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Childhood cancer and traffic-related air pollution in Switzerland: A nationwide census-based cohort study

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ABSTRACT

Motor vehicle exhaust is a major contributor to air pollution, and exposure to benzene or other carcinogenic components may increase cancer risks. We aimed to investigate the association between traffic-related air pollution and risk of childhood cancer in a nationwide cohort study in Switzerland. We identified incident cases from the Swiss Childhood Cancer Registry diagnosed < 16 years of age between 1990 and 2015 and linked them probabilistically with the census-based Swiss National Cohort study. We developed land use regression models to estimate annual mean ambient levels of nitrogen dioxide (NO_2) and benzene outside 1.4 million children's homes. We used risk-set sampling to facilitate the analysis of time-varying exposure and fitted conditional logistic regression models adjusting for neighborhood socio-economic position, level of urbanization, and background ionizing radiation. We included 2,960 cancer cases in the analyses. The adjusted hazard ratios (HR) and 95% confidence intervals for exposure to NO_2 per 10 μg/m^3 were 1.00 (95%-CI 0.88–1.13) for acute lymphoblastic leukemia (ALL) and 1.31 (95%-CI 1.00–1.71) for acute myeloid leukemia (AML). Using exposure lagged by 1 to 5 years instead of current exposure attenuated the effect for AML. The adjusted HR for exposure to benzene per 1 μg/m^3 was 1.03 (95%-CI 0.86–1.23) for ALL and 1.29 (95%-CI 0.86–1.95) for AML. We also observed increased HRs for other diagnostic groups, notably non-Hodgkin lymphoma. Our study adds to the existing evidence that exposure to traffic-related air pollution is associated with an increased risk of childhood leukemia, particularly AML.

1. Introduction

Motor vehicle exhaust from combustion engines is an important contributor to air pollution that is associated with several chronic diseases including cancer, notably lung cancer (IARC, 2016). Particulate matter (PM) as a mixture and specific components of traffic emissions (1,3-butadiene and benzene) have been classified as Group I carcinogens by the International Agency for Research on Cancer (IARC) (IARC, 2017). Benzene was observed to increase the risk of leukemia and lymphoma subtypes among occupationally exposed adults (Vlaanderen et al., 2012; Vlaanderen et al., 2011) and has been found to be associated with acute lymphoblastic leukemia (ALL) in their offspring (Heck et al., 2019; Spycher et al., 2017).

Several studies have investigated the association between outdoor air pollution and childhood cancers, particularly leukemia. Common measures of exposure in these studies include modeled or measured ambient levels of nitrogen dioxide (NO_2), $PM_{2.5}$, PM_{10}, 1,3-butadiene, and benzene or measures of traffic density and proximity to major roads. A recent systematic review and *meta*-analysis of 29 studies of childhood leukemia found evidence of an elevated risk in relation to benzene exposure, most notably for the subtype of acute myeloid leukemia (AML) (Filippini et al., 2019). The relative risk was higher for children under 6 years of age and for exposure at time of diagnosis than during gestation or at birth (Filippini et al., 2019). Fewer studies have

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investigated associations between outdoor air pollution and lymphomas, central nervous system (CNS) tumors, or other childhood cancers. Evidence of increased risks has been reported for lymphoma (Raaschou-Nielsen et al., 2001), Hodgkin lymphoma (Raaschou-Nielsen et al., 2001; Ribeiro et al., 2021), non-Hodgkin lymphoma (Hvidtfeldt et al., 2020), CNS tumors (Danysh et al., 2016; Danysh et al., 2015), ependymoma (Danysh et al., 2016), astrocytoma (Danysh et al., 2015; Lavigne et al., 2017), medulloblastoma (Danysh et al., 2015; Raaschou-Nielsen et al., 2018; von Ehrenstein et al., 2016), CNS primitive neuroectodermal tumors (von Ehrenstein et al., 2016), or retinoblastoma (Ghosh et al., 2013; Heck et al., 2013) for various measures of traffic-related air pollution but the evidence base for childhood cancers other than leukemia is limited and inconclusive.

