000 Bq/m^3 × y for gamma radiation and radon, respectively) (not

shown). The parameter estimates were slightly higher in the 0-6 year-old group, with quite large 95% confidence intervals (SIR = 1.33 (0.88,2.01) for 5 mSv and SIR = 1.24 (0.84,1.83) for 1000 Bq/m^3 × y for gamma radiation and radon, respectively) (not shown). The interactions were not statistically significant.

The results were mostly unchanged when cumulative gamma radiation and radon exposures were considered simultaneously in a multivariate regression model. Interestingly, for pilocytic astrocytomas, only the positive association with gamma radiation seemed to persist (SIR = 1.19 (0.91,1.55) for 5 mSv, p = 0.21 and SIR = 0.99 (0.75,1.31) for 1000 Bq/m^3 × y, p = 0.95, for gamma radiation and radon, respectively, Table 7).

3.3. Estimated brain NBR dose and CNST

The total dose to the brain was estimated to be 6.3 mSv on average (IQR = 2.9-8.8 mSv, Table 2), with a large contribution of gamma radiation exposure (96.8% on average, range: 78.6% to 99.3%). After exclusion of the tumors not localized in skull bone, 5,265 childhood CNST remained, with 3,221 gliomas (1,154 pilocytic astrocytomas, 2,067 other gliomas). Considering the estimated total dose to the brain, a positive association with CNST was observed for gliomas and pilocytic astrocytomas (SIR = 1.10 (1.00,1.21) and SIR = 1.16 (0.99,1.37) for a 5 mSv increase, respectively (Table 8)). No significant association was observed for other CNST subgroups.

4. Discussion

Our results suggest an increase in the incidence rate of childhood pilocytic astrocytomas with an increase in the level of exposure to NBR in the municipality of residence at the time of diagnosis. Positive associations were also evidenced with cumulative NBR exposures for that CNST subgroup. No other subgroup of childhood CNST was associated with NBR exposure levels on the municipality scale.

This study aimed to characterize the level of environmental NBR exposure and describe exposure contrasts on the municipality scale in relation to childhood CNST incidence rate. The total individual IR exposure was not estimated. In particular, we did not consider internal exposure to natural radiation due to ingestion of radionuclides. This source of exposure contributes to, on average, 12% of the total individual exposure to IR, and greatly depends on individual lifestyle (IRSN 2015). We did not consider medical irradiation during childhood, due to CT-scans or radiographies. Several studies have suggested an increased risk of brain tumors after exposure to CT-scans, but IR-induced cancers mainly occur after age 15 years (Pearce et al. 2012; Mathews et al. 2013).

Our study was based on high-quality data: the completeness of the RNCE between 2000 and 2012 ensured the accuracy of incidence-rate estimates in France, with no participation bias; the long study period resulted in about 5,500 cases, despite the scarcity of childhood CNST, enabling fairly high statistical power overall and in almost all subgroup analyses; objective and high quality NBR exposure estimates were available on the fine scale of 36,280 municipalities.

The NBR exposure models used in this study were validated by the IRSN. The cokriging model for gamma radiation exposure showed an excellent internal predictive capacity, based on a cross validation procedure with several learning sets of different size (Marquant et al. 2018; Warnery et al. 2015). The cokriged estimate was a smoothed value of exposure in the municipality. Based on this approach, it was estimated that 65% of the variance of gamma dose rate measurements and 32% of the variance of indoor radon measurements was explained by the spatial coordinates of the home location (IRSN 2012; Warnery et al. 2015). These figures indicate that the geographic coordinates of the place of residence did not totally explain the NBR variability, especially for radon. The same observation has been made in Denmark (r^2 = 0.45, (Raaschou-Nielsen et al. 2008)) and Switzerland (r^2 = 0.20, (Hauri et al. 2013)) for radon exposure, and in Great-Britain for gamma radiation (r^2 = 0.23 (Chernyavskiy et al. 2016)). The cokriged estimates used in the present study do not reflect the exposure to NBR in a given building. In particular, indoor radon exposure varies greatly depending on several factors, such as building material, ventilation, season, and lifestyle characteristics (Demoury et al. 2013).

With regard to crude indicators of gamma radiation exposure, i.e. not taking into account the spatial distribution of the population, the average exposure in France (100 nSv/h), is slightly higher than in Great Britain (94.7 nGy/h (Kendall et al. 2013)) or Germany (0.817 mSv/y, i.e. 93.2 nSv/h (Spix et al. 2017)), and slightly less than in Switzerland (109 nSv/h (Spycher et al. 2015)). With regard to indoor radon, the annual average concentration in France is higher than in the UK and Denmark, and slightly lower than in Switzerland (Hauri et al. 2013) and Norway (Del Risco Kollerud et al. 2014). The ranges of exposures in France (54.4-254.8 nSv/h for gamma radiation, 12.5-827.5 Bq/m^3 for radon concentration) are moderately greater than in other countries, due to the diversity of geological characteristics in France. Population-weighted average levels may be slightly different, as is the case in France, as fewer people live in the most exposed mountainous areas (probably less frequently than in Switzerland, for example).

We did not evidence any significant association between childhood CNST, taken together, and NBR exposures, which is consistent with most of the recent studies (Table 1). In particular, with regard to radon exposure, no significant association was found in Denmark

(RR = 0.92 (0.69,1.22) for 1,000 Bq/m^3 × y (Raaschou-Nielsen et al. 2008)), Switzerland (HR = 1.19 (0.91,1.17) for 100 Bq/m^3, (Hauri et al. 2013)) or Great-Britain (RR = 1.14 (0.94,1.37) for 100 Bq/m^3 (Kendall et al. 2013)). The British study did not find any significant association with gamma radiation exposure indicators, for either ambient exposure (RR = 1.08 (0.91,1.28) for 1 µGy/day) or cumulative exposure (RR = 1.02 (0.96,1.09) per mGy). In contrast, a German study reported a statistically significant result with gamma radiation exposure (RR = 1.35 (1.17,1.57) for exposure of 1.5 mSv/h vs. 0.5 mSv/h (Spix et al. 2017), and a positive association was observed with cumulative gamma radiation exposure in a Swiss study (RR = 1.04 (1.00,1.08) per mSv (Spycher et al. 2015)). Interestingly, when converted to the same unit (Table 1), the results are of the same order of magnitude in almost all the studies, although not systematically statistically significant.

Only the Danish study considered subgroups of childhood CNST separately (ependymomas, astrocytomas and medulloblastomas). No significant association was found with radon exposure, while the association with gamma radiation exposure was not investigated (Raaschou-Nielsen et al. 2008). In the present study, we observed a specific association with pilocytic astrocytomas (36% of the glioma group, and about 60% of all childhood astrocytomas), a low-grade infra-tentorial tumor mainly diagnosed in children. Childhood CNST diagnoses are complex, and, in particular, it may be difficult to separate malignant from non-malignant tumors and characterize glioma subgroups. Spatial differences in clinical practices and classification bias are likely. Therefore, we decided to consider a large group of gliomas, and then to distinguish specifically pilocytic astrocytomas from other gliomas. We cannot rule out that the observed association between NBR and childhood CNST may not be restricted to pilocytic astrocytomas, and may extend to other subtypes included in the “other gliomas” group.

We grouped the municipalities into several exposure categories (10 and 20 categories), and assigned the population-weighted average exposure to each category. Overall, the results were consistent with a linear no-threshold relationship between IR and cancer, but we cannot formally rule out the possibility of a threshold and an increased risk only in the highest exposure categories.

An association between NBR exposure level and pilocytic astrocytomas incidence rate was evidenced with both ambient and cumulative exposures. Our estimates of the cumulative NBR exposure of the population were based on the municipality of residence at diagnosis and the residential histories of the children were not taken into account. The cumulative estimates were obtained directly from the exposure at the residence at diagnosis, multiplied by age. In the ESCALE study, a French national case-control study, it was shown that 66% of the children

lived in the same municipality at the times of birth and diagnosis (Demoury et al. 2017). Several studies have used information based on residential history to estimate the cumulative exposure (Del Risco Kollerud et al. 2014; Hauri et al. 2013; Raaschou-Nielsen et al. 2008; Spycher et al. 2015), and the British study used the coordinates of the mother's residence at birth, considering that exposure was constant from birth to diagnosis (Kendall et al. 2013). The latter study also considered the NBR levels in the place of residence at the time of birth, and no association with childhood CNST was reported (Kendall et al. 2013). However, the periods surrounding conception and birth may be important time windows, because of a potential susceptibility of the gametes, embryo and young child to environmental factors, in particular IR.

Our work constitutes the first study to estimate a total brain dose, using conversion coefficients to account for the biological effect of the two types of NBR. For radon, we used coefficients given by Kendall and derived from biokinetic and dosimetric models (Kendall and Smith 2005). We had already used them for a previous analysis of childhood leukemia and red-bone marrow dose (Demoury et al. 2017). The coefficients for the dose to the brain (e.g. 0.08 mSv for a 10 year-old child exposed to an annual dose of 200 Bq/m^3) are far smaller than those for the lungs (181.2 mSv) or even bone marrow (0.63 mSv). We considered that all gamma rays pass through skull bone and used a conversion coefficient of 1. Unsurprisingly, the results were similar to those observed with cumulative gamma radiation exposure, which constituted more than 90% of the total dose received by the brain, on average.

The specific association between each source of NBR exposure and the risk of pilocytic astrocytoma is difficult to determine because of the intrinsic correlation between indoor radon and terrestrial gamma radiation. The positive association observed with gamma radiation persisted when we excluded the municipalities with the highest radon levels. The reverse analysis, which would consist in excluding municipalities with higher level of gamma radiation to investigate the association between childhood CNST and radon, was not feasible since those municipalities were also those with the highest radon levels. Gamma rays produce low linear energy transfer (LET) radiation, transmitting energy via photons, which may lead to ionization of molecules in a cell when photons pass through it. Highly reactive free radicals that may damage DNA are produced. They are less ionizing than the alpha particles emitted by radon disintegration but have a high penetrating power, which explains why they can pass through skull bone and damage brain cells. Even though radon and its decay products are alpha emitters, they are less likely to cross the blood brain barrier, which is reflected in the low conversion coefficients for brain (Kendall and Smith 2005). As gamma radiation constitutes more than 90% of the estimated brain dose, it is likely that the associations observed with pilocytic astrocytomas are mostly attributable to gamma radiation. In that case, the

associations observed with radon may just reflect the correlation between the two exposure estimates.

Our results might also reflect the effect of confounding factors, if municipalities with higher levels of NBR differed with respect to other factors associated with childhood CNST. Known risk factors for childhood CNST (genetic syndromes, high dose IR) are unlikely to be confounders for the association between NBR exposure and CNST incidence rate on the municipality scale and there are no other obvious potential confounding candidates. We considered the degrees of deprivation and urbanization of the municipalities as potential confounders, as they are likely to be associated with several other characteristics of the place of residence, and lifestyle. A previous French study did not find any significant association between those indicators and various subgroups of childhood CNST (Marquant et al. 2016). We came to the same conclusion. In the present study, those contextual indicators were associated with NBR exposures, positively for the deprivation index and negatively for the degree of urbanization. In particular, the NBR level is lower in the Paris area, which strongly contributes to the least deprived and most urban categories. However, the results for NBR and childhood CNST were almost unchanged when the contextual indicators were accounted for.

5. Conclusion

In conclusion, this study made use of high-quality incidence data and objective and precise NBR exposure estimates on the municipality scale. With more than 5,000 childhood CNST cases, the statistical power was high, which enabled specific CNST subgroups to be considered. Overall, there was no significant association between NBR exposure and childhood CNST, but a statistically significant association was found for pilocytic astrocytomas. The physical properties of the various types of NBR have led us to opt for a role of gamma radiation rather than radon. It remains possible that the observed associations may be due to confounding by some unknown CNST risk factor that is associated with NBR levels on the municipality scale.

References

Baldwin RT, Preston-Martin S. 2004. Epidemiology of brain tumors in childhood--a review. Toxicol Appl Pharmacol 199:118–131; doi:10.1016/j.taap.2003.12.029.

Breslow NE, Day NE. 1987. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies - International Agency for Research on Cancer.

