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Incidence of childhood leukemia before and after shut down of nuclear power plants in Germany in 2011: A population-based register study during 2004 to 2019

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Abstract

The association between leukemia and proximity to nuclear-power-plants (NPPs) has been assessed in several countries with inconsistent results. A case-control study from Germany had shown an increased risk for childhood leukemia (diagnoses 1980-2003) near NPPs. Germany began shutting down nuclear reactors in 2011, following the Fukushima disaster. We tested whether the previously observed association between leukemia and proximity to NPP persisted despite the shutdown. We used an ecological study design to investigate the incidence of leukemia during 2004 to 2019 in children aged 0 to 14 years living near NPPs where at least one reactor was shut down in 2011. We defined study and control areas as municipalities whose surface area was at least 75% within 10 km or between 10 and 50 km of NPPs, respectively. We calculated age-standardized rates and incidence rate ratios (IRR) using control-areas as the reference. We also computed standardized incidence ratios (SIR) separately for each NPP using incidence rates of the German population as a reference. IRR decreased from 1.20 (95% confidence interval: 0.81-1.77) in 2004 to 2011 to 1.12 (0.75-1.68) in 2012 to 2019. Analyses of single plants showed an excess of childhood leukemia during 2004 to 2019 for the Unterweser-NPP, based only on three cases, and the Krümmel-NPP (n = 14; SIR: 1.98, 1.17-3.35). We found slightly decreasing of leukemia incidence rate ratios after the shutdown of nuclear reactors in 2011. Due to the small number of cases, risk estimates have large uncertainty. Further research including a longer follow-up is warranted. The consistent excess of incidence cases around Krümmel may require analytical epidemiological analysis.

KEYWORDS
childhood leukemia, Germany, nuclear power plant, register-based study

Abbreviations: ASIR, age-standardized incidence rate; CI, confidence interval; IRR, incidence rate ratio; NPP, nuclear power plant; SIR, standardized incidence ratio.

What's new?

The association between leukemia and proximity to nuclear power plants has been assessed in several countries with inconsistent results. Here, using an ecological study design, the authors found that the incidence of leukemia slightly decreased among children aged <15 living near nuclear power plants in Germany where at least one reactor was shut down after the Fukushima disaster in 2011. Compared with the corresponding German population, children living in municipalities near the Krümmel nuclear power plant had persistently higher leukemia incidence rates during the 2004 to 2019 period, as found in other studies.

1 | INTRODUCTION

Leukemia is the most frequent malignancy in children and accounts for about one third of all childhood cancers in European countries.[1] Lymphoblastic leukemia is the most common type of childhood leukemia and represents more than 75% of all leukemia cases, followed by acute myeloid leukemia with about 15% to 18%. Chronic leukemia and other leukemia types very rarely occur at young ages.[2] Although a growing body of research has addressed a broad range of potential etiologic factors, the etiology remains poorly understood, and confirmed risk factors explain only a small proportion of all cases. Established risk factors include some chromosomal and genetic conditions, exposure to high-dose ionizing radiation, advanced maternal age at child's birth and high and low birth weight. A recent review found convincing evidence for elevated leukemia risk following exposure to pesticides before conception and during pregnancy[3] while previous reviews emphasized methodological concerns.[2,4]

The association between childhood leukemia and residence near nuclear power plants (NPPs) has been investigated in several countries, but results were conflicting and inconclusive.[5-10]

A positive association was found in a case-control study conducted in Germany that investigated incident cases of leukemia diagnosed in 1980 to 2003 in children under 5 years of age living near NPPs compared with those living further away. An odds ratio (OR) of 2.19 based on 37 cases, with a lower 95% confidence limit (CL) of 1.51 was found for children living within 5 km of NPPs and an OR of 1.33 (lower 95% CL 1.06) based on 95 cases for children living within 10 km of NPPs.[5] Furthermore, a cluster of leukemia cases in children under the age of 15 has been observed in the municipalities of Geesthacht, Drage, Marschacht and Tespe, all close to the Krümmel-NPP, which was not explained by the environmental exposure to radiation in the area.[11]