The majority of previous studies were case-control or ecological studies; there have only been a few large cohort studies (Danysh et al., 2015; Lavigne et al., 2017; Spycher et al., 2015). Outdoor air pollution varies considerably at a small spatial scale as a function of distance to heavy traffic roads or highways (Zhou and Levy, 2007; Liu et al., 2019). Capturing exposure contrasts at this scale requires exact information on ambient pollution levels and precise geocoded information on children's place of residence, which were not available to many previous studies. Moreover, ambient concentrations of various air toxins have fallen in many developed countries over the last few decades (IARC, 2016), but only few studies had time-varying levels of exposure available and could thus account for the long-term decline in air pollution (Ghosh et al., 2013).

We aimed to investigate the association between traffic-related air pollution and risk of childhood cancer in Switzerland using data from a nationwide census-based cohort study. Following up on our previous study in Switzerland (Spycher et al., 2015), which found evidence of an increased risk of leukemia in children under 5 years of age living <100 m away from a highway, we aimed to improve exposure assessment by modeling exposure to ambient levels of NO_2, a frequently monitored marker of traffic-related air pollution, and benzene. We developed land use regression (LUR) models to estimate the annual mean level of exposure outside children's place of residence between 1991 and 2014, capturing the decline in ambient levels of these air pollutants over this period.

2. Methodology

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 register-based censuses between 2010 and 2015. Children entered the cohort on the date of the first census following their birth or immigration. Data were obtained from the Swiss National Cohort (SNC) study, a research platform linking the national censuses with routine data sets on births, mortality, and migration (Bopp et al., 2009; Spoerri et al., 2010). The SNC contains demographic and socio-economic information including exact geocodes of place of residence.

Incident cases of childhood cancer were identified from the Swiss Childhood Cancer Registry (SCCR) through probabilistic record linkage with the SNC. The SCCR is a population-based cancer registry that has recorded children and adolescents diagnosed with cancer in Switzerland since 1976. The completeness of the SCCR has been estimated to be 95% since the mid-1990s (Schindler et al., 2015). Linkage with the SNC was done based on sex, date of birth, maternal and paternal dates of birth, geocoded residence at census, municipality of residence at census, and nationality. We included all incident cases of cancer diagnosed under the age of 16 years between 1990 and 2015 who were resident in Switzerland at time of diagnosis and could be linked to a record in the SNC. Children diagnosed with cancer prior to the first census of their lifetime were not included.

2.2. Outcomes

We studied the following outcomes as classified by the International Classification of Childhood Cancers, Third Edition (ICCC-3) (Steliarova-Foucher et al., 2005): all cancers (ICCC-3 diagnostic groups I-XII), leukemia (I), lymphoid leukemia (Ia), acute myeloid leukemia (Ib), lymphomas (II), Hodgkin lymphomas (HL) (IIa), Non-Hodgkin lymphomas (NHL) (IIb), tumors of the central nervous system (III), astrocytomas (IIIb), intracranial and intraspinal embryonal tumors (IIIc), malignant bone tumors (VIII), and soft tissue sarcomas (IX). Chronic lymphocytic leukemia (included in Ia) is extremely rare in children; there were no cases in our study sample. We thus refer to ICCC-3 subgroup Ia as acute lymphoblastic leukemia (ALL).

2.3. Exposure modelling

Outdoor air concentrations of NO_2 at children's place of residence were estimated by combining two common approaches of modeling air pollution, dispersion modeling and LUR (Hoek, 2017) as explained in detail in the online supplement. In brief, a dispersion model of NO_2 for Switzerland, PolluMap, has been developed by Meteotest (Heldstab et al., 2011). PolluMap estimates emissions from various sources (roads, housing, industry, airports etc.) for a grid of 200 m × 200 m cells covering all of Switzerland and models the dispersion of these emissions taking into account regional meteorological patterns to estimate concentrations for every grid cell. Meteotest has thus estimated the annual mean ambient concentration of NO_2 for each year between 1990 and 2015 (Heldstab et al., 2011). Using the PolluMap dispersion modeling approach, Meteotest has also produced maps of modelled outdoor levels of benzene but only for the years 1990 and 2010 (SAEFL, 2000).