Chernyavskiy P, Kendall GM, Wakeford R, Little MP. 2016. Spatial prediction of naturally occurring gamma radiation in Great Britain. J Environ Radioact 164:300–311; doi:10.1016/j.jenvrad.2016.07.029.

Collman GW, Loomis DP, Sandler DP. 1991. Childhood cancer mortality and radon concentration in drinking water in North Carolina. Br J Cancer 63: 626–629.

Del Risco Kollerud R, Blaasaas KG, Claussen B. 2014. Risk of leukaemia or cancer in the central nervous system among children living in an area with high indoor radon concentrations: results from a cohort study in Norway. Br J Cancer 111:1413–1420; doi:10.1038/bjc.2014.400.

Demoury C, Ielsch G, Hemon D, Laurent O, Laurier D, Clavel J, et al. 2013. A statistical evaluation of the influence of housing characteristics and geogenic radon potential on indoor radon concentrations in France. J Environ Radioact 126:216–225; doi:10.1016/j.jenvrad.2013.08.006.

Demoury C, Marquant F, Ielsch G, Goujon S, Debayle C, Faure L, et al. 2017. Residential Exposure to Natural Background Radiation and Risk of Childhood Acute Leukemia in France, 1990-2009. Environ Health Perspect 125:714–720; doi:10.1289/EHP296.

Goujon S, Kyrimi E, Faure L, Guissou S, Hémon D, Lacour B, et al. 2018. Spatial and temporal variations of childhood cancers: Literature review and contribution of the French national registry. Cancer Med 7:5299–5314; doi:10.1002/cam4.1774.

Hauri D, Spycher B, Huss A, Zimmermann F, Grotzer M, von der Weid N, et al. 2013. Domestic radon exposure and risk of childhood cancer: a prospective census-based cohort study. Environ Health Perspect 121:1239–1244; doi:10.1289/ehp.1306500.

Henshaw DL, Eatough JP, Richardson RB. 1990. Radon as a causative factor in induction of myeloid leukaemia and other cancers. Lancet Lond Engl 335: 1008–1012.

IARC (International Agency for Research on Cancer). 2000. Monographs on the evaluation of carcinogenic risks to humans. Volume 75 - Ionizing radiation, Part 1 : X- and gamma-radiation, and neutrons.

Ielsch G, Cushing ME, Combes P, Cuney M. 2010. Mapping of the geogenic radon potential in France to improve radon risk management: methodology and first application to region Bourgogne. J Environ Radioact 101:813–820; doi:10.1016/j.jenvrad.2010.04.006.

IRSN (Institut de Radioprotection et de Sureté Nucléaire). 2012. IRSN RT/PRP-DGE/2012-018-Analyse spatiale et cartographie du radon sur le territoire métropolitain par l'utilisation de méthodes géostatistiques [in French].

IRSN (Institut de Radioprotection et de Sureté Nucléaire). 2015. IRSN/2015-00001 Exposition de la population française aux rayonnements ionisants [in French].

Johnson KJ, Cullen J, Barnholtz-Sloan JS, Ostrom QT, Langer CE, Turner MC, et al. 2014. Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 23:2716–2736; doi:10.1158/1055-9965.EPI-14-0207.

Kaletsch U, Kaatsch P, Meinert R, Schüz J, Czarwinski R, Michaelis J. 1999. Childhood cancer and residential radon exposure - results of a population-based case-control study in Lower Saxony (Germany). Radiat Environ Biophys 38: 211–215.

Kendall GM, Little MP, Wakeford R, Bunch KJ, Miles JCH, Vincent TJ, et al. 2013. A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980-2006. Leukemia 27:3–9; doi:10.1038/leu.2012.151.

Kendall GM, Smith TJ. 2005. Doses from radon and its decay products to children. J Radiol Prot Off J Soc Radiol Prot 25:241–256; doi:10.1088/0952-4746/25/3/002.

Marquant F, Demoury C, Ielsch G, Laurier D, Hémon D, Clavel J. 2018. Response to comment on “Indoor terrestrial gamma dose rate mapping in France: A case study using two different geostatistical models” by Warnery et al. J Environ Radioact 182:174–176; doi:10.1016/j.jenvrad.2017.11.030.

Marquant F, Goujon S, Faure L, Guissou S, Orsi L, Hémon D, et al. 2016. Risk of Childhood Cancer and Socio-economic Disparities: Results of the French Nationwide Study Geocap 2002-2010. Paediatr Perinat Epidemiol 30:612–622; doi:10.1111/ppe.12313.

Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. 2013. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 346:f2360–f2360; doi:10.1136/bmj.f2360.

McKinney PA. 2005. Central nervous system tumours in children: epidemiology and risk factors. Bioelectromagnetics Suppl 7:S60-68; doi:10.1002/bem.20149.

NCRP (National Council on Radiation Protection and Measurements). 2018. Commentary No.27 : Implications of Recent epidemiologic Studies for the Linear NonThreshold Model and Radiation Protection.

Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. 2012. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 380:499–505; doi:10.1016/S0140-6736(12)60815-0.

Raaschou-Nielsen O, Andersen CE, Andersen HP, Gravesen P, Lind M, Schüz J, et al. 2008. Domestic radon and childhood cancer in Denmark. Epidemiol Camb Mass 19:536–543; doi:10.1097/EDE.0b013e318176bfcd.

Rey G, Jougla E, Fouillet A, Hémon D. 2009. Ecological association between a deprivation index and mortality in France over the period 1997 - 2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. BMC Public Health 9:33; doi:10.1186/1471-2458-9-33.

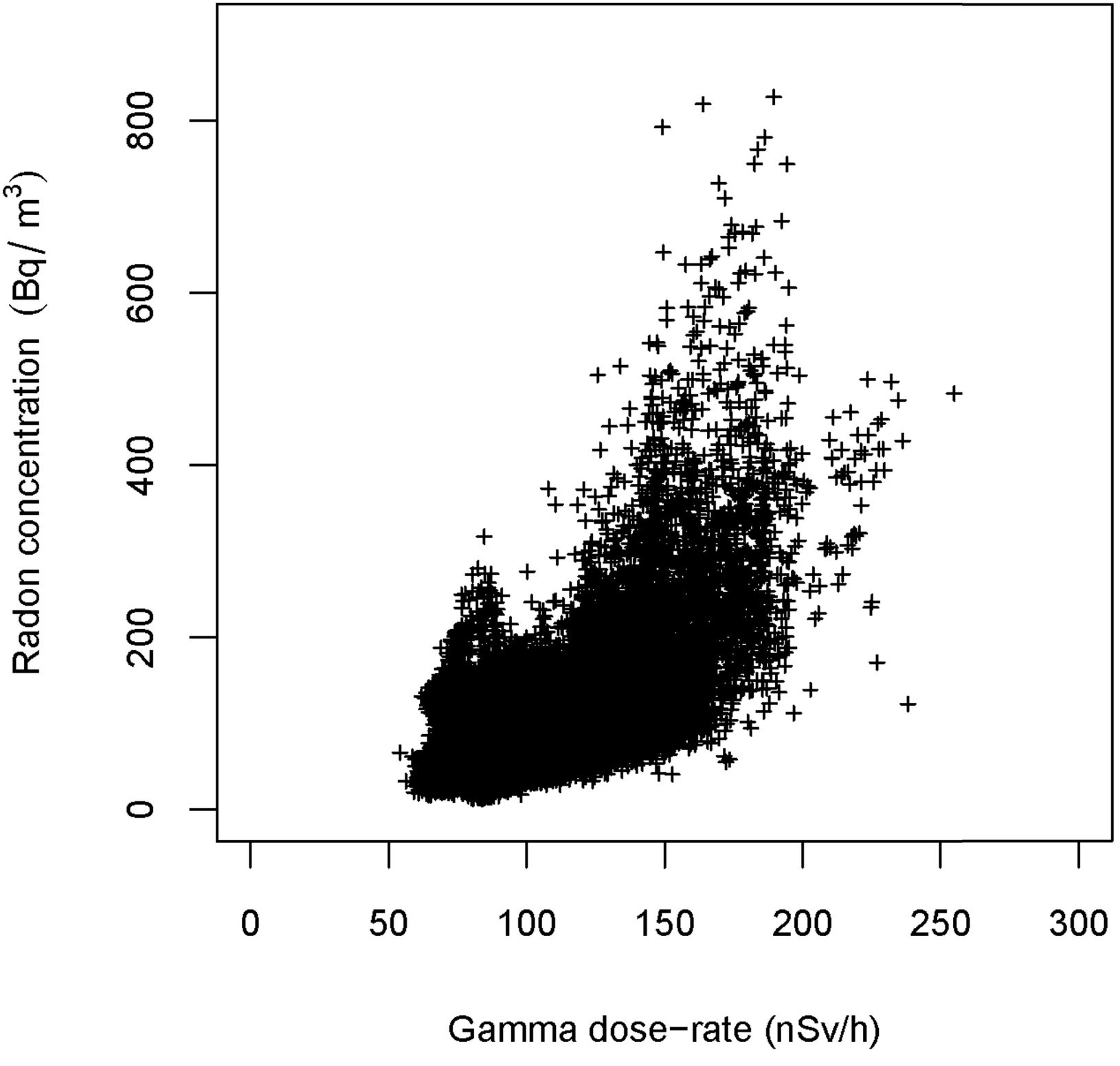
Spix C, Grosche B, Bleher M, Kaatsch P, Scholz-Kreisel P, Blettner M. 2017. Background gamma radiation and childhood cancer in Germany: an ecological study. Radiat Environ Biophys 56:127–138; doi:10.1007/s00411-017-0689-2.

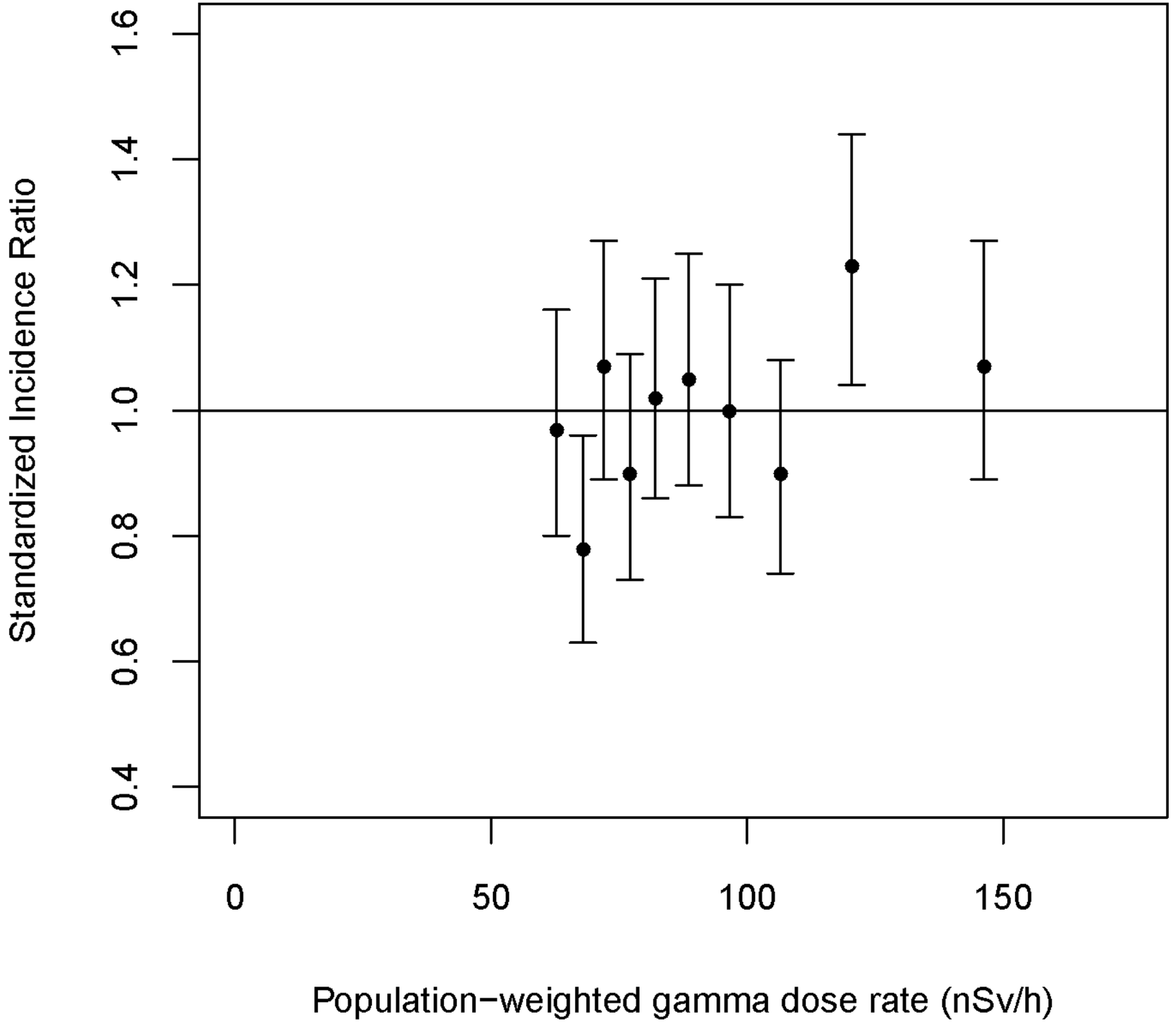
Spycher BD, Lupatsch JE, Zwahlen M, Röösli M, Niggli F, Grotzer MA, et al. 2015. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. Environ Health Perspect 123:622–628; doi:10.1289/ehp.1408548.

