Received: 16 April 2024 | Revised: 4 September 2024 | Accepted: 17 September 2024

DOI: 10.1002/ijc.35214

RESEARCH ARTICLE

Cancer Epidemiology

IJC INTERNATIONAL JOURNAL of CANCER | UICC

# Residential exposure to solar ultraviolet radiation and risk of childhood hematological malignancies in Switzerland: A census-based cohort study

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**Funding information**
Swiss Cancer League, Grant/Award Numbers: KLS-4592-08-2018, KLS-5432-08-2021; Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und -direktoren; Swiss Paediatric Oncology Group; National Institute of Cancer Epidemiology and Registration; Swiss National Science Foundation, Grant/Award Number: 320030_176218; Kinderkrebshilfe Schweiz; Swiss Cancer Research Foundation; Federal Office of Public Health

## Abstract

Still little is known about possible environmental risk factors of childhood hematological malignancies (CHM). Previous studies suggest that ultraviolet radiation (UVR) exposure is associated with a lower risk of acute lymphoblastic leukemia (ALL) in children. We investigated the association between solar UVR exposure and risk of CHM in Switzerland, a country with greatly varying topography and weather conditions. We included all resident children aged 0–15 years from the Swiss National Cohort during 1990–2016 and identified incident cancer cases through probabilistic record linkage with the Swiss Childhood Cancer Registry. We estimated the overall annual mean UV level and the mean level for the month of July during 2004–2018 at children's homes using a climatological model of the midday (11 am–3 pm) UV-index (UVI) with a spatial resolution of 1.5–2 km. Using risk-set sampling, we obtained a nested case–control data set matched by birth year and fitted conditional logistic regression models (virtually equivalent to analyzing full cohort data using proportional hazards models) adjusting for sex, neighborhood socio-economic position, urbanization, air pollution, and background ionizing radiation. Our analyses included 1446 cases of CHM. Estimated adjusted hazard ratios (HR) per unit increase in UVI in July were 0.76 (95% CI 0.59–0.98) for leukemia and 0.74 (0.55–0.98) for ALL. Results for annual exposure were similar but confidence intervals were wider and included one. We found no evidence for an association for lymphoma overall (HR 1.14, 95% CI 0.59–2.19 for annual exposure) or diagnostic subgroups. Our study provides further support for an inverse association between exposure to ambient solar UVR and childhood ALL.

**KEYWORDS**
children, cohort study, hematological malignancies, sun exposure, ultraviolet radiation

Astrid Coste and Christian Kreis contributed equally to this study.

**What's new?**

Little is known about the etiology of childhood hematological malignancies (CHM). Ultraviolet radiation (UVR) could have an impact on these cancers through different pathways, such as its immunosuppressive effects or photosynthesis of vitamin D. The authors investigated if ambient solar UVR exposure was associated with CHM in Switzerland, a country with varying UVR. They observed a decreased risk of 24% for acute lymphoblastic leukemia per one-unit increase of UV Index.

## 1 | BACKGROUND

Childhood hematological malignancies (CHM) are the most common pediatric cancers globally, including in Switzerland, where they account for about 44% of cases diagnosed.[1] CHM includes two major diagnostic groups: leukemia and lymphoma, representing about 32% and 12% of pediatric cancers, respectively.

Little is known about risk factors for CHM. Rare genetic conditions, including Down syndrome, are known to increase the risk of leukemia in children, but they account for only a small fraction of cases. Among environmental exposures, moderate-to-high doses of ionizing radiation for leukemia[2] and some infectious diseases with immunosuppressive effects for lymphoma (e.g., Epstein–Barr virus) are established risk factors.[3] Exposure to non-ionizing radiation, particularly extremely-low-frequency magnetic fields from high-voltage power lines, has also been suspected to be a risk factor of childhood leukemia, but the evidence is inconclusive.[4,5]

Solar ultraviolet radiation (UVR) is non-ionizing radiation to which humans are chronically exposed. Individual doses vary greatly according to geographic location, season, time of the day, and personal behavior.[6,7] UVR is subdivided according to its wavelengths and biological effects into UVA (315–400 nm, 95% of UVR reaching Earth); UVB (280–315 nm, 5% of UVR reaching Earth), and UVC (100–280 nm, mostly blocked by the ozone layer). Carcinogenic effects of UVB and UVA have been shown for skin, lip, and eye cancers, particularly in fair-skinned populations.[8,9] The effects of UVR on other cells or organs remain unclear, however. A parallel increase in the incidence of melanoma and non-Hodgkin's lymphoma (NHL) in adults during the 1970s and 1980s gave rise to the hypothesis of a common etiology of these cancers.[10,11] The known immunosuppressive effects of UVB[9] offered a plausible biological mechanism. Subsequent studies showed conflicting results, however, with an international pooled study of case–control studies[12] even finding a consistent inverse association based on self-reported recreational sun exposure. This observation led to the hypothesis of a protective effect of UVB through photosynthesis of vitamin D.[12] However, the effect of UVR on CHM may differ in strength and underlying mechanisms from a corresponding effect in adulthood. Childhood ALL, the most frequent CHM, develops at very young ages with early genetic alterations occurring in utero, leaving only a short, though critical, time window for environmental exposures such as UVR to have an effect. Also, exposure levels are typically lower in children. In most Western countries, parents are recommended to protect their children from direct exposure to UVR in the first years of life. It has also been proposed that childhood ALL may have an infectious origin.[13] UVR exposure (or lack thereof) might thus affect the risk of childhood ALL by acting on the immune system.