Estimating air pollution for 200 m × 200 m grid cells, PolluMap tends to underestimate pollution levels in the proximity of traffic-related heavy pollution sources such as highways or major roads. In order to model air pollution at a finer spatial scale, we complemented the PolluMap dispersion model with LUR modeling. We thus developed separate LUR regression models for each year between 1991 and 2014, modelling the annual mean level of ambient NO_2 as measured by 2,936 passive sampling monitoring sites scattered across Switzerland as dependent variable. As predictor variables, we included besides the PolluMap NO_2 estimate of the corresponding year other spatial covariates on the topography, land-use, population density, road and traffic density, and the building footprint for the location of the monitoring sites or surrounding buffers. We used elastic net regularization for variable selection and parameter estimation, and then used the trained LUR models to predict annual levels of NO_2 outside the 1.4 million children's residencies in the cohort (as described elsewhere (Héritier et al., 2019). In internal validation based on 300 randomly selected monitoring sites (approximately 10% of the dataset) that were not used for model development, the average adjusted R^2 of the annual models fitting model predictions against measurements was 0.69 (range: 0.54–0.78; Supplementary Table S1).

For benzene, by contrast, development of LUR models was not feasible due to the small number of monitoring sites. Instead, we directly extracted the PolluMap estimate for benzene for the years 1990 and 2010 as level of exposure outside children's homes (with a grid resolution of 200 m × 200 m). In order to obtain annual estimates also for benzene, we linearly interpolated the PolluMap estimates for 1990 and 2010 on the log scale, and extrapolated this trend up to 2015. The average adjusted R^2 of linear models fitting these inter-/extrapolated annual benzene estimates against the measurements from the 4–12 monitoring sites for the period 1995–2014 was 0.50 (range: −0.02–0.66; Supplementary Table S1).

A detailed description of the methodology and results of exposure modelling and prediction is provided in the online supplementary material.

2.4. Potential confounding

We considered confounding by factors associated with location of residence that have been reported to be associated with childhood cancer risk in the literature. We included the following potential confounders: socio-economic position of the immediate neighborhood (Swiss-SEP in quintiles) (Panczak et al., 2012), level of urbanization of the municipality of residence (urban, suburban, or rural), and background ionizing radiation (total dosage from terrestrial gamma and cosmic radiation) (Rybach et al., 2002). Evidence of an association between cancer risk (leukemia, CNS tumors) and background ionizing radiation has been reported for Switzerland (Mazzei-Abba et al., 2021; Spycher et al., 2015). Potential confounders were time-updated for every census point or intermittent change in residential address.

2.5. Statistical analysis

We prepared the SNC cohort as time-to-event data with age as the underlying time scale. Follow-up began on the day of the earliest census in which a child was recorded and ended on the date of diagnosis, death, 16th birthday, emigration, loss to follow-up, or end of follow-up, whichever occurred first. For children who relocated between censuses, the date of relocation was set to the exact date if reported or to the mid-point between the two closest dates for which the location of residence was known. Information on place of residence in 1995 was partially available from the questionnaire data of the 2000 census, and annually updated residential information was available from 2010 onward when register-based censuses began. Furthermore, from the 2011 census, information was available on the date of relocation to the current residence. In order to facilitate the fitting of regression models to time-varying exposure and covariate data, we sampled 100 controls per case matching on age and year of birth from the SNC population at risk at the time of a case's failure (risk set sampling).