In Germany in 2011, following the Fukushima nuclear disaster, the authorization for power operation expired for eight of the 11 reactors operating in seven NPPs, leaving the authorization of the remaining nuclear power plants unchanged.[12] To investigate the possible association between the incidence of childhood leukemia and proximity to NPPs before and after shutdown, we aimed to:

1. Compare incidence rates of childhood leukemia near NPPs to those further away, and to analyze whether these rates were different after shutdown;
2. Specifically analyze the time-series of standardized incidence ratios (SIR) in the municipalities around the Krümmel-NPP.

2 | MATERIALS AND METHODS

We used data from the national German Childhood Cancer Registry (GCCR) and identified all incident diagnoses of a first leukemia in 0 to 14-year-olds classified, according to the International Classification of Childhood Cancer third edition (ICCC-3), in Germany between 2004 and 2019. In addition to the characteristics of the child's cancer diagnosis, sex, date of birth and place of residence at diagnosis was obtained.

Annual population estimates by age and municipality were obtained from the Federal Statistical Office.[13] As population estimates were only available at a municipal level, we included data from communities whose area is at least 75% within 10 km of NPPs (study area) or between 10 and 50 km from NPPs (control area). The seven NPPs analyzed are: Biblis, where both reactors were shut down in 2011; Brunsbüttel, Krümmel and Unterweser, where the only reactor was shut down in 2011; Isar, Neckarwestheim, Philippsburg, where one of the two reactors was shut down in 2011.[12] The analysis was conducted excluding municipalities within 10 km of NPPs other than those listed, to take into account the overlap between the areas of the NPPs (Figure 1).

We also performed two sensitivity analyses by classifying the study and control areas differently: in the first case, municipalities located completely (100%) within 10 km (study area) or between 10 and 50 km from the seven included NPPs (control area); in the second case, municipalities located mostly (51%) within 10 km (study area) or between 10-50 km from the seven included NPPs (control area).

As an example, Figure 1 shows the municipalities included as the study area for the Krümmel-NPP using the different inclusion criteria.

For the combined seven NPPs, we estimated period-specific (2004-2011 and 2012-2019) age-standardized incidence rates (ASIR) for the study and control areas, with 95% confidence intervals (95% CI).[14] Standardization was performed for four age groups (0, 1-4; 5-9, 10-14 years) using Segi world population weights to allow for international comparison.[15] Furthermore, Mantel-Haenszel age-adjusted incidence rate ratios (IRRs) were calculated using the control areas as a reference. We estimated also the interaction on an additive and multiplicative scale between the reactors operating status (in operation or shut down) and the residential distance from the NPPs (study or control area).[16] We also used a Poisson regression model to estimate incidence