Few studies have investigated the link between solar UVR and risk of CHM, and these differed widely in their designs and methods of exposure assessment.[14–18] Two large record-based studies using objective measurements of residential ambient UVR exposure found conflicting results: a Californian case–control study found an inverse association for ALL and NHL but no association with other CHM subtypes.[15] A French ecological study found a positive association of mean UVR levels in the municipality of residence at diagnosis with precursor-B cell ALL (PBC-ALL), but no evidence of an association for other types of CHM.[14] In the subsequent pooled case–control studies, the same authors found similar associations with PBC-ALL for ambient UV exposure assessed both at birth and diagnosis.[19] To date no cohort study has been conducted on this subject.

We aimed to investigate the association between residential exposure to solar UVR and CHM in a nationwide census-based cohort study in Switzerland. Roughly 60% of the Swiss territory represents mountainous regions, and 20% of the population living in these areas are exposed to elevated doses of ambient UVR at higher altitudes. In addition, the resident population is predominantly fair-skinned, and incidence rates of skin melanoma are high by international comparison.[20]

## 2 | MATERIALS AND METHODS

### 2.1 | Population

The study cohort consisted of the Swiss resident population under 16 years of age recorded in the decennial censuses of 1990 and 2000 and the annual population-registry-based censuses between 2010 and 2016. We obtained the population data from the Swiss National Cohort (SNC, source: Federal Statistical Office), a cohort study based on record linkage of national censuses since 1990 with each other and with national datasets on birth, mortality, and migration.[21,22] The SNC records socio-demographic information as well as the geocodes of the residential address of all Swiss residents. Children residing in temporary dwellings or with unknown residences were excluded from the analysis. We identified first primary cases of hematological cancer from the Childhood Cancer Registry of Switzerland (ChCR), a population-based nationwide cancer registry operating since 1976.

Estimations suggest that the ChCR includes≥95% of cases diagnosed since 1995.[23] We used the Canadian probabilistic record linkage software *G-Link* to match SNC records with cancer diagnoses recorded in the ChCR based on sex, date of birth, maternal and paternal dates of birth, geocoded residence at census, municipality of residence at census and at birth, and nationality. We included a diagnosis of a malignant hematological cancer if it occurred during the study period 1991–2016, could be linked to a subject in our study population, and was the first registered primary cancer diagnosed in that child. Children diagnosed with cancer before they entered the cohort, that is, those with a registered diagnosis before the first census of their lifetime, were excluded from the analysis.

## 2.2 | Outcomes

We investigated the following diagnostic groups according to the International Classification of Childhood Cancer, Third Edition (ICCC-3)[24]: all hematological cancers combined (ICCC-3 diagnostic groups I + II), leukemia (I), lymphoid leukemia (I.a), acute myeloid leukemia (AML) (I.b), lymphomas (II), Hodgkin lymphomas (HL) (II.a), and non-Hodgkin lymphomas (NHL) (II.b). Chronic lymphoid leukemia (CLL; included in diagnostic subgroup I.a) is extremely rare in children and there were no cases of CLL in our study sample; we thus refer to ICCC-3 diagnostic subgroup I.a as acute lymphoblastic leukemia (ALL).

## 2.3 | Exposure modeling

A climatological UV model specific to Switzerland was used to estimate ambient erythemal UV irradiance. A detailed description of the methodology of the model is given elsewhere.[25] Briefly, the model combines the libRadtran clear-sky surface UV irradiance and the HelioMont cloud forcing to estimate the all-sky surface UV irradiance, with an erythemal action spectrum applied. The Swiss UV climatology covers the period from 2004 to 2018, with a spatial resolution of 1.5–2 km and a temporal resolution of 1 h. Climatologically modeled ground-level UV radiation was validated against ground-level irradiance measurements from three stations located in distinct geographical areas of Switzerland: Davos, Locarno-Monti, and Payerne. Comparison of measured and modeled values under varying meteorological conditions showed a good correlation, with an average RMSE of 0.21. A recent study using SNC data and a similar exposure model reported a positive association between malignant melanoma mortality and estimated ambient UV levels.[26]

Solar UV radiation at children's places of residence was defined as the midday (11 am–3 pm) UV index (UVI) estimated using this climatological model. We prepared the UVI data as a raster file and extracted exposure levels for children's geocoded home address locations. Despite the UVI being a whole number indicator of UV irradiance, we treated our model-based estimates as continuous measures (interval scale) with 1 unit corresponding to 1 integer step on the UVI scale. As we observed little variation in UVI levels between individual years, we calculated the overall annual mean during 2004–2018 and the overall mean level for the month of July (the month with the highest UVI values of the year) at place of residence at diagnosis. UVI exposure levels were time-updated as of the first day of a change in residential location recorded in the SNC data. If the exact date of relocation was not known, it was imputed as the midpoint between the two closest time points for which the address location was known from the SNC.