UKCCS Investigators. 2002. The United Kingdom Childhood Cancer Study of exposure to domestic sources of ionising radiation: 1: radon gas. Br J Cancer 86:1721–1726; doi:10.1038/sj.bjc.6600276.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). 2013. Sources, effects and risks of ionizing radiation. Volume II Scientific Annex B Effects of radiation exposure to children.

Warnery E, Ielsch G, Lajaunie C, Cale E, Wackernagel H, Debayle C, et al. 2015. Indoor terrestrial gamma dose rate mapping in France: a case study using two different geostatistical models. J Environ Radioact 139:140–148; doi:10.1016/j.jenvrad.2014.10.002.


Radon concentration (Bq/ m3)
0
200
400
600
800
0
50
100
150
200
250
300
Gamma dose−rate (nSv/h)


Standardized Incidence Ratio
0.4
0.6
0.8
1.0
1.2
1.4
1.6
0
50
100
150
Population−weighted gamma dose rate (nSv/h)

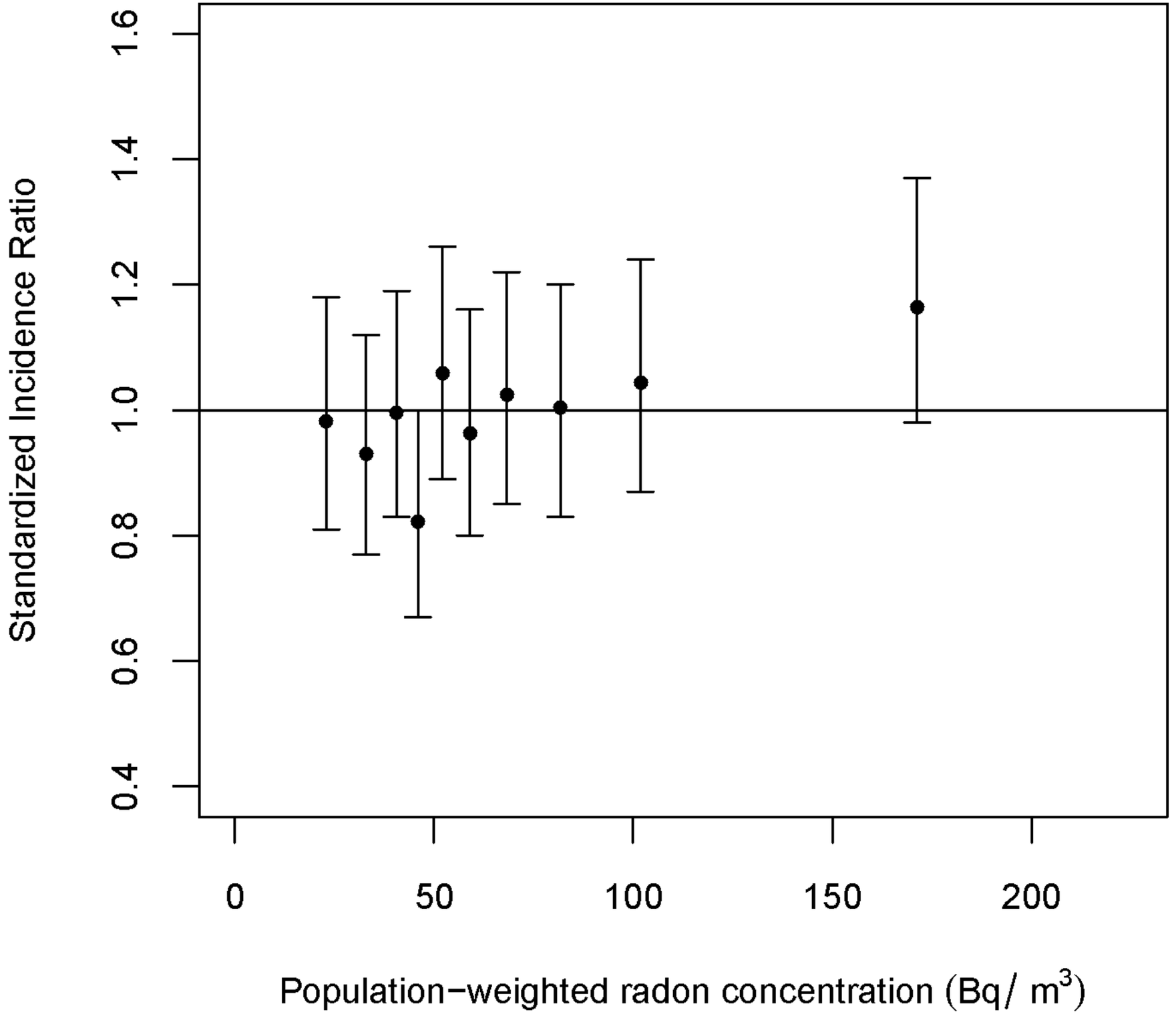

Standardized Incidence Ratio
0.4
0.6
0.8
1.0
1.2
1.4
1.6
0
50
100
150
200
Population−weighted radon concentration (Bq/ m3)

Table 1: Summary of the recent nationwide record-linkage studies on natural background radiation (NBR) exposure and childhood central nervous system tumors (CNST)

Reference **Country** **Study period**	**Study design** **Age** **Nb subjects**	**Source of data on NBR**	**Type of radiation**	**Level of exposure**	**Results and 95%CI**
Raaschou-Nielsen et al. *Epidemiology* 2008 Denmark 1968-1994	Case-control study 0-14 y. 903 CNST cases 2,684 controls	Radon exposure estimated by a predictive model based on: - 3116 indoor measurements - geographical region - digital map of soil - house characteristics Residential history (18,899 geocoded addresses)	Indoor ambient radon Cumulative radon exposure	Mean: 48 Bq/m^3 p10: 10 Bq/m^3 p50: 41 Bq/m^3 p90: 102 Bq/m^3 p50: 260 Bq/m^3 × y p90: 890 Bq/m^3 × y	Radon cumulative exposure in 1,000 Bq/m^3×y <0.26: RR=1.00 ref. <0.89: RR=0.92 (0.76;1.12) ≥0.89: RR=1.11 (0.81;1.51) Per 1,000 Bq/m^3 ×y: RR=0.92 (0.69;1.22) Ependymomas: NS Astrocytomas: NS Medulloblastomas: NS
Hauri et al. *EHP* 2013 Swiss 2000- 2008	Cohort study 0-15 y. 258 CNST cases	Indoor ambient radon exposure in 2000 estimated by a predictive model based on 35,706 measurements (validated with independent data)	Indoor ambient radon	Mean: 85.9 Bq/m^3 Min: 0.7 Bq/m^3 p50: 77.7 Bq/m^3 p90: 139.9 Bq/m^3 Max: 490.1 Bq/m^3	Ambient radon in Bq/m^3 (adjusted model[a]) < 77.7: HR=1.00 ref <139.9: HR=0.95 (0.73,1.23) > 139.9 : HR=1.05 (0.68,1.61) Per 100 Bq/m^3: HR=1.19 (0.91,1.57)
Kendall et al. *Leukemia* 2013 Great Britain 1980 -2006	Case-control study 0-15 y. 6,585 CNST cases 8,997 controls	- National survey of NBR with gamma and radon indoor measurements (2283 homes) Mean gamma and radon exposure in each county district (459 units) -predictive map for radon exposure based on 400,000 indoor measurements and geological information. Mothers' addresses of residence at birth	Indoor ambient radon Indoor ambient gamma Cumulative radon and gamma exposures (main analyses)	Mean: 21.3 Bq/m^3 Min: 1.2 Bq/m^3 Max : 692 Bq/m^3 Mean: 94.7 nGy/h Min: 38.1 nGy/h Max: 159.7 nGy/h	- Ambient exposures (joint effects[b]) Radon: RR=1.14 (0.94,1.37) per 100 Bq/m^3 Gamma: RR=1.08 (0.91,1.28) per µGy/day RR[c]=1.10 (0.89,1.34) per 50 nSv/h (Main analyses in the referring paper) - Cumulative exposures (joint effects[b]) Radon: RR=1.15 (0.88,1.50) per 1KBq/m^3 × y Gamma: RR=1.02 (0.96,1.09) per mGy RR[c]=1.10 (0.81,1.54) per 5 mSv

Reference **Country** **Study period**	**Study design** **Age** **Nb subjects**	**Source of data on NBR**	**Type of radiation**	**Level of exposure**	**Results and 95%CI**
Del Risco Kollerud et al. *BJC* 2014 Norway 1967-2009	Cohort study 0-15 y. 417 cases	Estimated indoor radon at residences each year since birth with a buffer model (radius from 300 m to 2,000 m) - 41,515 measurements Average radon exposure over three time windows Residential history with geocoded addresses	Ambient indoor radon	Min: 1 Bq/m^3 p33: 56.8 Bq/m^3 p66: 93.2 Bq/m^3 Max: 6315 Bq/m^3 <u>In the cohort:</u> Mean: 90 Bq/m^3 p50: 74 Bq/m^3	Crude estimates per 100 Bq/m^3 OR=1.15 (1.02,1.30) average exp. 0-15 y. OR=1.17 (1.04,1.32) average exp. <1 y. Adjusted estimates[d] per 100 Bq/m^3 OR=1.13 (0.99,1.28) average exp. 0-15 y. OR=1.13 (1.00,1.29) average exp. <1 y.
Spycher et al. *EHP* 2015 Switzerland 1990-2008	Cohort study 0-15 y. 423 cases	2 × 2 km grid of gamma radiation combining - cosmic dose rate - airborne γ-ray spectro. - in situ γ-ray spectro. (166 sites) - in situ dose rate measurements (837 sites) - laboratory measurements of rock samples (612 sites) - 1,615 ground data points - 137Cs depositing measurements Residential history partly known (geocoded addresses at birth and census years)	Ambient outdoor gamma dose rate Cumulative gamma dose	Mean : 109 nSv/h p25 : 95 nSv/h p75 : 112 nSv/h Mean : 9.1 mSv p25 : 5.6 mSv p75 : 12.1 mSv	per 100 nSv/h (adjusted estimates[e]): - Entire cohort :HR=1.32 (0.91,1.91) p=0.14 - Sub-cohort[f] :HR=1.42 (0.96,2.12) p=0.08 Converted estimate per 50 nSv/h[c]: Entire cohort :HR=1.15 (0.95,1.38) Sub-cohort[f] :HR=1.19 (0.98,1.46) per mSv (adjusted estimate[e]): - Entire cohort :HR=1.04 (1.00,1.08) p=0.04 - Sub-cohort[f] :HR=1.06 (1.02,1.11) p=0.008 Converted estimate [c] per 5 mSv: - Entire cohort: HR=1.23 (1.00,1.47) p=0.04 - Sub-cohort[f]:HR=1.34 (1.10,1.68) p=0.008
Spix et al. *Radiat Environ Biophys.*	Ecological study	Ambient gamma dose rate 1,800 measurement stations (outdoor)	Ambient outdoor gamma dose rate	Mean*: 0.817 mSv/y (93.2 nSv/h)[a] Min: 0.499 mSv/y	>0.817 mSv/y *vs*< 0.817 mSv/y RR[g]=1.06 (1.02,1.11) Non-linear model:

Reference Country Study period	Study design Age Nb subjects	Source of data on NBR	Type of radiation	Level of exposure	Results and 95%CI
2017 Germany 1987-2011	9,048 CNS 5,552 malign.	Spatial distance-based interpolation for each community of residence at diagnosis (11,292 units)		(56.9 nSv/h)[a] Max 1.508 mSv/y (172 nSv/h)[a]	$RR^{g}_{1.5mSv/y\ vs\ 0.5mSv/y}$ =1.35 (1.16,1.56) Converted estimate[c] per 50 nSv/h RR^{g} = 1.14 (1.07,1.22)

NBR : natural background radiation; CNST : central nervous system tumors; 95%CI: 95% confidence interval; pop.: population; y: year; p : percentile; ; RR: rate ratio; NS : not significant according to the authors (results not shown in the published paper); EHP: Environmental Health Perspectives; Min : minimum; Max : maximum; HR: hazard ratio; BJC: British Journal of Cancer; OR=odd ratio; Exp : exposure; spectro. : spectrometry; malign.: malignant; Mean*: population weighted average

[a] model with adjustment for age, child sex, birth order, socioeconomic status of the parents, environmental gamma radiation, and period

[b] joint model with radon and gamma exposures and adjustment for Carstairs' socioeconomic index

[c] original results were converted to the unit used in the present paper: increase per 50 nSv/h and per 100 Bq/m^3 for gamma radiation exposure and radon concentration, respectively; increase per 5mSv and per 1,000 $Bq/m^3 \times y$ for cumulative gamma radiation and cumulative radon exposures, respectively

[d] model with adjustment for parity, birth weight, gender, congenital malformations, family income, mother's and father's education level

[e] model with adjustment for gender and year of birth

[f] sub-cohort composed of children with stable residence between birth and diagnosis (66.5% of the entire cohort)

[g] model with adjustment for a deprivation index and an East-West indicator

Table 2. Distribution of the ambient and cumulative exposures to natural background radiation (radon and gamma radiation) and the estimated total dose to the brain in the 36,280 French municipalities

Type of exposure	Mean ± SE	Min	p5%	p25%	p50%	p75%	p95%	Max	IQR
Gamma radiation									
Crude exposure (nSv/h)	100.0 ± 25.6	54.4	68.9	80.4	94.7	114.1	149.8	254.8	33.7
Population-weighted exposure (nSv/h)	92.2 ± 1,613.1	54.4	62.6	72.0	85.2	106.2	143.7	254.8	34.2
Cumulative population-weighted exposure[a] (mSv)	6.1 ± 254.0	0.2	0.5	2.8	5.7	8.6	13.4	32.4	5.7
Radon concentration									
Crude exposure (Bq/m^3)	91.8 ± 63.4	12.5	38.3	54.2	72.6	107.7	203.4	827.5	53.5
Population-weighted exposure (Bq/m^3)	67.8 ± 2,974.0	12.5	22.5	41.0	55.6	82.0	145.6	827.5	41.0
Cumulative population-weighted exposure[a] (Bq /m^3×y)	508.7 ± 31,810.0	6.2	36.5	187.2	385.8	668.5	1,385.8	11,988.2	481.3
Total dose to the brain									
Cumulative population-weighted exposure[b] (mSv)	6.3 ± 264,2	0.3	0.5	2.9	5.9	8.8	13.9	35.2	5.9

Note: radon concentration and gamma radiation were estimated at the town hall of each municipality.
Mean: arithmetic mean, SE: standard error, Min: minimum, p: percentile, Max: maximum, IQR: interquartile range

[a] The cumulative population-weighted exposure was estimated as follows: $X_{ia}^{cum} = X_i \times (a + 0.5)$ in which X_{ia}^{cum} is the cumulative exposure level (due to gamma radiation or radon) estimated for a child aged 'a' who had been living in municipality 'i' since birth, and X_i the crude exposure level in municipality 'i'

[b] The total dose to the brain was estimated using conversion coefficients estimated with gas diffusion models from air to different organs in a child body for radon (Kendall and Smith 2005), and a unit coefficient for gamma radiation.

Table 3. Association between childhood CNST (and main CNST subgroups) and gamma radiation exposure level in the municipality of residence at the time of diagnosis (France, 2000-2012)

	All CNST (N = 5,471)			Ependymomas (N = 532)			Embryonal CNST (N = 1,079)		
Gamma radiation (nSv/h)	O	E	SIR 95%CI	O	E	SIR 95%CI	O	E	SIR 95%CI
]54.4,65.8]	577	547.0	1.05 (0.97,1.14)	64	54.5	1.17 (0.90,1.50)	109	109.1	1.00 (0.82,1.21)
]65.8,70.1]	533	545.9	0.98 (0.90,1.06)	59	53.4	1.10 (0.84,1.42)	123	108.1	1.14 (0.95,1.36)
]70.1,74.4]	530	548.4	0.97 (0.89,1.05)	45	53.5	0.84 (0.61,1.13)	102	108.3	0.94 (0.77,1.14)
]74.4,79.7]	485	501.1	0.97 (0.88,1.06)	52	48.7	1.07 (0.80,1.40)	106	98.8	1.07 (0.88,1.30)
]79.7,85.2]	563	593.2	0.95 (0.87,1.03)	54	57.6	0.94 (0.70,1.22)	104	116.8	0.89 (0.73,1.08)
]85.2,92.2]	541	546.9	0.99 (0.91,1.08)	65	52.9	1.23 (0.95,1.57)	96	107.6	0.89 (0.72,1.09)
]92.2,101.6]	563	547.2	1.03 (0.95,1.12)	51	52.8	0.97 (0.72,1.27)	113	107.6	1.05 (0.87,1.26)
]101.6,112.7]	524	547.1	0.96 (0.88,1.04)	38	52.8	0.72 (0.51,0.99)	111	107.6	1.03 (0.85,1.24)
]112.7,129.0]	586	547.0	1.07 (0.99,1.16)	53	53.0	1.00 (0.75,1.31)	93	107.7	0.86 (0.70,1.06)
]129.0,254.8]	569	547.3	1.04 (0.96,1.13)	51	52.8	0.97 (0.72,1.27)	122	107.5	1.13 (0.94,1.36)
$p_{heterog.}$[a]			0.37			0.27			0.35
$p_{log\text{-}linearity}$[b]			0.43			0.25			0.27
Trend: ERR per 50 nSv/h[c]			1.04 (0.98,1.09)			0.91 (0.76,1.08)			1.02 (0.91,1.15)
p[c]			0.19			0.28			0.74
	All gliomas (N = 3,340)			Pilocytic astrocytomas (N = 1,215)			Other gliomas (N = 2,125)		
Gamma radiation (nSv/h)	O	E	SIR 95%CI	O	E	SIR 95%CI	O	E	SIR 95%CI
]54.4,65.8]	357	332.4	1.07 (0.97,1.19)	117	121.1	0.97 (0.80,1.16)	240	211.3	1.14 (1.00,1.29)
]65.8,70.1]	295	332.9	0.89 (0.79,0.99)	95	121.2	0.78 (0.63,0.96)	200	211.7	0.94 (0.82,1.09)
]70.1,74.4]	333	334.6	1.00 (0.89,1.11)	130	121.8	1.07 (0.89,1.27)	203	212.8	0.95 (0.83,1.09)
]74.4,79.7]	274	305.9	0.90 (0.79,1.01)	100	111.3	0.90 (0.73,1.09)	174	194.6	0.89 (0.77,1.04)
]79.7,85.2]	357	362.2	0.99 (0.89,1.09)	135	131.7	1.02 (0.86,1.21)	222	230.5	0.96 (0.84,1.10)
]85.2,92.2]	324	334.3	0.97 (0.87,1.08)	128	121.5	1.05 (0.88,1.25)	196	212.7	0.92 (0.80,1.06)
]92.2,101.6]	344	334.5	1.03 (0.92,1.14)	122	121.6	1.00 (0.83,1.20)	222	212.9	1.04 (0.91,1.19)
]101.6,112.7]	332	334.4	0.99 (0.89,1.11)	109	121.6	0.90 (0.74,1.08)	223	212.8	1.05 (0.91,1.19)
]112.7,129.0]	382	334.2	1.14 (1.03,1.26)	149	121.5	1.23 (1.04,1.44)	233	212.6	1.10 (0.96,1.25)
]129.0,254.8]	342	334.7	1.02 (0.92,1.14)	130	121.7	1.07 (0.89,1.27)	212	213.0	1.00 (0.87,1.14)
$p_{heterog.}$[a]			0.05			0.07			0.23
$p_{log\text{-}linearity}$[b]			0.08			0.15			0.20
Trend: ERR by 50 nSv/h[c]			1.06 (0.99,1.14)			1.12 (1.00,1.25)			1.03 (0.95,1.12)
p[c]			0.07			0.04			0.48

Note: CNST: central nervous system tumor; N: total number of cases; O: number of observed cases in each exposure category; E: number of cases expected in each exposure category under the hypothesis of homogeneous age-specific incidence ratios throughout France; ERR: excess relative risk per unit of exposure; SIR: standardized incidence ratio defined as O/E; 95% CI: 95% confidence interval of the SIR.

[a]p-value of the Chi-square test for heterogeneity in SIRs between gamma radiation exposure categories.

[b]p-value of the test of departure from log-linearity.

[c]results from a Poisson regression model under the hypothesis of a log-linear association between childhood CNST and gamma radiation exposure level (population weighted average exposure in the ten categories). p: p-value of the Chi-square test for the slope parameter estimate.

Table 4. Association between childhood CNST (and main CNST subgroups) and radon concentration in the municipality of residence at time of diagnosis (France, 2000-2012)