We fitted conditional logistic regression models to the matched case-control sets to investigate the risk of childhood cancers by levels of exposure to traffic-related air pollution. This approach is asymptotically equivalent to estimating Cox proportional hazards models of the full cohort (Goldstein and Langholz, 1992). We therefore refer to the odds ratios resulting from conditional logistic regression models as hazard ratios. We fitted univariable and fully adjusted models including the potential confounders listed above. We ran conditional logistic regression models for all outcomes including exposure to NO_2 and benzene as a linear term in increments of 10 $\mu g/m^3$ and 1 $\mu g/m^3$, respectively. We formally tested for non-linearity by comparing adjusted models including the exposure in quintile categories with models including a linear term of the mean exposure level by category (quintile means) using likelihood ratio (LR) tests. In the online supplement, we also report results from models including exposures as categorical variables. Because our exposure data was highly skewed, we categorized the NO_2 and benzene estimates, using below median levels as reference category and the 75th and 90th percentiles as additional cut points. All regression models were based on complete-case analyses.

Our primary analysis investigated cancer risks at time of diagnosis using current levels of exposure to NO_2 and benzene. In additional analyses, we investigated cancer risks associated with exposure levels 1, 2, 3, 4, and 5-years prior to diagnosis. If there was no address information because the beginning of the lag period predated the entry date into the cohort, we used the earliest address information available, assuming stable residency during the time before follow-up. In a sensitivity analysis, we re-estimated all conditional logistic regression models including only cases and matched controls that had already entered the SNC cohort at the relevant time point of exposure. Case-control sets, for which the case's age at diagnosis was smaller than the lag period, were dropped from the lagged analyses.

All statistical analyses were performed in the R language for statistical computing version 3.6.0 (R Core Team. R, 2019) using packages glmnet (Friedman et al., 2010), gstat (Pebesma, 2004), and survival (Therneau, 2002).

3. Results

3.1. Characteristics of the study population

In total, we identified 5,383 primary diagnoses of cancer among children under 16 years of age between 1990 and 2015. 1,833 of them (34.0%) had been diagnosed prior to the first census following their birth and could thus not be included in the cohort because they were no longer at risk. From the remaining 3,550 eligible cases, 446 (12.6%) could not be linked to a record in the SNC, i.e. due to incomplete identifying information no matching record was found, 129 (3.6%) had missing geocodes, and 15 (0.4%) were censored prior to diagnosis (due to temporary emigration or intermittently missing geocodes) (Fig. 1). We thus included 2,960 cases of childhood cancer in the analyses, of which 902 were leukemias, 464 lymphomas, 669 CNS tumors, 187 malignant bone tumors, 196 soft-tissue sarcomas, and 542 other cancers (Table 1). The full cohort included 3,522,874 children under the age of 16 years resident in Switzerland who were recorded in at least one of the national censuses of 1990, 2000, and 2010–2015. 29,105 children had to be excluded due to missing geocodes, leaving 3,493,769 children for analysis. From among this population, we sampled 100 individuals per case from those still at risk at the moment of a case's failure (Fig. 1).

The characteristics of the study population are presented in Table 2 stratified by levels of exposure to NO_2 used for the categorical analyses. Compared to children in the category of below median level (<22.4 $\mu g/m^3$), children in the highest exposure category (≥33.1 $\mu g/m^3$) were more likely to be born before 1990, to live in an urban municipality, and to be exposed to an intermediate level of background ionizing radiation between 100 nSv/h and 150 nSv/h (Table 2).