## 2.4 | Potential confounding

We considered the following potential confounders: sex, neighborhood socio-economic position (Swiss-SEP in quintiles),[27] level of urbanization (urban, suburban, and rural), modeled air pollution (ambient levels of $NO_2$ in $\mu g/m^3$) at diagnosis,[28] and modeled background ionizing radiation (total cumulative dose from terrestrial gamma and cosmic radiation since birth in mSv).[29] We also included presence (yes/no) of a general cancer registry in the canton of residence at diagnosis to account for potential under-ascertainment of cases in cantons without such a registry. In cantons with such registries, data exchanges with the ChCR is likely to have resulted in a more complete ascertainment of cases. All covariates were time-updated for every census point or known or imputed intermittent change in home address location.

## 2.5 | Statistical analysis

We prepared the SNC cohort as a time-to-event dataset with age as the underlying time scale. Follow-up began on the day of the first census in a child's lifetime and ended on the date of diagnosis, death, 16th birthday, emigration, loss to follow-up, or end of administrative follow-up on December 31, 2016, whichever occurred first. In order to facilitate the analyses using time-varying covariates, we sampled 100 controls for each case matched by age and year of birth from the population at risk at the time of a case's diagnosis (risk-set sampling).

We fitted conditional logistic regression models to the matched case–control data conditioning on the risk sets. This procedure is approximately equivalent to estimating Cox proportional hazards models on the full cohort and we therefore interpret odds ratios as hazard ratios (HR).[30] We ran likelihood ratio (LR) tests comparing models including the exposure in quintiles (unrestricted model) with a model including the quintile means of the exposure as a linear term (linearly restricted model) to test for evidence on non-linearity in the association with the outcome. As the LR-tests showed no evidence of non-linearity ($p$-value LR-test >0.05), we present the analyses of UVI as a linear exposure term (unrestricted climatological model estimates) as the main analyses but also report models including the exposure variable categorized into quintiles for comparison. We fitted both univariable and fully adjusted models including the potential confounders listed above. All models were complete case analyses.

We ran all statistical analyses using the R language for statistical computing version 4.2.3.

## 3 | RESULTS

### 3.1 | Characteristics of the study population

In total, we identified 5627 incident cases of childhood cancer diagnosed between 1990 and 2016 from the ChCR, 3777 of which were diagnosed after the first census in their lifetime and thus potentially eligible for inclusion in the study. A total of 495 eligible cases could not be linked to a record in the SNC, 129 had missing geocodes, and 16 were censored prior to diagnosis. Of the remaining 3137 childhood cancers, 1446 cases were hematological malignancies, 951 leukemias, and 495 lymphomas (Figure 1).

The characteristics of the study population are presented in Table 1 stratified by the July mean levels of UVI exposure used for the categorical analyses. The mean level of the UVI in July at the place of residence of the study population ranged between 4.54 and 6.32. Compared to the children in the lowest exposure quintile, children in the highest quintile were less likely to live in a rural municipality and be exposed to higher levels of ambient air pollution. The distribution of the study population by annual mean levels of UVI exposure was somewhat different, with higher proportions of highly exposed children living in a rural area, exposed to low levels of air pollution, and residing in a neighborhood ranked lower on the Swiss-SEP (Table S1).

As expected, children living in Southern and Western Switzerland were exposed to higher levels of solar UVR in July than children in Northwestern, Northeastern, Central, and Eastern Switzerland (Figure 2). The highest UVI values were estimated for the highest mountainous regions, inhabited by few people if at all. The spatial variation of the annual mean UVI levels was rather similar, albeit with less overall variation and a clearer divide between the mountainous Alpine regions and the low-lying Central Plateau, home to the biggest urban areas and the majority of the population (Figure S1). The annual mean level of UVI at the place of residence of the study population ranged between 2.46 and 3.83 (Table S1 and Figure S2).

### 3.2 | Childhood hematological cancer risk and exposure to solar UV radiation

LR tests showed no evidence of a departure from linearity neither for all hematological cancers combined nor for any diagnostic group or subgroup individually for July exposure ($p$-values >0.4; Table S4). $P$-values of LR-tests of models for annual exposure were similar (>0.3; Table S5). We therefore included exposure as a linear term in our main analyses and based our interpretation of results on these models. Since these LR-tests may have been underpowered, we also report the analyses of the categorical models.

After adjusting for potential confounders, we found some evidence that higher ambient UVI levels in July were associated with reduced risks of leukemia and ALL (Table 2): adjusted HRs per unit increase in July UVI levels were 0.76 (95% confidence interval [CI] 0.59–0.98) for leukemia and 0.74 (95%-CI: 0.55–0.98) for ALL (Table 2). Corresponding point estimates for models including annual UVI exposure were similar but confidence intervals wider (Leukemia: adj. HR 0.71, 95%-CI 0.44–1.14; ALL: 0.70, 0.41–1.19; Table S2). By contrast, there was no evidence of an association for AML. Models also showed no evidence of association for lymphomas (0.96; 0.67–1.38 for July exposure; Table 2). Adjusting the models for potential confounders generally resulted in lower point estimates of the HR (Table 2).

In the analyses including exposure as a categorical term (quintiles), there was no evidence for an association overall nor for any diagnostic group or subgroup with $p$-values of LR-tests comparing categorical (quintile) models with the null models without the exposure >0.2 for both July and annual exposure (Tables 3, S3, S5, and S6). Comparable with the results of models with exposure as a linear term, categorical models for leukemia and ALL showed slightly reduced risks for the highest quintile exposure category but confidence intervals included 1 both for July and annual exposure (Tables 3 and S3).