	All CNST (N = 5,471)			Ependymomas (N = 532)			Embryonal CNST (N = 1,079)		
Radon concentration (Bq/m^3)	O	E	SIR 95%CI	O	E	SIR 95%CI	O	E	SIR 95%CI
]12.5,28.8]	572	547.0	1.05 (0.96,1.14)	60	54.7	1.10 (0.84,1.41)	115	109.3	1.05 (0.87,1.26)
]28.8,37.2]	582	546.7	1.06 (0.98,1.15)	55	53.6	1.03 (0.77,1.33)	132	108.3	1.22 (1.02,1.45)
]37.2,42.9]	529	546.9	0.97 (0.89,1.05)	49	53.4	0.92 (0.68,1.21)	105	108.1	0.97 (0.79,1.18)
]42.9,49.1]	494	547.1	0.90 (0.83,0.99)	46	53.0	0.87 (0.64,1.16)	88	107.7	0.82 (0.66,1.01)
]49.1,55.5]	537	547.7	0.98 (0.90,1.07)	53	53.1	1.00 (0.75,1.31)	129	107.8	1.20 (1.00,1.42)
]55.5,63.1]	498	546.1	0.91 (0.83,1.00)	54	52.8	1.02 (0.77,1.33)	81	107.4	0.75 (0.60,0.94)
]63.1,74.3]	554	548.2	1.01 (0.93,1.10)	55	53.0	1.04 (0.78,1.35)	101	107.8	0.94 (0.76,1.14)
]74.3,89.9]	568	546.6	1.04 (0.96,1.13)	54	52.9	1.02 (0.77,1.33)	126	107.6	1.17 (0.98,1.39)
]89.9,119.9]	559	542.8	1.03 (0.95,1.12)	57	52.3	1.09 (0.83,1.41)	90	106.7	0.84 (0.68,1.04)
]119.9,827.5]	578	552.0	1.05 (0.96,1.14)	49	53.2	0.92 (0.68,1.22)	112	108.4	1.03 (0.85,1.24)
$p_{heterog.}$[a]			0.06			0.97			0.002
$p_{log\text{-}linearity}$[b]			0.06			0.95			0.26
Trend: ERR by 100 Bq/m^3 [c]			1.04 (0.97,1.11)			0.97 (0.79,1.19)			0.97 (0.77,1.22)[d]
p[c]			0.26			0.76			0.78[d]
	All gliomas (N = 3,340)			Pilocytic astrocytomas (N = 1,215)			Other gliomas (N = 2,125)		
Radon concentration (Bq/m^3)	O	E	SIR 95%CI	O	E	SIR 95%CI	O	E	SIR 95%CI
]12.5,28.8]	352	332.2	1.06 (0.95,1.18)	119	121.1	0.98 (0.81,1.18)	233	211.1	1.10 (0.97,1.26)
]28.8,37.2]	340	333.2	1.02 (0.91,1.14)	113	121.3	0.93 (0.77,1.12)	227	211.9	1.07 (0.94,1.22)
]37.2,42.9]	324	333.6	0.97 (0.87,1.08)	121	121.4	1.00 (0.83,1.19)	203	212.2	0.96 (0.83,1.10)
]42.9,49.1]	305	334.3	0.91 (0.81,1.02)	100	121.5	0.82 (0.67,1.00)	205	212.7	0.96 (0.84,1.11)
]49.1,55.5]	310	334.6	0.93 (0.83,1.04)	129	121.7	1.06 (0.89,1.26)	181	212.9	0.85 (0.73,0.98)
]55.5,63.1]	312	333.7	0.93 (0.83,1.04)	117	121.3	0.96 (0.80,1.16)	195	212.4	0.92 (0.79,1.06)
]63.1,74.3]	343	335.1	1.02 (0.92,1.14)	125	121.8	1.03 (0.85,1.22)	218	213.3	1.02 (0.89,1.17)
]74.3,89.9]	343	334.0	1.03 (0.92,1.14)	122	121.5	1.00 (0.83,1.20)	221	212.5	1.04 (0.91,1.19)
]89.9,119.9]	356	331.9	1.07 (0.96,1.19)	126	120.7	1.04 (0.87,1.24)	230	211.2	1.09 (0.95,1.24)
]119.9,827.5]	355	337.5	1.05 (0.95,1.17)	143	122.7	1.17 (0.98,1.37)	212	214.8	0.99 (0.86,1.13)
$p_{heterog.}$[a]			0.31			0.47			0.19
$p_{log\text{-}linearity}$[b]			0.35			0.83			0.13
Trend: ERR by 100 Bq/m^3 [c]			1.06 (0.97,1.14)			1.15 (1.01,1.32)			1.00 (0.90,1.11)
p[c]			0.19			0.03			0.99

Note: CNST: central nervous system tumor; N: total number of cases; ERR: excess relative risk per unit of exposure; O: number of observed cases in each exposure category; E: number of cases expected in each exposure category under the hypothesis of homogeneous age-specific incidence ratios throughout France; SIR: standardized incidence ratio defined as O/E; 95% CI: 95% confidence interval of SIR.

[a]p-value of the Chi-square test for heterogeneity in SIRs between radon exposure categories.

[b]p-value of the test of departure from log-linearity.

[c] results from a Poisson regression model under the hypothesis of a log-linear association between childhood CNST and radon exposure level (population weighted average exposure in the ten categories). p: p-value of the Chi-square test for the slope parameter estimate.

[d]results from a negative binomial model (Over-dispersion detected by the Dean and Lawless test using the Poisson regression

Table 5. Joint[a] effects of gamma radiation and radon concentration at the place of residence at diagnosis in the risk of childhood CNST (France, 2000-2012)

		Gamma radiation		Radon		LR Test[d]
Diagnostic group	O	Trend ERR by 50 nSv/h[b]	p	Trend ERR by 100 Bq/m^3[c]	p	
All CNST	5,471	1.03 (0.95,1.11)	0.50	1.02 (0.93,1.12)	0.73	0.36
Ependymomas	532	0.84 (0.65,1.09)	0.20	1.12 (0.82,1.52)	0.47	0.41
Embryonal CNST	1,079	1.05 (0.86,1.30)[e]	0.62[e]	0.92 (0.72,1.19)[e]	0.54[e]	0.82
Gliomas	3,340	1.07 (0.97,1.19)	0.18	0.99 (0.88,1.11)	0.86	0.19
Pilocytic astrocytomas	1,215	1.07 (0.90,1.26)	0.44	1.08 (0.89,1.31)	0.45	0.10
Other gliomas	2,125	1.07 (0.95,1.22)	0.27	0.94 (0.81,1.09)	0.42	0.55

Note: CNST: Central nervous system tumors; ERR: excess relative risk per unit of exposure; O: total number of cases; p: p-value of the Chi-square test for the slope parameter

[a] Results from a multivariate Poisson regression model

[b] ERR for a 50 nSv/h increase in gamma exposure and its 95% confidence interval

[c] ERR for a 100 Bq/m^3 increase in radon concentration and its 95% confidence interval

[d] p-value of the likelihood ratio test for the joint effect of gamma radiation and radon exposures (comparison to the null model)

[e] results from a negative binomial model (Over-dispersion detected by the Dean and Lawless test using the Poisson regression)

Table 6: Cumulative residential exposure to natural background radiation and risk of childhood CNST (France, 2000-2012)

		Gamma radiation			Radon		
Diagnostic group	O	Trend ERR by 5 mSv[a]		p	Trend ERR by 1,000 Bq/m^3× y[b]		p
All CNST	5,471	1.07	(0.99,1.16)	0.09	1.05	(0.96,1.14)	0.29
Ependymomas	532	0.88	(0.65,1.21)	0.44	1.06	(0.77,1.46)	0.73
Embryonal CNST	1,079	1.03	(0.84,1.27)	0.76	0.93	(0.75,1.16)	0.54
Gliomas	3,340	1.11	(1.00,1.23)	0.04	1.05	(0.95,1.17)	0.35
Pilocytic astrocytomas	1,215	1.18	(1.00,1.40)	0.05	1.14	(0.96,1.36)	0.15
Other gliomas	2,125	1.07	(0.95,1.21)	0.26	1.01	(0.88,1.15)	0.92

Note: CNST: central nervous system tumors; ERR: excess relative risk per unit of exposure; O: total number of cases; p: p-value of the Chi-square test for the parameter estimate

[a] ERR for a 5 mSv increase in cumulative gamma radiation exposure and its 95% confidence interval

[b] ERR for a 1000 Bq/m^3 × y increase in cumulative radon exposure and its 95% confidence interval

Table 7: Joint[a] effects of cumulative exposures to gamma radiation and radon concentration and risk of childhood CNST (France, 2000-2012)

		Gamma radiation			Radon			LR Test[d]
Diagnostic group	O	Trend ERR by 5 mSv[b]		p	Trend ERR by 1,000 Bq/m^3 × y[c]		p	
All CNST	5,471	1.07	(0.94,1.22)	0.28	1.00	(0.87,1.14)	0.98	0.24
Ependymomas	532	0.72	(0.44,1.17)	0.19	1.32	(0.80,2.20)	0.28	0.42
Embryonal CNST	1,079	1.09	(0.79,1.50)	0.60	0.90	(0.65,1.27)	0.56	0.84
Gliomas	3,340	1.15	(0.99,1.35)	0.08	0.94	(0.80,1.12)	0.50	0.11
Pilocytic astrocytomas	1,215	1.19	(0.91,1.55)	0.21	0.99	(0.75,1.31)	0.95	0.15
Other gliomas	2,125	1.14	(0.93,1.38)	0.20	0.92	(0.75,1.13)	0.42	0.41

Note: CNST: central nervous system tumors; ERR: excess relative risk per unit of exposure; O: total number of cases; p: p-value of the Chi-square test for the parameter estimate

[a] Results from a multivariate Poisson regression model

[b] ERR for a 5 mSv increase in cumulative gamma exposure and its 95% confidence interval

[c] ERR for a 1,000 Bq/m^3 × y increase in cumulative radon exposure and its 95% confidence interval

[d] p-value of the likelihood ratio test for the joint effect of cumulative gamma radiation and cumulative radon exposures (comparison to the null model)

Table 8: Association between childhood CNST incidence and estimated cumulative brain dose due to natural background radiation (France, 2000-2012)

Diagnostic group	O	Trend ERR by 5 mSv[a]		p
All CNST	5,265	1.07	(0.99,1.15)	0.11
Ependymomas	471	0.99	(0.70,1.40)	0.96
Embryonal CNS tumors	1,065	0.99	(0.82,1.21)	0.95
All gliomas	3,221	1.10	(1.00,1.21)	0.06
Pilocytic astrocytomas	1,154	1.16	(0.99,1.37)	0.07
Other gliomas	2,067	1.06	(0.94,1.20)	0.32

Note: Only intracranial childhood CNST (central nervous system tumors) were considered in the analysis. ERR: excess relative risk per unit of exposure; O: total number of cases; p: p-value of the Chi-square test for the parameter estimate

[a] results from a Poisson regression model under the hypothesis of a log-linear association between childhood CNST and cumulative total brain dose from birth to diagnosis. ERR for a 5 mSv increase in cumulative total brain dose and its 95% confidence interval

Figure 1: Correlation between gamma radiation (nSv/h) and indoor radon concentration (Bq/m^3) on the municipality scale (36,280 units)

Figure 2: Association between gamma-radiation exposure in the municipality of residence at diagnosis (grouped into population decile categories) and standardized incidence ratios (SIR) of pilocytic astrocytomas – France 2000-2012 (1,215 cases)

Note: The error bars represent the 95% confidence interval for the SIR calculated with the Byar's approximation

Figure 3: Association between indoor radon concentration in the municipality of residence at diagnosis (grouped into decile population categories) and standardized incidence ratios (SIR) of pilocytic astrocytomas – France 2000-2012 (1,215 cases)

Note: The error bars represent the 95% confidence interval for the SIR calculated with the Byar's approximation

Supplemental Material

Association between childhood central nervous system tumors and residential exposure to natural background radiation in France, 2000-2012

Justine Berlivet, Denis Hémon, Énora Cléro, Géraldine Ielsch, Dominique Laurier, Sandra Guissou, Brigitte Lacour, Jacqueline Clavel, Stéphanie Goujon

Table of contents

Table S1: Distribution of the 2006 population in the 36,280 French municipalities and 95 French *départements*

	Mean	Min	p5%	p25%	p50%	p75%	p95%	Max
Municipalities (N = 36,280)								
Population all ages	1,679	0	68	186	409	1,004	5,134	2,181,374
Population 0-14 y.	307	0	10	33	78	195	964	313,870
Départements (N = 95)								
Population all ages	646,313	76,806	146,283	299,000	534,291	882,998	15,360,956	2,565,258
Population 0-14 y.	118,421	12,281	23,531	52,681	95,972	163,316	312,114	519,077

Note: Min: minimum; p: percentile; Max: maximum; y.: years

Table S2: Statistical power estimates for the 5% error rate, two-sided test of association between natural background radiation and childhood CNST under various alternative hypotheses (5000 simulations[a])

Type of radiation	ERR[b]	All CNST	Ependymal	Embryonal tumors	Gliomas		
					All	Piloc. astroc.	Other gliomas
		N = 5,471	N = 532	N = 1,215	N = 3,340	N = 1,215	N = 2,125
Gamma radiation (per 50 nSv/h)	5%	0.42	0.08	0.13	0.30	0.13	0.20
	10%	0.97	0.24	0.40	0.86	0.45	0.68
	15%	1.00	0.41	0.69	0.99	0.74	0.93
	20%	1.00	0.64	0.91	1.00	0.94	1.00
	25%	1.00	0.83	0.99	1.00	0.99	1.00
	30%	1.00	0.94	1.00	1.00	1.00	1.00
Cumulative[c] gamma radiation exposure (per 5 mSv)	5%	0.22	0.06	0.07	0.16	0.09	0.12
	10%	0.72	0.11	0.17	0.52	0.22	0.37
	15%	0.95	0.15	0.30	0.83	0.41	0.66
	20%	1.00	0.25	0.49	0.97	0.65	0.89
	25%	1.00	0.36	0.67	1.00	0.82	0.97
	30%	1.00	0.51	0.83	1.00	0.94	1.00
Radon concentration (per 100 Bq/m^3)	5%	0.34	0.08	0.10	0.22	0.11	0.16
	10%	0.91	0.18	0.32	0.74	0.34	0.54
	15%	1.00	0.30	0.55	0.96	0.61	0.83
	20%	1.00	0.52	0.83	1.00	0.87	0.98
	25%	1.00	0.73	0.95	1.00	0.97	1.00
	30%	1.00	0.87	0.99	1.00	1.00	1.00
Cumulative[c] radon exposure (per 1,000 Bq/m^3 × y)	5%	0.21	0.06	0.07	0.15	0.08	0.11
	10%	0.70	0.10	0.16	0.52	0.22	0.37
	15%	0.94	0.15	0.30	0.82	0.40	0.65
	20%	1.00	0.25	0.48	0.97	0.64	0.88
	25%	1.00	0.38	0.68	1.00	0.83	0.98
	30%	1.00	0.52	0.84	1.00	0.95	1.00