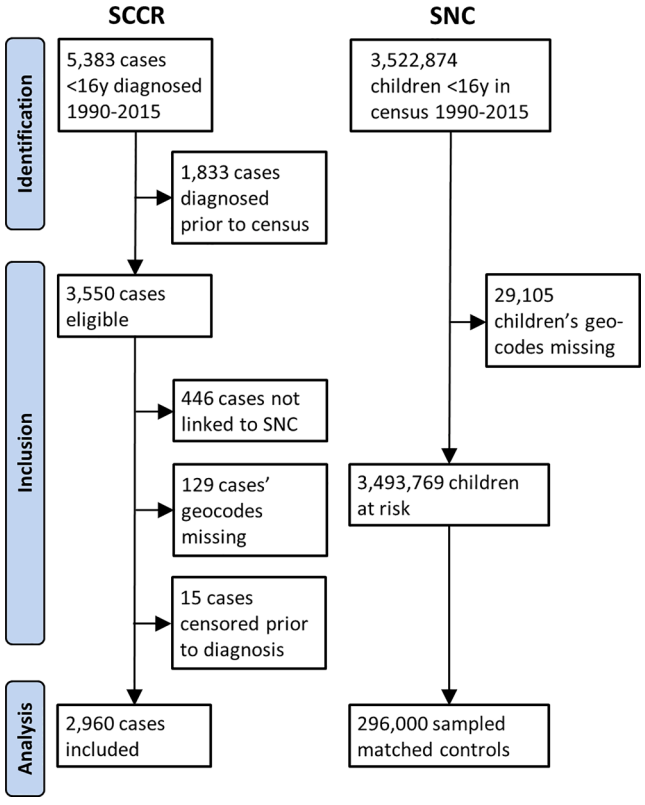

Fig. 1. Flow diagram of study population. SCCR: Swiss Childhood Cancer Registry; SNC: Swiss National Cohort study.

Table 1
Number of cancer cases by diagnostic group (classified by the International Classification of Childhood Cancers, Third Edition).

Diagnostic group	N
All cancers (I-XII)	**2,960**
Leukemias (I)[1]	**902**
Leukemia, 0–4 years	314
Leukemia, 5–15 years	588
Acute lymphoid leukemia (Ia)	710
Acute lymphoid leukemia, 0–4 years	273
Acute lymphoid leukemia, 5–15 years	437
Acute myeloid leukemia (Ib)	131
Acute myeloid leukemia, 0–4 years	30
Acute myeloid leukemia, 5–15 years	101
Lymphomas (II)	**464**
Hodgkin lymphomas (IIa)	219
Non-Hodgkin lymphomas (IIb)	149
CNS tumors (III)	**669**
Astrocytomas (IIIb)	299
Intracranial and intraspinal embryonal tumors (IIIc)	119
Malignant bone tumors (VIII)	**187**
Soft tissue sarcomas (IX)	**196**

[1] Including 61 cases classified as ICCC-3 category Ic, Id, or Ie.

3.2. Childhood cancer risks and exposure to NO_2

LR tests provided no evidence of any departure from linearity of the dose–response curve (Supplementary Table S2). The estimated adjusted hazard ratio (HR) and 95% confidence interval (95%-CI) for all childhood cancers combined was 1.02 (95%-CI 0.96–1.08) per 10 μg/m^3 difference in NO_2 concentration (Table 3). There was some indication of an increased risk for childhood leukemia overall (HR 1.06, 95%-CI 0.95–1.18) and for leukemias diagnosed under the age of 5 years (HR 1.06, 95%-CI 0.88–1.26) and between 5 and 15 years (HR 1.07, 95%-CI 0.93–1.22). The strongest evidence of increased risks was found for the subgroup of AML (HR 1.31, 95%-CI 1.00–1.71), whereas for ALL, there was no indication of higher risks overall (HR 1.00, 95%-CI 0.88–1.13) nor for age subgroups (Table 3). There was little evidence of associations for non-leukemia diagnostic groups, although point estimates did indicate elevated risks in some instances, notably for lymphoma (HR 1.03, 95%-CI 0.89–1.19), NHL (HR 1.11, 95%-CI 0.87–1.43), intracranial and intraspinal embryonal tumors (HR 1.10, 95%-CI 0.83–1.47), and for soft-tissue sarcomas (HR 1.05, 95%-CI 0.83–1.33) (Table 3). Adjusting for potential confounders generally had little effect on the observed associations except for lymphomas (crude HR: 1.09, 95%-CI 0.98–1.23) and intracranial and intraspinal embryonal tumors (crude HR: 1.15, 95%-CI 0.91–1.46), for which effect estimates were reduced (Table 3). Re-running the analyses including NO_2 as a categorical variable produced no evidence of increasing risks for any diagnostic group except for AML with an almost 2-fold increase (HR 1.97, 95%-CI 1.03–3.77) comparing children in the highest exposure category (≥33.1 μg/m^3) with the reference category of below median levels (<22.4 μg/m^3) (Table S4).