As recommended by a reviewer, we also ran separate, age-stratified analyses for leukemia and ALL to allow for possibly differing effects between young (0–4 years) and older children (5–15 years). For leukemia, the adjusted HR for exposure in July (entered as a linear term) were slightly higher for children aged 0–4 years (0.89, 0.58–1.38) than for children aged 5–15 years (0.74, 0.53–1.02). Results for ALL were similar (Table 2). For annual mean exposure, adjusted HR for leukemia were virtually identical for children aged 0–4 years (0.75, 0.34–1.69) and for children aged 5–15 years (0.76, 0.42–1.39), whereas, for ALL, adjusted HR were slightly lower for children aged 0–4 years (0.64, 0.27–1.52) and slightly higher for children aged 5–15 years (0.84, 0.42–1.67; Table S2).

## 4 | DISCUSSION

This nationwide census-based cohort study investigating the association between exposure to solar UVR and childhood hematological cancer found some evidence of a reduced risk of childhood leukemia, specifically with ALL, in Switzerland. The inverse association was stronger in models including predicted ambient UVI levels for the month of July as a linear exposure term and adjusting for various potential confounders (socio-economic status, level of urbanization, modeled traffic-related air pollution, and external background ionizing radiation). Similar associations were found in adjusted models including annual mean UVI exposure, albeit with wider confidence intervals. By contrast, there was little evidence of an association of ambient UVI exposure for AML or for lymphomas.

The few other studies that have investigated associations between UV exposure and the risk of cancer in children showed conflicting results.[14–18] A large record-based case–control study conducted in California focusing on children aged less than 6 years reported an inverse association between ALL and NHL risk and

**TABLE 1** Characteristics of the study population (controls only, n=313, 700) by quintiles of UV index, mean levels in July.

| Characteristics | [4.54, 5.01] | (%) | (5.01, 5.1] | (%) | (5.1, 5.2] | (%) | (5.2, 5.47] | (%) | (5.47, 6.32] | (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Total | 63,042 | (100.0) | 62,466 | (100.0) | 62,981 | (100.0) | 62,593 | (100.0) | 62,618 | (100.0) |
| Sex | | | | | | | | | | |
| Male | 32,008 | (50.8) | 32,342 | (51.8) | 32,290 | (51.3) | 31,941 | (51.0) | 31,988 | (51.1) |
| Female | 31,034 | (49.2) | 30,124 | (48.2) | 30,691 | (48.7) | 30,652 | (49.0) | 30,630 | (48.9) |
| Year of birth | | | | | | | | | | |
| 1975–1979 | 1495 | (2.4) | 1310 | (2.1) | 1374 | (2.2) | 1491 | (2.4) | 1430 | (2.3) |
| 1980–1984 | 5675 | (9.0) | 5205 | (8.3) | 5332 | (8.5) | 5305 | (8.5) | 4783 | (7.6) |
| 1985–1989 | 12,100 | (19.2) | 11,376 | (18.2) | 11,387 | (18.1) | 11,452 | (18.3) | 10,585 | (16.9) |
| 1990–1994 | 10,992 | (17.4) | 10,357 | (16.6) | 10,549 | (16.7) | 10,658 | (17.0) | 10,144 | (16.2) |
| 1995–1999 | 12,994 | (20.6) | 12,791 | (20.5) | 12,821 | (20.4) | 12,927 | (20.7) | 13,367 | (21.3) |
| 2000–2004 | 7404 | (11.7) | 7956 | (12.7) | 8011 | (12.7) | 7895 | (12.6) | 8434 | (13.5) |
| 2005–2009 | 6901 | (10.9) | 7537 | (12.1) | 7660 | (12.2) | 7213 | (11.5) | 8089 | (12.9) |
| 2010–2015 | 5481 | (8.7) | 5934 | (9.5) | 5847 | (9.3) | 5652 | (9.0) | 5786 | (9.2) |
| Year of cohort entry | | | | | | | | | | |
| 1990 | 22,431 | (35.6) | 20,810 | (33.3) | 21,150 | (33.6) | 21,577 | (34.5) | 19,412 | (31.0) |
| 2000 | 23,270 | (36.9) | 22,876 | (36.6) | 22,897 | (36.4) | 22,771 | (36.4) | 23,183 | (37.0) |
| 2010 | 13,050 | (20.7) | 14,155 | (22.7) | 14,300 | (22.7) | 13,810 | (22.1) | 15,187 | (24.3) |
| 2011–2014 | 4291 | (6.8) | 4625 | (7.4) | 4634 | (7.4) | 4435 | (7.1) | 4836 | (7.7) |
| Degree of urbanization | | | | | | | | | | |
| Urban | 14,980 | (23.8) | 18,815 | (30.1) | 11,795 | (18.7) | 12,922 | (20.6) | 16,808 | (26.8) |
| Peri-Urban | 26,837 | (42.6) | 29,785 | (47.7) | 29,251 | (46.4) | 25,402 | (40.6) | 33,128 | (52.9) |
| Rural | 21,225 | (33.7) | 13,866 | (22.2) | 21,935 | (34.8) | 24,269 | (38.8) | 12,682 | (20.3) |
| Swiss-SEP index[a] | | | | | | | | | | |
| first quintile (low SEP) | 18,031 | (28.6) | 12,199 | (19.5) | 11,873 | (18.9) | 17,806 | (28.4) | 20,441 | (32.6) |
| Second quintile | 14,141 | (22.4) | 11,755 | (18.8) | 11,880 | (18.9) | 14,607 | (23.3) | 12,622 | (20.2) |
| Third quintile | 11,382 | (18.1) | 12,621 | (20.2) | 12,720 | (20.2) | 13,299 | (21.2) | 10,568 | (16.9) |
| fourth quintile | 10,213 | (16.2) | 13,514 | (21.6) | 13,558 | (21.5) | 10,664 | (17.0) | 10,073 | (16.1) |
| Fifth quintile (high SEP) | 9275 | (14.7) | 12,377 | (19.8) | 12,950 | (20.6) | 6217 | (9.9) | 8914 | (14.2) |
| Cantonal cancer registry | | | | | | | | | | |
| No | 16,818 | (26.7) | 21,510 | (34.4) | 22,250 | (35.3) | 32,079 | (51.3) | 3328 | (5.3) |
| Yes | 46,224 | (73.3) | 40,956 | (65.6) | 40,731 | (64.7) | 30,514 | (48.7) | 59,290 | (94.7) |
| $NO_2$ ($\mu g/m^3$) | | | | | | | | | | |
| ≤17.9 | 16,987 | (26.9) | 10,445 | (16.7) | 14,503 | (23.0) | 22,757 | (36.4) | 12,687 | (20.3) |
| >17.9–21.9 | 14,071 | (22.3) | 15,393 | (24.6) | 19,387 | (30.8) | 16,958 | (27.1) | 10,701 | (17.1) |
| >21.9–26.7 | 14,590 | (23.1) | 18,208 | (29.1) | 17,178 | (27.3) | 13,170 | (21.0) | 14,645 | (23.4) |
| >26.7 | 17,391 | (27.6) | 18,420 | (29.5) | 11,912 | (18.9) | 9708 | (15.5) | 24,567 | (39.2) |
| Missing | 3 | (0.0) | 0 | (0.0) | 1 | (0.0) | 0 | (0.0) | 18 | (0.0) |
| Background ionizing radiation (mSv) | | | | | | | | | | |
| ≤4.68 | 16,522 | (26.2) | 17,972 | (28.8) | 17,602 | (27.9) | 16,483 | (26.3) | 15,317 | (24.5) |
| >4.68–8.48 | 16,102 | (25.5) | 16,667 | (26.7) | 16,524 | (26.2) | 15,799 | (25.2) | 14,778 | (23.6) |
| >8.48–11.3 | 15,366 | (24.4) | 16,080 | (25.7) | 16,476 | (26.2) | 15,203 | (24.3) | 13,018 | (20.8) |
| >11.3–31.2 | 15,052 | (23.9) | 11,747 | (18.8) | 12,379 | (19.7) | 15,108 | (24.1) | 19,505 | (31.1) |