CNST: central nervous system tumor; Ependymomas: ependymomas; ERR: excess relative risk; N: total number of cases in each simulated dataset; Piloc. Astroc.: pilocytic astrocytomas

[a]Simulations under linear Poisson regression model with hypothetical values of ERR defined in the second column of the table

[b] ERR by unit of exposure (50 nSv/h and 100 Bq/m^3 for gamma radiation and radon concentration, respectively; 5 mSv and 1,000 Bq/m^3 × y for cumulative gamma and radon exposures, respectively)

[c] The cumulative exposure estimate was derived from the ambient exposure in the municipality of residence at diagnosis under the assumption that the level of exposure remained stable from birth to diagnosis

Table S3: Sensitivity analyses for the association between natural background radiation exposure level of the municipality of residence at diagnosis and childhood gliomas subgroups (France, 2000-2012)

				Gamma radiation			Radon concentration		
Diagnostic group			O	Trend ERR by 50 nSv/h[a]		p	Trend ERR by 100 Bq/m^3[b]		p
All gliomas	Main analyses	2000-2012	3,340	1.06	(0.99,1.14)	0.07	1.06	(0.97,1.14)	0.19
	By Period	2000-2005	1,447	1.05	(0.95,1.16)	0.37	1.06	(0.94,1.20)	0.35
		2006-2012	1,893	1.07	(0.98,1.18)	0.11	1.05	(0.94,1.17)	0.36
	Excluding the Occitanie region		3,013	1.04	(0.97,1.12)	0.29	1.05	(0.96,1.14)	0.30
Pilocytic astrocytomas	Main analyses	2000-2012	1,215	1.12	(1.00,1.25)	0.04	1.15	(1.01,1.32)	0.03
	By period	2000-2005	570	1.13	(0.96,1.33)	0.13	1.18	(0.97,1.42)	0.10
		2006-2012	645	1.11	(0.95,1.29)	0.17	1.14	(0.95,1.29)	0.17
	Excluding the Occitanie region		1,105	1.12	(1.00,1.26)	0.05	1.17	(1.02,1.34)	0.02
	Age	0-6 y.	665	1.14	(0.98,1.32)	0.09	1.22	(1.02,1.45)	0.03
		7-14 y.	550	1.11	(0.94,1.30)	0.22	1.09	(0.89,1.32)	0.41
Other gliomas	Main analyses	2000-2012	2,125	1.03	(0.95,1.12)	0.48	1.00	(0.90,1.11)	0.99
	By period	2000-2005	877	1.00	(0.87,1.14)	0.95	0.99	(0.84,1.16)	0.88
		2006-2012	1,248	1.06	(0.95,1.18)	0.34	1.01	(0.88,1.15)	0.89
	Excluding the Occitanie region		1,908	0.99	(0.91,1.09)	0.88	0.98	(0.88,1.09)	0.68

CNST: central nervous system tumor; y.: years; ERR: excess relative risk per unit of exposure; 95% CI: 95% confidence interval.
p: p-value of the chi-square test for the slope parameter estimate
[a] ERR and its 95% confidence interval for a 50 nSv/h increase in gamma radiation exposure
[b] ERR and its 95% confidence interval for a 100 Bq/m^3 increase in radon concentration

Table S4: Standardized incidence ratio of pilocytic astrocytoma incidence in 20 groups of municipalities with increasing levels of gamma radiation and radon[a] (France, 2000-2012)

Gamma radiation					Radon concentration				
Exposure category[a] (nSv/h)	O	E	SIR	95% CI	Exposure category[a] (Bq/m^3)	O	E	SIR	95% CI
]54.4,62.5]	61	59.5	1.02	(0.78,1.32)	]12.5,22.4]	61	60.4	1.01	(0.77,1.30)
]62.5,65.8]	56	61.6	0.91	(0.69,1.18)	]22.4,28.9]	58	60.7	0.95	(0.72,1.23)
]65.8,68.1]	53	60.6	0.87	(0.66,1.14)	]28.9,33.3]	63	60.7	1.04	(0.80,1.33)
]68.1,70.1]	42	60.6	0.69	(0.50,0.94)	]33.3,37.2]	50	60.6	0.83	(0.61,1.09)
]70.1,71.9]	62	60.8	1.02	(0.78.1,31)	]37.2,41.0]	60	60.9	0.99	(0.75,1.27)
]71.9,74.4]	68	60.9	1.12	(0.87,1.41)	]41.0,42.9]	61	60.5	1.01	(0.77,1.29)
]74.4,77.5]	61	60.6	1.01	(0.77,1.29)	]42.9,45.9]	47	58.3	0.81	(0.59,1.07)
]77.5,79.7]	39	50.6	0.77	(0.55,1.05)	]45.9,49.1]	53	63.2	0.84	(0.63,1.10)
]79.7,82.3]	72	70.6	1.02	(0.80,1.28)	]49.1,52.1]	67	55.3	1.21	(0.94,1.54)
]82.3,85.2]	63	61.1	1.03	(0.79,1.32)	]52.1,55.5]	62	66.3	0.93	(0.72,1.20)
]85.2,88.6]	54	60.4	0.89	(0.67.1,17)	]55.5,58.9]	59	58.6	1.01	(0.77,1.30)
]88.6,92.2]	74	60.8	1.22	(0.96,1.53)	]58.9,63.1]	58	62.7	0.92	(0.70,1.20)
]92.2,96.7]	61	60.7	1.00	(0.77,1.29)	]63.1,67.9]	71	61.0	1.16	(0.91,1.47)
]96.7,101.6]	61	60.9	1.00	(0.77,1.29)	]67.9,74.3]	54	60.8	0.89	(0.67,1.16)
]101.6,106.1]	57	60.8	0.94	(0.71,1.21)	]74.3,82.0]	64	60.8	1.05	(0.81,1.34)
]106.1,112.7]	52	60.8	0.86	(0.64,1.12)	]82.0,89.9]	58	60.6	0.96	(0.73,1.24)
]112.7,120.1]	61	54.3	1.12	(0.86,1.44)	]89.9,100.8]	70	60.3	1.16	(0.90,1.47)
]120.1,129.0]	88	67.2	1.31	(1.05,1.61)	]100.8,119.9]	56	60.4	0.93	(0.70,1.20)
]129.0,143.5]	57	60.8	0.94	(0.71,1.21)	]119.9,145.6]	69	60.2	1.15	(0.89,1.45)
]143.5,254.8]	73	60.8	1.20	(0.94,1.51)	]145.6,827.5]	74	62.5	1.18	(0.93,1.49)
Total	1,215	1,215			Total	1,215	1,215		
$p_{heterog}$[b]			0.14		$p_{heterog}$[b]			0.59	
$p_{log.linearity}$[c]			0.29		$p_{log.linearity}$[c]			0.78	
Trend ERR by 50nSv/h[d]			1.13	(1.02,1.26)	Trend ERR by100 Bq/m^3[e]			1.13	(1.00,1.28)
p				0.03	p				0.05

O: total number of cases; E: expected number of cases in each group under the hypothesis of homogeneous age-specific incidence ratios throughout France; ERR: excess relative risk per unit of exposure; SIR: standardized incidence ratio; 95% : 95% confidence interval; p: p-value of the Chi-square test for the slope parameter estimate

[a] groups of municipalities based on gamma radiation (radon concentration) levels. Each category contained 5% of the French pediatric population.

[b] p-value of the Chi-square test for heterogeneity in SIRs between gamma radiation (radon concentration) categories.

[c] p-value of the test of departure from log-linearity.

[d] results from a Poisson regression model under the hypothesis of a log-linear association between childhood CNST and gamma radiation exposure level (population-weighted average exposure in the twenty categories). ERR and its 95% confidence interval for a 50 nSv/h increase in gamma radiation exposure.

[e] results from a Poisson regression model under the hypothesis of a log-linear association between childhood CNST and radon concentration (population-weighted average exposure in the twenty categories). ERR and its 95% confidence interval for a 100 Bq/m^3 increase in radon concentration

Table S5: Association between childhood CNST and two contextual indexes of deprivation and urbanization (France, 2000-2012)

		Deprivation					Urbanization				
Diagnostic group	Stratum[a]	O	E	SIR	95% CI	p	O	E	SIR	95% CI	p
All CNST	1	1,019	1,085.4	0.94	(0.88,1.00)		1,450	1,454.2	1.00	(0.95,1.05)	
	2	1,096	1,085.0	1.01	(0.95,1.07)		656	640.9	1.02	(0.95,1.11)	
	3	1,094	1,082.1	1.01	(0.95,1.07)	0.20	886	958.0	0.92	(0.86,0.99)	0.07
	4	1,089	1,087.8	1.00	(0.94,1.06)		1,473	1,462.1	1.01	(0.96,1.06)	
	5	1,127	1,084.6	1.04	(0.98,1.10)		1,006	955.9	1.05	(0.99,1.12)	
Ependymomas	1	87	105.3	0.83	(0.66,1.02)		153	139.6	1.10	(0.93,1.28)	
	2	115	105.0	1.09	(0.90,1.31)		71	61.4	1.16	(0.90,1.46)	
	3	101	104.7	0.96	(0.79,1.17)	0.29	75	92.7	0.81	(0.64,1.01)	0.07
	4	113	105.2	1.07	(0.88,1.29)		128	143.2	0.89	(0.75,1.06)	
	5	109	104.7	1.04	(0.85,1.26)		105	95.2	1.10	(0.90,1.34)	
Embryonal tumors	1	194	214.1	0.91	(0.78,1.04)		265	286.0	0.93	(0.82,1.05)	
	2	214	213.9	1.00	(0.87,1.14)		121	125.5	0.96	(0.80,1.15)	
	3	196	213.2	0.92	(0.80,1.06)	0.16	178	188.0	0.95	(0.81,1.10)	0.25
	4	233	214.3	1.09	(0.95,1.24)		302	288.7	1.05	(0.93,1.17)	
	5	232	213.5	1.09	(0.95,1.24)		213	190.8	1.12	(0.97,1.28)	
All gliomas	1	639	662.6	0.96	(0.89,1.04)		901	889.6	1.01	(0.95,1.08)	
	2	667	662.6	1.01	(0.93,1.09)		402	392.4	1.02	(0.93,1.13)	
	3	693	660.9	1.05	(0.97,1.13)	0.53	539	585.6	0.92	(0.84,1.00)	0.34
	4	644	664.3	0.97	(0.90,1.05)		905	891.6	1.02	(0.95,1.08)	
	5	670	662.6	1.01	(0.94,1.09)		593	580.8	1.02	(0.94,1.11)	
Pilocytic astrocytomas	1	240	241.3	0.99	(0.87,1.13)		343	323.6	1.06	(0.95,1.18)	
	2	229	241.2	0.95	(0.83,1.08)		146	142.5	1.02	(0.86,1.20)	
	3	267	240.6	1.11	(0.98,1.25)	0.42	189	212.7	0.89	(0.77,1.02)	0.24

Diagnostic group	Stratum[a]	Deprivation					Urbanization				
		O	E	SIR	95% CI	p	O	E	SIR	95% CI	p
	4	234	241.9	0.97	(0.85,1.10)		339	324.3	1.05	(0.94,1.16)	
	5	236	241.1	0.98	(0.86,1.11)		198	211.8	0.93	(0.81,1.07)	
Other gliomas	1	399	421.3	0.95	(0.86,1.04)		558	566.0	0.99	(0.91,1.07)	
	2	438	421.3	1.04	(0.94,1.14)		256	249.9	1.02	(0.90,1.16)	
	3	426	420.3	1.01	(0.92,1.11)	0.62	350	372.8	0.94	(0.84,1.04)	0.48
	4	410	422.5	0.97	(0.88,1.07)		566	567.3	1.00	(0.92,1.08)	
	5	434	421.6	1.03	(0.93,1.13)		395	369.1	1.07	(0.97,1.18)	

CNST: central nervous system tumor; O: observed cases in each stratum of deprivation or urbanization; E: expected number of cases in each stratum under the hypothesis of homogeneous age-specific incidence ratios throughout France; SIR: standardized incidence ratio; 95% CI: 95% confidence interval; p: p-value of the Chi-square test for heterogeneity in SIRs between deprivation or urbanization strata.