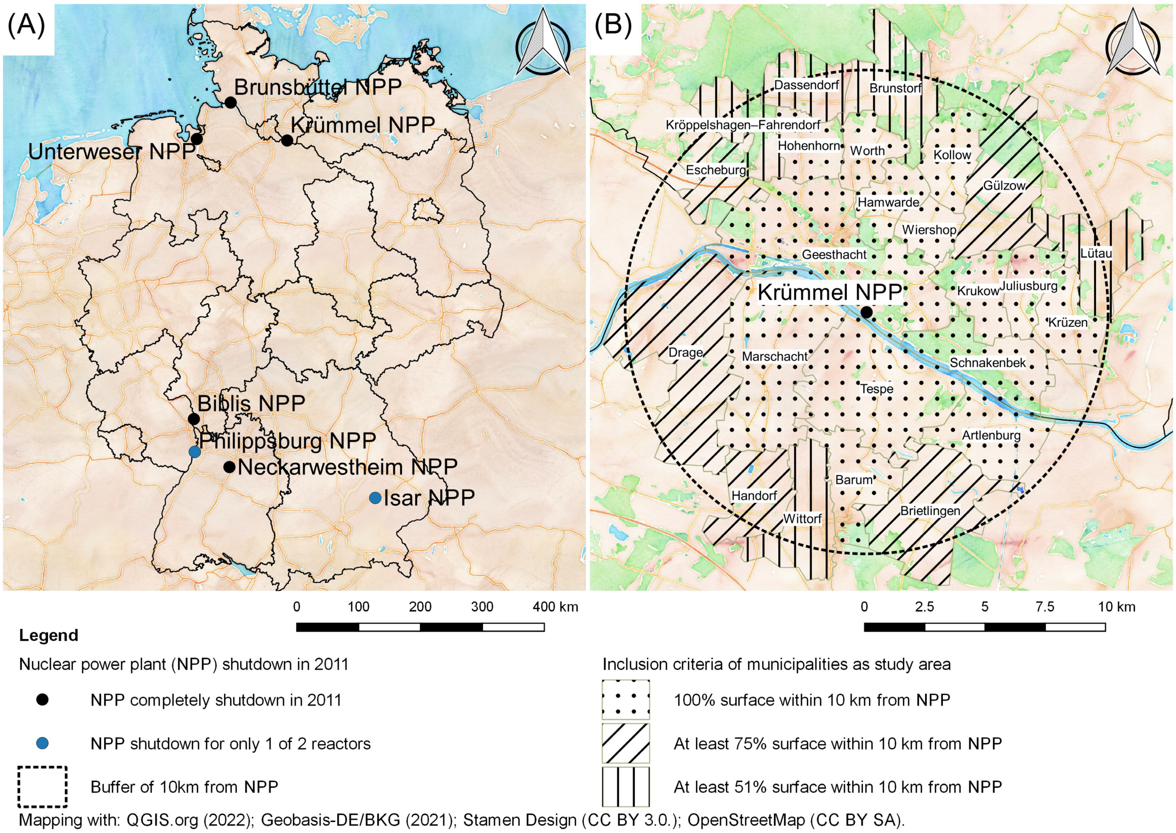

FIGURE 1 Nuclear power plants (NPPs) considered in the study (A) and a focus on the municipalities considered in the analysis of the Krümmel-NPP using different inclusion criteria (B)

TABLE 1 Observed incidence cases of overall leukemia in under 15-year-olds (n), person years (PY), crude incidence rates (IR), age-standardized incidence rates (ASIR) per million, combined Mantel-Haenszel incidence ratios (IRR) with associated 95% confidence intervals (95% CI) according to period and distance from a nuclear power plant (NPP) with at least one reactor shut down in 2011

Period/Inclusion criteria[a]	Distance to NPPs[b]	n	PY	Crude IR	ASIR[c]	(95% CI)	IRR[d]	(95% CI)
At least 75% of municipal area within 10 km of NPPs or between 10 and 50 km								
2004-2011 (all reactors in operation)	<10 km	26	434 116	59.9	64.8	(39.4-90.3)	1.20	(0.81–1.77)
	10-50 km	800	15 743 508	50.8	54.4	(50.6–58.2)	1 (reference)	
2012-2019 (at least one reactor shut down)	<10 km	24	408 316	58.8	60.9	(36.4-85.5)	1.12	(0.75–1.68)
	10-50 km	815	15 396 825	52.9	55.7	(51.8–59.5)	1 (reference)	
2004-2019	<10 km	50	842 432	59.4	62.6	(45.0-80.2)	1.16	(0.88-1.54)
	10-50 km	1615	31 140 333	51.9	55.1	(52.3-57.8)	1 (reference)	
At least 51% of municipal area within 10 km of NPPs or between 10 and 50 km								
2004-2011 (all reactors in operation)	<10 km	42	639 913	65.6	71.3	(49.3-93.3)	1.34	(0.98-1.82)
	10-50 km	873	17 432 281	50.1	53.5	(49.9-57.1)	1 (reference)	
2012-2019 (at least one reactor shut down)	<10 km	33	595 092	55.5	56.5	(37.0-75.9)	1.06	(0.75-1.5)
	10-50 km	910	17 168 002	53.0	55.6	(52.0-59.3)	1 (reference)	
2004-2019	<10 km	75	1 235 005	60.7	63.7	(49.1-78.3)	1.20	(0.95-1.51)
	10-50 km	1783	34 600 283	51.5	54.6	(52.0-57.1)	1 (reference)	

Note: Period 2004 to 2019.