*Note*: Values represent counts (column percentages).

[a]The SEP-index is an area-based measure of socio-economic position for Switzerland, estimated for neighborhoods of 50 households using a principal component analysis of four socio-economic variables, with data from the 2000 census.

ambient UVR at birth address but no association with other CHM subtypes.[15] We also observed an inverse association with ALL but not with NHL. By contrast, a French ecological study using small areal units (municipalities) found a positive association between the most common subtype of ALL, the precursor-B cell ALL (PBC-ALL), and ambient UVR at diagnosis.[14] No associations were observed for other

types of CHM. A replication of this study pooling two French population-based case–control studies (ESCALE and ESTELLE studies) produced the same results, even after adjustment for potential individual-level confounders. The study also found the same association when considering residential ambient UVR at time of birth instead of diagnosis.[19] The French and Californian studies both considered the whole UV spectrum in the exposure assessment, whereas, in our study, we focused on ambient erythemal UV doses by using UV Index estimates. The earlier French study observed that annual ambient UVA and UVB radiation at the municipality level were highly correlated and that it was impossible to analyze them separately.[14] It is, therefore, unlikely that the discrepancy of results observed compared to the French study are due to differences in the ambient UVR indicators selected.

Furthermore, a Finnish study observed a lower incidence of ALL in the dark season versus the light season, but only for the age group of 2–4 year olds, and no association for other age groups or with childhood AML.[18] A multi-country ecological study observed an inverse association between leukemia and ambient UVR but no evidence of association with lymphoma.[16] A Greek case–control study found an inverse association between sunbathing for more than 15 days per year and risk of childhood NHL.[17] These studies all differed notably from ours regarding study design, exposure assessment, and the range of UV exposure.

We found stronger evidence of an inverse association with ALL when using UVI levels in July instead of the annual average. The Californian study observed seasonality in the effect of UVR with a

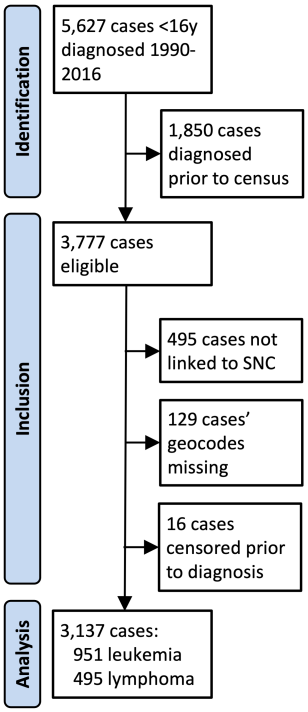


**FIGURE 1** Flow diagram of the study inclusion of the childhood hematological cancer cases.

**TABLE 2** Hazard ratios (HR) for childhood hematological malignancies per 1 unit of UV Index increase (interval scale) in ambient UV irradiance in July.