Using time-updated ambient levels of NO_2 at 1, 2, 3, 4, or 5 years prior to diagnosis instead of current exposure generally had a small effect on the results in that the effect estimates for AML, NHL, and intracranial and intraspinal embryonal tumors were gradually attenuated with increasing lag time (Table 4). In a sensitivity analysis, we included only cases who had already entered the cohort at the relevant time point of exposure. In the analysis for a 5-year lag period, this almost halved the number of incident cases (n = 1,086 instead of n = 1,950 for the study sample assuming stable residency). However, this did not materially alter our results (Supplementary Table S6).

3.3. Childhood cancer risks and exposure to benzene

LR tests provided evidence for a departure from a linear dose–response curve for the analysis of all cancers combined but not for any diagnostic group specifically (Supplementary Table S3). The adjusted HR and 95% confidence interval for exposure to benzene per 1 μg/m^3 for all childhood cancers combined was 1.05 (95%-CI 0.96–1.15) (Table 5). There was some indication of an increased risk for childhood leukemia

Table 2
Characteristics of the study population by ambient levels of NO_2 (μg/m^3) at place of residence at time of cases' diagnosis.

Characteristics	0.40-<22.4	(%)	22.4-<27.3	(%)	27.3-<33.1	(%)	≥33.1	(%)
N	149,470	(100.0)	74,704	(100.0)	44,846	(100.0)	29,904	(100.0)
Sex								
Male	76,742	(51.3)	38,404	(51.4)	22,881	(51.0)	15,458	(51.7)
Female	72,728	(48.7)	36,300	(48.6)	21,965	(49.0)	14,446	(48.3)
Year of birth								
1975–1979	1,864	(1.2)	1,544	(2.1)	1,772	(4.0)	1,990	(6.7)
1980–1984	8,011	(5.4)	6,847	(9.2)	6,287	(14.0)	5,411	(18.1)
1985–1989	21,060	(14.1)	14,697	(19.7)	11,807	(26.3)	9,896	(33.1)
1990–1994	27,906	(18.7)	13,075	(17.5)	7,279	(16.2)	4,962	(16.6)
1995–1999	37,680	(25.2)	16,710	(22.4)	7,665	(17.1)	3,489	(11.7)
2000–2004	20,567	(13.8)	8,178	(10.9)	3,700	(8.3)	1,587	(5.3)
2005–2009	19,430	(13.0)	8,244	(11.0)	3,747	(8.4)	1,502	(5.0)
2010–2014	12,952	(8.7)	5,409	(7.2)	2,589	(5.8)	1,067	(3.6)
Degree of urbanisation								
Urban	15,531	(10.4)	19,871	(26.6)	18,484	(41.2)	18,783	(62.8)
Peri-Urban	62,703	(42.0)	42,414	(56.8)	22,508	(50.2)	10,417	(34.8)
Rural	71,236	(47.7)	12,419	(16.6)	3,854	(8.6)	704	(2.4)
Swiss-SEP index[1]								
1st quintile (low SEP)	38,747	(25.9)	17,419	(23.3)	12,721	(28.4)	9,071	(30.3)
2nd quintile	31,971	(21.4)	14,624	(19.6)	9,133	(20.4)	6,049	(20.2)
3rd quintile	29,055	(19.4)	14,434	(19.3)	8,297	(18.5)	5,322	(17.8)
4th quintile	27,063	(18.1)	14,627	(19.6)	7,871	(17.6)	5,150	(17.2)
5th quintile (high SEP)	22,634	(15.1)	13,600	(18.2)	6,824	(15.2)	4,312	(14.4)
Background ionizing radiation[2]								
<100 nSv/h	65,000	(43.5)	29,569	(39.6)	14,750	(32.9)	6,843	(22.9)
100-<150 nSv/h	74,441	(49.8)	40,861	(54.7)	26,978	(60.2)	20,535	(68.7)
150-<200 nSv/h	7,887	(5.3)	3,852	(5.2)	2,867	(6.4)	2,350	(7.9)
≥200 nSv/h	2,087	(1.4)	420	(0.6)	251	(0.6)	176	(0.6)
Missing	55	(0.0)	2	(0.0)	0	(0.0)	0	(0.0)