[a]Since no municipality could be included in the study area for the Unterweser-NPP, the 100%-criterion is not reported in table.

[b]Nuclear power plants with at least one reactor shut down in 2011: Biblis, Brunsbüttel, Isar, Krümmel, Neckarwestheim, Philippsburg and Unterweser.

[c]Segi world standard population used as a reference.

[d]Combined Mantel-Haenszel incidence rate ratio comparing area within 10 km of nuclear power plants (study area) with those between 10 and 50 km away (control area).

TABLE 2 Observed incident cases of overall leukemia in under 15-year-olds (n) within 10 km of nuclear power plant (NPP), person-years (PY), standardized incidence ratios (SIR) with associated 95% confidence intervals (95% CI) according to different criteria for inclusion of municipalities

Inclusion criteria/nuclear power plant	n	PY	SIR[a]	(95% CI)
100% of municipal area within 10 km of NPPs				
Biblis	1	64 129	0.30	(0.04-2.15)
Brunsbüttel	0	5477	0.00	
Krümmel	10	100 049	1.94	(1.04-3.6)
Unterweser		na		
Subtotal for NPPs completely shut down in 2011	11	169 655	1.26	(0.7-2.27)
Isar	1	24 800	0.78	(0.11-5.56)
Neckarwestheim	8	129 269	1.20	(0.6-2.39)
Philippsburg	5	178 947	0.54	(0.22-1.3)
Subtotal for NPPs shut down only for one reactor in 2011	14	333 016	0.81	(0.48-1.37)
Total	25	502 671	0.96	(0.65-1.42)
At least 75% of municipal area within 10 km of NPPs				
Biblis	6	126 633	0.92	(0.41-2.04)
Brunsbüttel	0	37 288	0.00	
Krümmel	14	137 372	1.98	(1.17-3.34)
Unterweser	3	17 635	3.41	(1.1-10.58)
Subtotal for NPPs completely shut down in 2011	23	318 928	1.40	(0.93-2.11)
Isar	2	65 719	0.59	(0.15-2.37)
Neckarwestheim	14	211 277	1.28	(0.76-2.17)
Philippsburg	11	246 508	0.86	(0.48-1.55)
Subtotal for NPPs shut down only for one reactor in 2011	27	523 504	1.00	(0.68-1.46)
Total	50	842 432	1.15	(0.87-1.52)
All German NPPs[b]	111	1 960 033	1.10	(0.91-1.33)
At least 51% of the area within 10 km of NPPs				
Biblis	7	166 858	0.81	(0.39-1.7)
Brunsbüttel	0	39 775		
Krümmel	17	155 552	2.12	(1.32-3.42)
Unterweser	6	115 873	1.02	(0.46-2.28)
Subtotal for NPPs completely shut down in 2011	30	478 058	1.22	(0.86-1.75)
Isar	2	65 719	0.59	(0.15–2.37)
Neckarwestheim	24	314 031	1.49	(1-2.22)
Philippsburg	19	377 197	0.97	(0.62-1.52)
Subtotal for NPPs shut down only for one reactor in 2011	45	756 947	1.15	(0.86-1.54)
Total	75	1 235 005	1.18	(0.94-1.48)

Note: Period 2004 to 2019.
Abbreviation: na, no municipality could be included following the 100% criterion.
[a]Corresponding German rates used as a reference.
[b]The following NPPs are included: Biblis, Brokdorf, Brunsbuttel, Grafenrheinfeld, Greifswald, Grohnde, Gundremmingen, Isar, Krümmel, Lingen-Emsland, Mühlheim-Kärlich, Neckarwestheim, Obrigheim, Philippsburg, Rheinsberg, Stade, Unterweser and Würgassen.

rate ratios (IRR) with 95% CI, accounting for age (0-4, 5-9, 10-14 years), distance (<10 km or between 10 and 50 km), the reactor's operating status (in operation or shut down) and the interaction term period-distance. Log-population was used as the offset in the models.