| Outcome | Cases | HR (95% CI)[a] | Adj HR (95% CI)[b] |
|---|---|---|---|
| Hematological | 1446 | 0.98 (0.82–1.18) | 0.83 (0.67–1.02) |
| Leukemia | 951 | 0.93 (0.74–1.17) | 0.76 (0.59–0.98) |
| 0–4 years | 339 | 0.87 (0.59–1.28) | 0.89 (0.58–1.38) |
| 5–15 years | 612 | 0.96 (0.73–1.28) | 0.74 (0.53–1.02) |
| ALL | 754 | 0.86 (0.67–1.12) | 0.74 (0.55–0.98) |
| 0–4 years | 296 | 0.79 (0.52–1.20) | 0.81 (0.51–1.30) |
| 5–15 years | 458 | 0.91 (0.66–1.26) | 0.74 (0.51–1.07) |
| AML | 133 | 1.71 (0.98–3.01) | 1.36 (0.71–2.62) |
| Lymphoma | 495 | 1.08 (0.79–1.47) | 0.96 (0.67–1.38) |
| HL | 234 | 1.00 (0.64–1.58) | 0.90 (0.53–1.52) |
| NHL | 163 | 1.34 (0.80–2.26) | 1.04 (0.56–1.93) |

[a]Model adjusted for sex, birth year, and year of entry into the cohort.
[b]Model adjusted for sex, birth year, year of entry into the cohort, Swiss-SEP index, level of urbanization, air pollution, existence of a cantonal registry, and background ionizing radiation.