[a] French deprivation index (FDep): 1 = least deprived to 5 = most deprived; the urbanization index is based on the population size of the urban unit of the municipality of residence (inhabitants) 1 = < 2,000; 2 = 2,000-9,999; 3 = 10,000-99,999; 4 = 100,000-1,999,9999; 5 = Paris urban unit

Table S6: Association between natural background radiation exposure level of the municipality of residence at diagnosis and childhood CNST with adjustment for the French deprivation index (FDep) (France, 2000-2012)

		Gamma radiation			Radon		
Diagnostic group	O	Trend ERR by 50nSv/h[a]		p	Trend ERR by 100Bq/m^3 [b]		p
All CNST	5,425	1.05	(1.00,1.11)	0.07	1.05[c]	(0.97,1.12)[c]	0.23[c]
Ependymomas	525	0.92	(0.77,1.11)	0.39	0.95	(0.76,1.18)	0.64
Embryonal CNS tumors	1,069	1.05	(0.92,1.19)	0.46	0.99[c]	(0.82,1.20)[c]	0.94[c]
All gliomas	3,313	1.07	(1.00,1.15)	0.05	1.05	(0.97,1.15)	0.21
Pilocytic astrocytomas	1,206	1.13	(1.00,1.26)	0.04	1.14	(0.99,1.30)	0.06
All other gliomas	2,107	1.04	(0.95,1.14)	0.37	1.01	(0.91,1.12)	0.88

Note: CNST: central nervous system tumor; ERR: excess relative risk per unit of exposure; O: number of observed cases in each exposure category; p-value of the Chi-square test for the slope parameter estimate

[a] results from a Poisson regression model under the hypothesis of a log-linear association between childhood CNST and gamma radiation exposure level. ERR and its 95% confidence interval for a 50 nSv/h increase in gamma radiation exposure

[b] results from a Poisson regression model under the hypothesis of a log-linear association between childhood CNST and radon exposure level. ERR and its 95% confidence interval for a 100 Bq/m^3 increase in radon exposure

[c] estimates given by a negative binomial model (Over-dispersion detected by the Dean and Lawless test using the Poisson regression)

Table S7: Association between natural background radiation exposure level of the municipality of residence at diagnosis and CNST adjusted on the degree of urbanization (France, 2000-2012)

		Gamma radiation			Radon		
Diagnostic group	O	Trend ERR by 50 nSv/h[a]		p	Trend ERR by 100 Bq/m^3[b]		p
All CNST	5,471	1.08	(1.01,1.15)	0.02	1.08	(1.01,1.16)	0.03
Ependymomas	532	0.91	(0.74,1.11)	0.36	0.97	(0.77,1.22)	0.79
Embryonal CNST	1,079	1.11	(0.97,1.27)	0.14	1.05[d]	(0.89,1.24)[d]	0.56[d]
All gliomas	3,340	1.10[c]	(1.01,1.20)[c]	0.02[c]	1.09	(0.99,1.19)	0.06
Pilocytic astrocytomas	1,215	1.12	(0.99,1.27)	0.08	1.14	(0.98,1.32)	0.09
All other gliomas	2,125	1.08	(0.98,1.19)	0.11	1.06[d]	(0.95,1.19)[d]	0.31[d]

Note: CNST: central nervous system tumor; ERR: excess relative risk per unit of exposure; O: number of observed cases in each exposure category

[a] results from a Poisson regression model under the hypothesis of a log-linear association between childhood CNST and gamma radiation exposure level. ERR and its 95% confidence interval for a 50 nSv/h increase in gamma radiation exposure

[b] results from a Poisson regression model under the hypothesis of a log-linear association between childhood CNST and radon exposure level. ERR and its 95% confidence interval for a 100 Bq/m^3 increase in radon concentration

p: p-value of the chi-square test for the parameter estimate

[c] estimates given by a negative binomial model (Over-dispersion detected by the Dean and Lawless test using the Poisson regression)

[d] significant result for the test of departure from log-linearity: results should be considered with caution

Table S8: Population-weighted distribution of the cumulative gamma radiation exposure levels (mSv) in the 36,280 French municipalities, by year of age

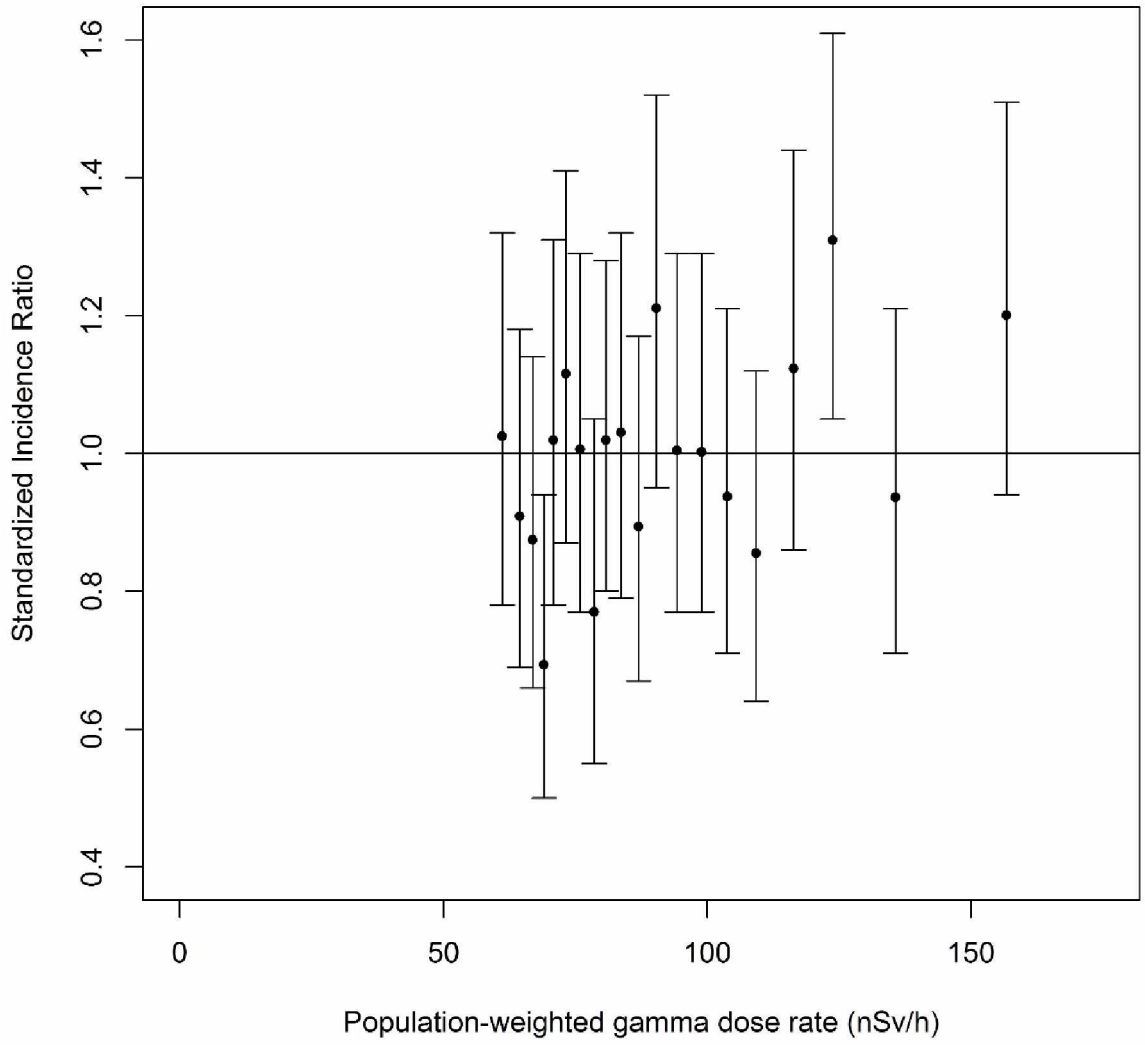
Age	Mean ± SD	Min	p5%	p25%	p50%	p75%	p95%	Max
0	0.40 ± 7.07	0.24	0.27	0.32	0.37	0.47	0.63	1.12
1	1.21 ± 21.2	0.71	0.82	0.95	1.12	1.40	1.89	3.35
2	2.02 ± 35.4	1.19	1.37	1.58	1.87	2.33	3.15	5.58
3	2.83 ± 49.5	1.67	1.92	2.21	2.61	3.26	4.41	7.82
4	3.64 ± 63.6	2.14	2.47	2.84	3.36	4.19	5.67	10.05
5	4.44 ± 77.7	2.62	3.02	3.47	4.11	5.12	6.93	12.28
6	5.25 ± 91.9	3.10	3.56	4.10	4.86	6.05	8.19	14.52
7	6.06 ± 106.1	3.57	4.11	4.73	5.60	6.98	9.45	16.75
8	6.87 ± 120.2	4.05	4.66	5.36	6.35	7.91	10.71	18.98
9	7.67 ± 134.3	4.53	5.21	5.99	7.10	8.84	11.97	21.21
10	8.48 ± 148.4	5.00	5.76	6.62	7.84	9.77	13.23	23.45
11	9.33 ± 162.6	5.48	6.31	7.26	8.59	10.70	14.49	25.68
12	10.29 ±178.8	5.96	6.85	7.89	9.34	11.64	15.75	27.91
13	10.91 ±190.9	6.43	7.40	8.52	10.08	12.57	17.01	30.15
14	11.71 ± 205.1	6.91	7.95	9.15	10.83	13.50	18.27	32.38
0-6 y.	2.83 ± 117.7	0.24	0.34	1.35	2.65	3.99	6.19	14.52
7-14 y.	8.89 ± 197.9	3.57	4.90	6.64	8.31	10.51	15.00	32.38
Total	6.06 ± 254.0	0.24	0.47	2.83	5.69	8.55	13.33	32.38

Note: population-weighted distribution of the cumulative gamma radiation level
Mean: arithmetic mean, SD: standard deviation, Min: minimum, p: percentile, Max: maximum; y.: years

Table S9: Population-weighted distribution of the cumulative radon exposure levels (Bq/m^3 × year) in the 36,280 French municipalities, by year of age