Standardized incidence ratios (SIR) with 95% CI were calculated using age groups (0, 1-4; 5-9, 10-14 years) and the incidence rates of the corresponding German population as a reference.[17] In addition age-group-specific SIRs for the seven NPPs combined were also calculated. For descriptive purposes, the overall SIR for all 18 German NPPs was calculated.

Concerning the second research question, 10-year moving averages of the annual SIRs were used, thereby applying a standard approach for the analysis of incidence rates in small areas.[11]

In addition, all analyses for the combined seven NPPs were conducted for the subgroup of children with lymphoblastic leukemia.

Analyses were performed using QGIS Geographic Information System (QGIS.org, 2022) and Stata software release 17 (StataCorp., 2021. College Station, TX: StataCorp LLC).

3 | RESULTS

For all seven NPPs combined, 50 cases of leukemia were observed in the study area over the period 2004 to 2019 (Table 1). The ASIRs were higher in the study area than in the control area, but confidence intervals were wide and overlapped largely. Incidence rates decreased in the study area from 64.8 per million in 2004 to 2011 to 60.9 in 2012 to 2019, while the incidence remained stable in the control area (2004-2011:54.4 [95% CI 50.6-58.2]; 2012-2019:55.7: [95% CI 51.8-59.5]). As a result, the IRRs decreased from 1.20 (95% CI 0.81-1.77) in 2004-2011 to 1.12 (95% CI 0.75-1.68) in 2012-2019.

Analysis restricted to lymphoblastic leukemia revealed similar results for the period 2004 to 2019 (IRR: 1.14; [95% CI 0.83-1.57]). However, given the smaller number of cases observed in the study area (n = 39), the results were characterized by a larger estimation uncertainty, particularly when stratified by period (Table S1).

A positive interaction between study period and case-control area both on the additive and on the multiplicative scales was detected (Table S5) but with wide statistical uncertainty (Table S6). Age-specific analysis for both overall and lymphoblastic leukemia is provided as supplementary material (Tables S2 and S3).

Plant-specific analysis showed an excess of pediatric leukemia cases over the period 2004 to 2019 in the municipalities around the Unterweser-NPP (n = 3, SIR: 3.42; [95% CI 1.10-10.60]) and the Krümmel-NPP (n = 14, SIR: 1. 98; [95% CI 1.17-3.35]) (Table 2).

The analysis of the 10-year moving averages of the SIRs showed persistent excesses over the period 2004 to 2019 among children living in municipalities close to the Krümmel-NPP (Figure 2 and Table S4).

The results of the sensitivity analysis were similar to those of the main analysis.

4 | DISCUSSION AND CONCLUSION

A higher incidence of overall leukemia was observed in the study area than in the control area, and this higher incidence decreased slightly in the period following the 2011 shutdown of the reactors after the Fukushima disaster. In contrast, for lymphoblastic leukemia, an increase in incidence was observed in the study area after the reactors were shut down. Therefore, the decrease in overall leukemia is mainly due to a decrease in acute myeloid leukemias (AML). An excess of overall leukemia was also observed in municipalities within 10 km from the 18 German NPPs combined.

Analysis by age group and leukemia subtype showed an excess of cases of lymphoblastic leukemia in the 2012 to 2019 period in the age group 5 to 9 for the NPPs pooled together, and the plant-specific analysis showed mainly an excess of pediatric leukemia cases limited to Krümmel-NPP.