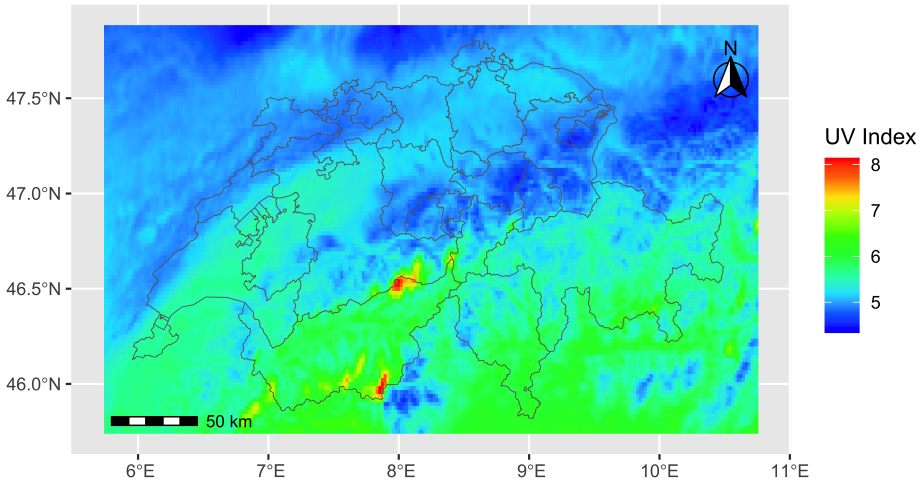


**FIGURE 2** Map of UV index distribution in Switzerland, mean evels in July between 11 am and 3 pm, 2004–2018.

**TABLE 3** Hazards ratios (HR) for childhood hematological malignancies per quintiles of UV index in July.

| Outcome | UVI | Cases | HR (95% CI)[a] | Adj HR (95% CI)[b] |
|---|---|---|---|---|
| Hematological | [4.54, 5.01] | 295 | 1.00 | 1.00 |
| | (5.01, 5.1] | 308 | 1.06 (0.90–1.24) | 1.05 (0.89–1.23) |
| | (5.1, 5.2] | 277 | 0.94 (0.80–1.11) | 0.96 (0.82–1.14) |
| | (5.2, 5.47] | 277 | 0.95 (0.81–1.12) | 0.97 (0.82–1.14) |
| | (5.47, 6.32] | 289 | 0.98 (0.84–1.16) | 0.89 (0.75–1.06) |
| Leukemia | [4.54, 5.01] | 190 | 1.00 | 1.00 |
| | (5.01, 5.1] | 203 | 1.07 (0.88–1.31) | 1.07 (0.87–1.31) |
| | (5.1, 5.2] | 191 | 1.00 (0.82–1.23) | 1.03 (0.84–1.27) |
| | (5.2, 5.47] | 185 | 0.98 (0.80–1.21) | 1.02 (0.83–1.25) |
| | (5.47, 6.32] | 182 | 0.95 (0.77–1.16) | 0.83 (0.67–1.03) |
| ALL | [4.54, 5.01] | 152 | 1.00 | 1.00 |
| | (5.01, 5.1] | 160 | 1.05 (0.84–1.31) | 1.04 (0.83–1.31) |
| | (5.1, 5.2] | 158 | 1.03 (0.82–1.29) | 1.05 (0.84–1.31) |
| | (5.2, 5.47] | 145 | 0.96 (0.76–1.21) | 0.99 (0.78–1.25) |
| | (5.47, 6.32] | 139 | 0.90 (0.71–1.13) | 0.80 (0.63–1.03) |
| AML | [4.54, 5.01] | 24 | 1.00 | 1.00 |
| | (5.01, 5.1] | 28 | 1.20 (0.70–2.08) | 1.19 (0.68–2.07) |
| | (5.1, 5.2] | 22 | 0.92 (0.52–1.65) | 0.96 (0.53–1.72) |
| | (5.2, 5.47] | 24 | 1.03 (0.59–1.83) | 1.05 (0.59–1.88) |
| | (5.47, 6.32] | 35 | 1.51 (0.89–2.54) | 1.34 (0.77–2.34) |
| Lymphoma | [4.54, 5.01] | 105 | 1.00 | 1.00 |
| | (5.01, 5.1] | 105 | 1.02 (0.78–1.35) | 1.01 (0.77–1.33) |
| | (5.1, 5.2] | 86 | 0.83 (0.62–1.10) | 0.85 (0.63–1.13) |
| | (5.2, 5.47] | 92 | 0.89 (0.67–1.18) | 0.88 (0.66–1.17) |
| | (5.47, 6.32] | 107 | 1.05 (0.80–1.38) | 1.03 (0.77–1.38) |
| HL | [4.54, 5.01] | 52 | 1.00 | 1.00 |
| | (5.01, 5.1] | 48 | 0.98 (0.66–1.45) | 0.95 (0.64–1.42) |
| | (5.1, 5.2] | 43 | 0.85 (0.56–1.27) | 0.86 (0.57–1.29) |
| | (5.2, 5.47] | 44 | 0.87 (0.58–1.30) | 0.85 (0.56–1.29) |
| | (5.47, 6.32] | 47 | 0.94 (0.63–1.40) | 0.91 (0.59–1.40) |
| NHL | [4.54, 5.01] | 35 | 1.00 | 1.00 |
| | (5.01, 5.1] | 28 | 0.82 (0.50–1.34) | 0.81 (0.49–1.35) |
| | (5.1, 5.2] | 31 | 0.89 (0.55–1.45) | 0.94 (0.57–1.53) |
| | (5.2, 5.47] | 32 | 0.95 (0.59–1.54) | 0.94 (0.57–1.54) |
| | (5.47, 6.32] | 37 | 1.13 (0.71–1.80) | 1.00 (0.60–1.66) |

[a]Model adjusted for sex, birth year, and year of entry into the cohort.
[b]Model adjusted for sex, birth year, year of entry into the cohort, Swiss-SEP index, level of urbanization, air pollution, existence of a cantonal registry, and background ionizing radiation.

stronger apparent protective effect for ALL when considering children born between April and September compared to children born between October and March.[15] Given that "both UVR and vitamin D were found to be protective against tuberculosis and influenza infections," and maternal influenza during pregnancy was positively associated to ALL in previous studies,[31] the authors concluded that this finding supported the role of UVR in "reducing cancer risk via reducing susceptibility to viral infections." However, UVR immune system modulation could equally promote the oncogenesis process through chronic inflammation or immunosuppression, as suggested by some animal studies.[32] A pan-cancer analysis performed among pediatric cancer cases showed a genome-wide mutational signature attributed to UV in eight aneuploid leukemias.[33] Also, a recent meta-analysis on sunbed use and risk of hematological malignancies in adulthood showed a positive association after adjusting for sun exposure, and UV sunbed lamps emit mostly UVA.[34] In summary, UVR exposure may affect the development of hematological malignancies in multiple ways.

The main strength of our study was the nationwide retrospective cohort design based on routine data sets, which maximizes sample size while minimizing the risk of selection bias. The study did not require active participation of subjects and we could include almost the whole childhood population of Switzerland. We used a climatological model of UV radiation to estimate the UV Index for all of Switzerland for a grid with resolution of 1.5–2 km. Given that solar UV radiation varies little at this scale, a greater resolution would not likely have increased the accuracy of exposure assessment. We identified all cases of hematological cancer from the ChCR, the Swiss population-based cancer registry with high coverage. UVI exposure was determined for both cases and controls based on geocodes of the residential address recorded in the SNC with correspondingly little risk of recall bias or differential misclassification bias. Finally, in our analyses, we could control for some important potential confounders like background ionizing radiation and ambient air pollution, which were shown to be associated with some hematological childhood cancers in Switzerland.[27–29]

As our UVR model estimated UVI exposure as a continuous measure, we fitted separate models with exposure both as a continuous (linear term) and as a categorical variable (quintiles). While both models showed an inverse association with ALL for the mean UVI in July, in the categorical model, the risk reduction was only apparent for the highest quintile of exposure with the LR test (quintiles versus null model, Table S4) showing no evidence of an association. However, there was no evidence of a deviation from linearity (quintiles vs. quintile means model, Table S4) and statistical power for detecting an (approximately linear) association was higher for the model with the linear term compared to the quintile model. We therefore think that the more parsimonious model with a linear term provides an adequate representation for the observed association.

Linkage between the ChCR and the SNC was done probabilistically, which likely resulted in some misclassification errors. Also, the climatological UVI model estimates ambient irradiance at children's home addresses, which may be a poor proxy for individual exposure (see below). We have no reason to believe that such misclassification could have been differential, but non-differential misclassification may have biased our results toward the null. A previous study into the completeness of the ChCR found evidence of regional differences in cancer registration.[23] We attempted to adjust for this in our models by including a time-varying variable indicating the existence of a (adult) cancer registry in the canton of children's place of residence. However, as can be inferred from the characteristics table of the study population (Table 1), children exposed to the highest levels of UVI exposure were more likely to reside in a canton with an existing cancer registry. The chance that we may have underestimated the risk of hematological cancer due to under-registration should therefore be small. Finally, we could not control for ethnicity in our study population which is known to be associated with cancer risk in many populations due to a lack of data.