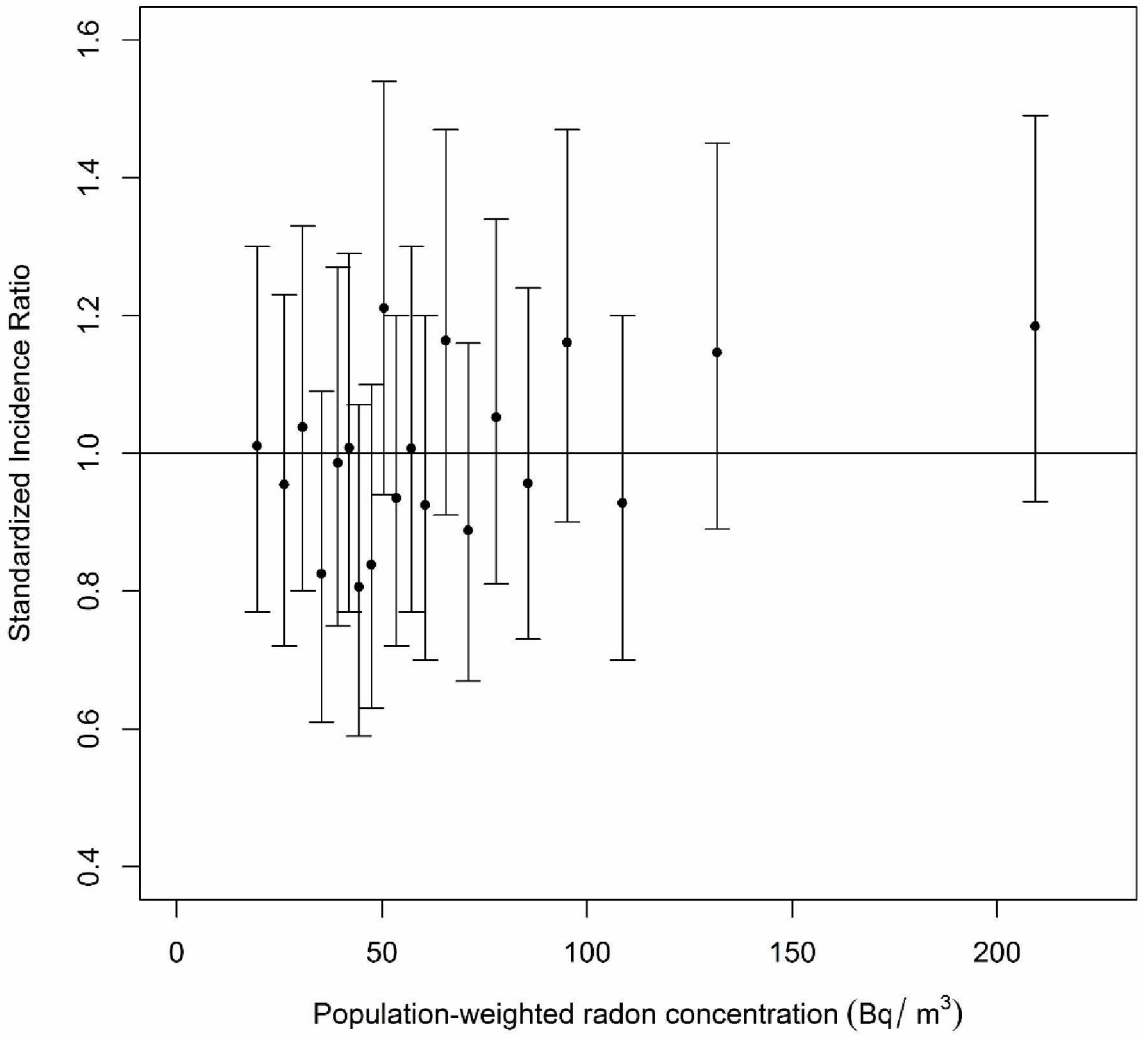
Age	Mean ± SD	Min	p5%	p25%	p50%	p75%	p95%	Max
0	33.9 ± 1,487.1	6.23	11.27	20.51	27.78	41.02	72.81	413.73
1	101.7 ± 4,461.4	18.69	33.81	61.52	83.33	123.05	218.43	1,241.19
2	169.6 ± 7,435.7	31.15	56.35	102.53	138.88	205.08	364.05	2,068.65
3	237.4 ± 10,409.9	43.61	78.89	143.54	194.43	287.11	509.67	2,896.11
4	305.2 ± 13,384.2	56.07	101.43	184.55	249.98	369.14	655.29	3,723.57
5	373.1 ± 16,358.5	68.53	123.97	225.56	305.53	451.17	800.91	4,551.03
6	440.8± 19,332.7	80.99	146.51	266.57	361.08	533.20	946.53	5,378.49
7	508.7 ± 22,307.0	93.45	169.05	307.58	416.63	615.23	1,092.15	6,205.95
8	576.5 ± 25,281.3	105.91	191.59	348.59	472.18	697.26	1,237.77	7,033.41
9	644.4 ± 28,255.5	118.37	214.13	389.60	527.73	779.29	1,383.39	7,860.87
10	712.2 ± 31,229.8	130.83	236.67	430.61	583.28	861.32	1,529.01	8,688.33
11	780.0 ± 34,204.1	143.29	259.21	471.62	638.83	943.35	1,674.63	9,515.79
12	847.84 ± 37,178.3	155.75	281.65	512.63	694.38	1,025.38	1,820.25	1,0343.25
13	915.7 ± 40,152.6	168.21	304.29	553.64	749.93	1,1107.41	1,965.87	1,1170.70
14	983.5 ± 43,126.9	180.67	326.83	594.65	805.48	1,189.44	2,111.49	11,998.71
0-6 y.	237.4 ± 14,784.2	6.23	22.99	86.90	181.00	312.33	646.31	5,378.49
7-14 y.	746.1 ± 34,857.13	93.45	240.07	415.91	605.81	899.65	1,709.00	11,998.17
Total	508.7 ± 31,810.3	6.23	36.48	187.16	385.8	668.5	1,385.78	11,998.17

Note: population-weighted distribution of the cumulative radon level
Mean: arithmetic mean, SD: standard deviation, Min: minimum, p: percentile, Max: maximum); y.: years



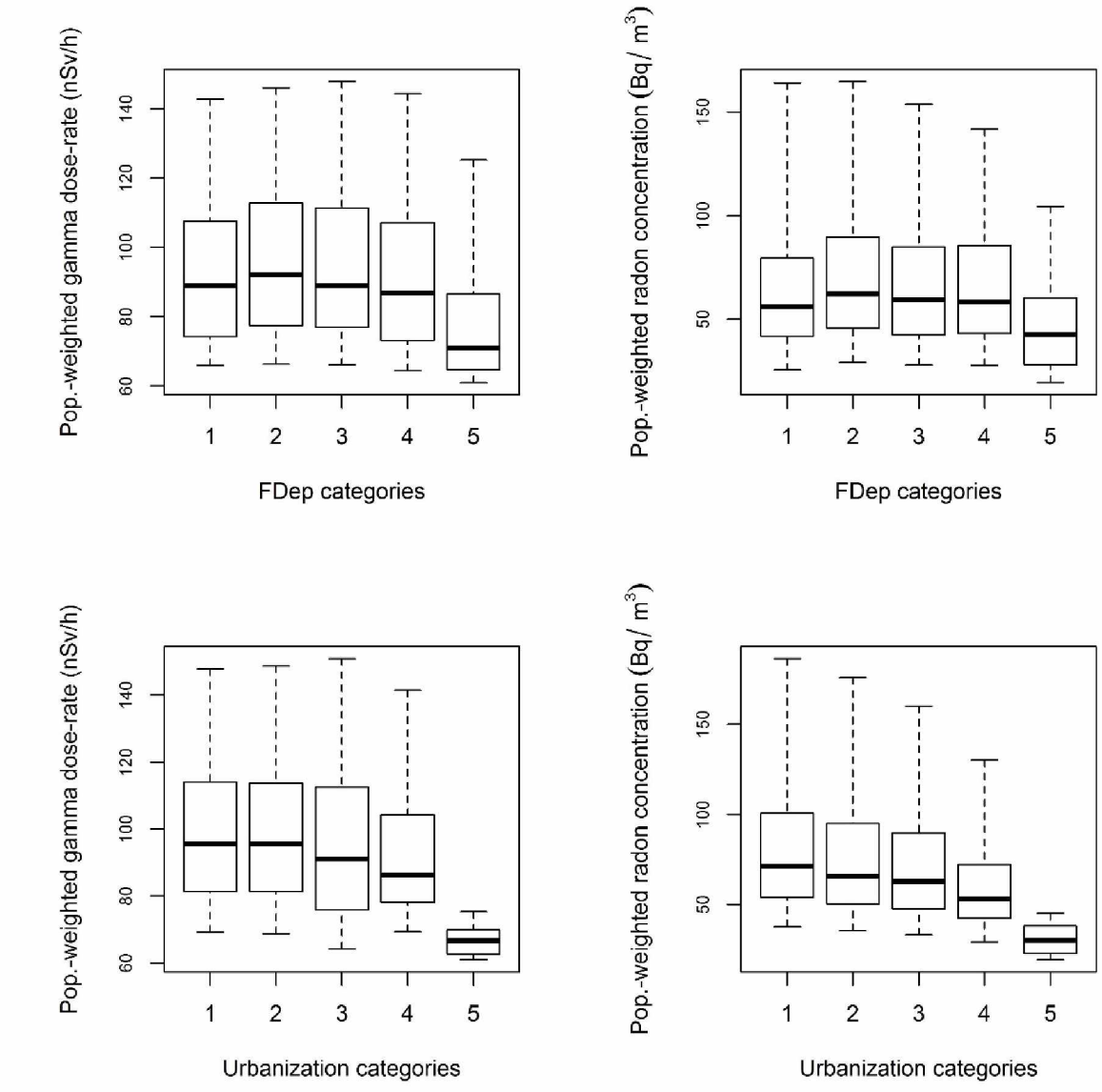
Note : The error bars represent the 95% confidence interval calculated with the Byar's approximation

Figure S1: Association between gamma-radiation exposure in the municipality of residence at diagnosis (grouped into 20 population categories) and standardized incidence ratios of pilocytic astrocytomas (France, 2000-2012, 1,215 cases)



Note : The error bars represent the 95% confidence interval calculated with the Byar's approximation

Figure S2: Association between indoor radon concentration in the municipality of residence at diagnosis (grouped into 20 population categories) and standardized incidence ratios of pilocytic astrocytomas (France, 2000-2012, 1,215 cases)



Note : FDep : French deprivation index : 1 = least deprived to 5 = most deprived.
The urbanization index is based on the population size of the urban unit of the municipality of residence 1 = < 2,000 inhabitants; 2 = 2,000-9,999 inhabitants; 3 = 10,000-99,999 inhabitants; 4 = 100,000-1,999,9999 inhabitants; 5 = Paris urban unit

Figure S3: Distribution of population-weighted gamma radiation exposure level and radon concentration in the 36,280 municipalities grouped by FDep categories or by degree of urbanization

Centre de Recherche Epidémiologie et Statistique Sorbonne Paris Cité
Inserm UMR 1153

EPICEA team – *epidemiology of childhood and adolescent cancer*

S. C. Sheppard,
Editor-in-Chief of *Journal of Environmental Radioactivity*

Justine Berlivet
Epidémiologie des Cancers de l'Enfant et de l'Adolescent
UMRS-1153 Equipe 7 (EPICEA), INSERM
16 avenue Paul Vaillant Couturier Bat 15/16
94807 Villejuif Cedex France
Email: **justine.berlivet@inserm.fr**

April 30th, 2019

Dear Editor-in-Chief,

We enclose a manuscript entitled « Association between childhood central nervous system tumors and residential exposure to natural background radiation in France, 2000-2012» for consideration for publication as a research original article in *Journal of Environmental Radioactivity*.

High-dose ionizing radiation is an established risk factor for childhood central nervous system tumors (CNST) but the role of low-dose exposures remains debated. In this paper, we test the hypothesis that natural background radiation (NBR, gamma radiation and radon) are associated with the risk of childhood CNST.

This work was based on high-quality data: we included more than 5,000 CNST cases diagnosed in mainland France during 2000-2012, and registered in the French national registry of childhood cancers. The NBR exposure levels were estimated on a fine geographical scale (36,280 municipalities) by the '*Institut de Radioprotection et de Sûreté Nucléaire*' (IRSN), from national measurements campaigns and geological data. The large number of cases enabled to consider CNST as a whole and by histological subgroups, while maintaining a high statistical power.

There was no association between all childhood CNST and NBR exposure levels in the municipality of residence at diagnosis. However, we found evidence supporting a positive association between gamma exposure and radon concentration and pilocytic astrocytomas, a well-defined subtype of gliomas (20% of childhood CNST). A positive association was also observed between pilocytic astrocytomas and cumulative NBR exposures estimated from birth to diagnosis.

We assessed the temporal stability of the results, by considering two calendar periods. We performed specific analyses for the younger children, who might be more sensitive to ionizing radiation. We also considered socio-demographic indicators as potential confounders in the association between NBR and CNST. While we could not disentangle the possible role of gamma radiation and radon, the physical properties of the various types of NBR have led us to favor the hypothesis of a role of gamma radiation rather than radon.

All authors have disclosed any actual or potential competing interests regarding the submitted manuscript. All of them have read and approved the paper and it has not been published previously nor is it being considered by any other peer-reviewed journal. This study did not involve human subjects.

We hope you will appreciate the strengths of this study and will be willing to consider this article for evaluation and publication.

Justine Berlivet