The present ecological analysis conducted in children below the age of 15 within 10 km of the seven NPPs under investigation is not comparable with the previous study by Kaatsch et al, whose case-control study assessed only young children of under 5 years of age near all German NPPs for a longer time span. We have extended the

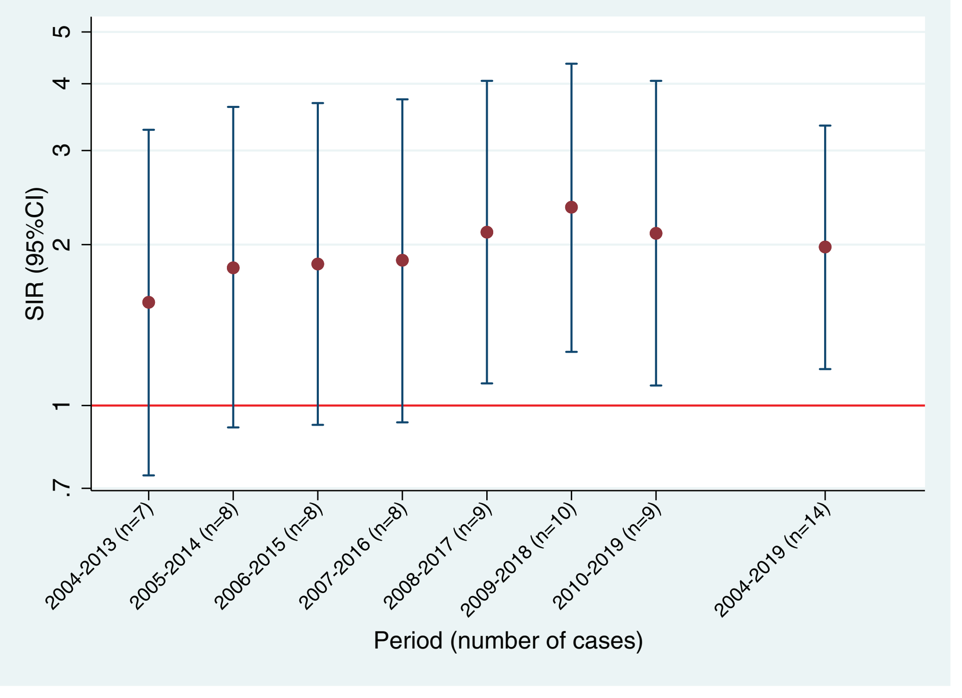

FIGURE 2 Sliding 10-year standardized incidence ratios (SIR), on a logarithmic scale, with 95% confidence intervals (95% CI) for childhood leukemia in under 15-year-olds. Data for municipalities with at least 75% of their surface area within 10 km from the Krümmel-NPP nuclear power plant. Corresponding German rates used as a reference. Period 2004 to 2019

age at diagnosis of cases, as already done in recent studies, in order to balance the small number of NPPs included.[8,11] We cannot exclude that the higher incidence rates in the study area, compared with the control area, is due to chance, given the small number of cases and the large overlap of the confidence intervals.

Around the Krümmel-NPP, which went into operation in 1984, an excess of leukemia cases had already emerged by examining the municipality of Geesthacht, located north of the Elbe River and where the NPP is based, and the joint community of Elbmarsch on the opposite bank of the Elbe (ie, Drage, Marschacht and Tespe). However, more recently incidence rates have been shown to be virtually comparable to the German rates (period 2007-2016, n = 3, SIR: 1.1, [95% CI 0.2-3.3]).[11] In our study, we found an excess of leukemia around the Krümmel-NPP by including three additional years and expanding the area considered by objectively defining three a priori criteria for inclusion of municipalities in the study area (100%, 75% and 51% of the municipality area within 10 km of the NPP).

There are several limitations in our analysis: the number of cases is small and the time since closing the reactors short. We used an ecological study design and the distance to the plants as the measure of exposure. However, we are aware that this may not reflect actually existing radiation exposure.