Individual exposure to UVR does not only depend on ambient levels but also on behavioral factors, the local environment (e.g., shading), and effective time spent outdoors. Indeed, a simulation study considering six European cities with different UVR levels showed that the within-city variation of facial UVR doses could be much higher than between-city variation as a result of individual behaviors.[35] Unfortunately, administrative data do not contain any information on behavioral aspects. Moreover, Switzerland is a multilingual and multicultural country, and health behaviors vary by language region. For instance, one study found higher mortality due to lung cancer in the French-speaking than in the German-speaking areas, presumably due to the higher prevalence of tobacco consumption in the French-speaking part.[36] Furthermore, another Swiss study showed lower incidence of skin melanoma than the national average in the cantons with the highest ambient UV levels namely Valais, Ticino, and Graubünden.[20] These observations could reflect genetic or lifestyle factors that have an impact on either skin sensitivity or individual UV exposures and could confound the association between ambient UVR and CHM. We cannot exclude spatial confounding by behavioral or genetic factors, or by other environmental factors not considered in our analyses.

In conclusion, our study provides further support for an inverse association between exposure to ambient solar UVR and childhood ALL. The evidence was stronger when using UVI levels in July instead of the overall annual mean, potentially indicating a seasonal dependence of an underlying causal pathway. As in previous studies, our analyses may be affected by exposure classification and residual confounding, and findings should be interpreted with caution. Ideally, future studies should include information on behavioral factors that are important determinants of individual UVR exposure; however, such studies would require the active participation of the study population, potentially leading to selection bias. Also, distinguishing exposure to UVA and UVB at different seasons could shed light on the importance of different causal pathways that could result in the development of childhood ALL.

## AUTHOR CONTRIBUTIONS

**Astrid Coste:** Conceptualization; data curation; funding acquisition; investigation; methodology; project administration; validation; writing – original draft; writing – review and editing. **Christian Kreis:** Data curation; formal analysis; funding acquisition; methodology; validation; writing – original draft; writing – review and editing. **Claudine Backes:** Data curation; methodology; resources; software; validation; writing – review and editing. **Jean-Luc Bulliard:** Methodology; validation; writing – review and editing. **Christophe Folly:** Validation; writing – review and editing. **Eva Brack:** Validation; writing – review and editing. **Raffaele Renella:** Validation; writing – review and editing. **David Vernez:** Data curation; resources; software; validation; writing – review and editing. **Ben D. Spycher:** Conceptualization; funding acquisition; investigation; methodology; supervision; validation; writing – review and editing.

## ACKNOWLEDGMENTS

Special thanks go to the Swiss Childhood Cancer Registry team and the Swiss Paediatric Oncology Group. We thank the Federal Statistical Office (FSO) for providing mortality and census data which made the

Swiss National Cohort and this study possible. The members of the Swiss National Cohort Scientific Board are Marcel Zwahlen (University of Bern), Matthias Egger (University of Bern), Viktor von Wyl (University of Zurich), Oliver Hämmig (University of Zurich), Murielle Bochud (University of Lausanne), Martin Röösli (University of Basel), and Markus Schwyn (Federal Statistical Office). We also thank Claudia Berlin from ISPM Bern for the data management support and Kurt Schmidlin for the linkage between the SNC and the Swiss Childhood Cancer Registry database. Open access funding provided by Universitat Bern.

## FUNDING INFORMATION

Support for this study was received from the Swiss National Science Foundation (320030_176218), the Swiss Cancer League (KLS-4592-08-2018 and KLS-5432-08-2021), and the Swiss Cancer Research (KFS-4012-08-2016). The data collection by the Swiss Childhood Cancer Registry was supported by the Swiss Paediatric Oncology Group (www.spog.ch), the Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und –direktoren (www.gdk-cds.ch), Swiss Cancer Research (www.krebsforschung.ch), Kinderkrebshilfe Schweiz (www.kinderkrebshilfe.ch), the Federal Office of Public Health (FOPH) and the National Institute of Cancer Epidemiology and Registration (www.nicer.org). The work of the Swiss National Cohort was supported by the Swiss National Science Foundation (3347CO-108806, 33CS30_134273, 33CS30_148415).

## CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

## DATA AVAILABILITY STATEMENT

To access the data from the Swiss National Cohort and the Childhood Cancer Registry please consult the respective websites: https://www.swissnationalcohort.ch/data-and-access/ https://www.childhoodcancerregistry.ch/data/. All source code is publicly available on Github: https://github.com/ISPMBern/UVR_ChildhoodCancer Further information is available from the corresponding author upon request.

## ETHICS STATEMENT

Ethics approval was granted through the Ethics Committee of the Canton of Bern to the SCCR on the July 22, 2014 (KEK-BE: 166/2014). According to that approval and national regulations, the need for informed consent from all participants was deemed unnecessary.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Coste A, Kreis C, Backes C, et al. Residential exposure to solar ultraviolet radiation and risk of childhood hematological malignancies in Switzerland: A census-based cohort study. *Int J Cancer*. 2024;1-10. doi:10.1002/ijc.35214