We used the residence at diagnosis as an indicator of exposure even though residence at birth might better reflect the period of greatest sensitivity to ionizing radiation, that is, intrauterine life and early childhood.[7] Nevertheless, in a Swiss cohort study, a similar association was observed while using addresses at birth or addresses at diagnosis.[7] We classified municipalities into study or control area conditional on whether at least 75% of their surfaces falls within 10 km or between 10 and 50 km from the NPPs, respectively. We cannot know whether cases from a municipality classified as a study area were actually residents of control area and vice versa. Thus, a nondifferential misclassification, probably biasing results towards the null value, cannot be ruled out.[18]

Considering a period of 8 years after shutdown may have been too short to show an effect in the incidence rate of leukemia, considering the role of latency, the possible persistence of NPP emissions in environmental matrices, and how the complex and not immediate start of the decontamination and dismantling process of the plant may involve specific risks.[19]

NPPs incidence rates in the entire study period are lower than those observed for the NPPs where all reactors where shut down. This result is unexpected and warrants further investigations.

A possible association between socioeconomic status (SES) and leukemia risk in Germany has not yet been analyzed. While most international studies reported evidence of an association between SES and childhood leukemia risk, the observed direction of the association was heterogeneous. Generally, higher SES was associated with higher risk, but rarely also inverse associations were reported.[20-23] In the absence of consistent and pertinent evidence, we did not adjust our analysis by SES.

Confidence intervals and *P* values were not adjusted for multiple comparisons, possibly raising the probability of false positive results. However, a pre-established statistical analysis plan defined a set of hypotheses before data analysis, separating confirmatory from exploratory analyses.[24]

The main strengths of our analysis are the use of high quality data from the GCCR, covering virtually all childhood leukemia cases in Germany, the use of an a priori methodology of classifying municipalities as study or control areas based on the proportion of their surface area being close to an NPP and the exploitation of the natural experiment of the simultaneous expiration of the operating licenses of seven nuclear power plants in 2011.[25]

The childhood leukemia cluster found around Krümmel-NPP does not appear to have any reasonable explanatory factors to date. Regarding the possible association with NPP emissions, it should moreover be noted that this NPP was officially shut down in 2011, even though, due to short circuits in the transformer, electricity production was initially interrupted in mid-2007 and then resumed, albeit for a very short period, in mid-2009.[26]

Furthermore, concerning Kinlen's hypothesis of a marked rural population mixing as an explanation for the leukemia clusters, it is pointed out that it is unlikely to be supported for Krümmel-NPP, as the municipalities have been subject to a constant population influx since 1975 and not to a marked rural population mixing; as well, the first case of leukemia occurred in 1990, 15 years after the population increase.[11,27] However, since the GCCR began collecting data in January 1980, it cannot be ruled out that an increase in cases may have occurred at the start of the population influx and escaped systematic registration.

In conclusion, we found a slight decrease in the incidence of childhood leukemia in areas close to nuclear power plants in contrast to areas used as control. However, due to the small number of cases, risk estimates have large degrees of uncertainty. The persistence over time of the site-specific excess related to the Krümmel-NPP cluster, which currently remains without explanatory factors, may require analytical epidemiological analysis and a multidisciplinary approach.

AUTHOR CONTRIBUTIONS

Emilio Gianicolo and Maria Blettner conceived the study and developed the design. Friederike Erdmann, Emilio Gianicolo and Antonello Russo contributed to the acquisition and preparation of data. Emilio Gianicolo, Maria Blettner and Antonello Russo developed the strategy for the statistical analysis. Antonello Russo conducted the statistical analysis and drafted the manuscript. All authors contributed to the data interpretation, critically reviewed the manuscript for important intellectual content, and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. The corresponding author confirms that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Under the assumption that national data protection requirements are fully met, access to aggregated or pseudonymized individual-level data may be made available upon reasonable request. All data access requests should be directed to the corresponding author.

ETHICS STATEMENT

No ethics approval or consent was required for this study, as no active participation of patients was required. This research was carried out in compliance with the requirements of the General Data Protection Regulation (GDPR).

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SUPPORTING INFORMATION

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

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