[1] Neighborhood socio-economic position (Swiss-SEP) (Panczak et al., 2012);
[2] Background ionizing radiation (estimated total dosage from terrestrial gamma and cosmic radiation) (Rybach et al., 2002).

Table 3
Association between exposure to estimated annual mean ambient levels of NO_2 (in increments of 10 μg/m^3) at place of residence at time of diagnosis and risk of childhood cancers diagnosed in Switzerland 1990–2015.

Outcome	Cases	Crude HR (95%-CI)[1]	Adj HR (95%-CI)[2]
All cancers	**2,959**	**1.03 (0.98–1.08)**	**1.02 (0.96–1.08)**
Leukemia	**902**	**1.08 (0.99–1.18)**	**1.06 (0.95–1.18)**
Leukemia, 0-4y	314	1.08 (0.93–1.25)	1.06 (0.88–1.26)
Leukemia, 5-15y	588	1.09 (0.97–1.22)	1.07 (0.93–1.22)
ALL	710	1.03 (0.93–1.14)	1.00 (0.88–1.13)
ALL, 0-4y	273	1.02 (0.87–1.19)	0.99 (0.81–1.20)
ALL, 5-15y	437	1.04 (0.92–1.19)	1.00 (0.85–1.18)
AML	131	1.27 (1.02–1.58)	1.31 (1.00–1.71)
AML, 0-4y	30	1.30 (0.88–1.94)	1.26 (0.77–2.07)
AML, 5-15y	101	1.26 (0.97–1.63)	1.34 (0.98–1.84)
Lymphoma	**464**	**1.09 (0.98–1.23)**	**1.03 (0.89–1.19)**
HL	219	1.08 (0.92–1.27)	0.99 (0.79–1.23)
NHL	149	1.15 (0.93–1.41)	1.11 (0.87–1.43)
CNS	**668**	**0.95 (0.85–1.06)**	**0.96 (0.84–1.09)**
Astrocytoma	299	0.90 (0.77–1.07)	0.93 (0.76–1.13)
Embryonal tumors	119	1.15 (0.91–1.46)	1.10 (0.83–1.47)
Malignant bone tumors	**187**	**0.96 (0.79–1.18)**	**0.94 (0.74–1.20)**
Soft tissue sarcomas	**196**	**1.03 (0.85–1.25)**	**1.05 (0.83–1.33)**

[1] Hazard ratio and 95% confidence interval based on conditional logistic regression models using a nested case-control data set obtained by risk set sampling from the Swiss National Cohort.

[2] Hazard ratio and 95% confidence interval based on conditional logistic regression models adjusted for neighborhood socio-economic position (Swiss-SEP in quintiles) (Panczak et al., 2012), level of urbanization (urban, suburban, or rural), and background ionizing radiation (total dosage from terrestrial gamma and cosmic radiation) (Rybach et al., 2002).

overall (HR 1.07, 95%-CI 0.92–1.26) and for children aged 5–15 years (HR 1.12, 95%-CI 0.92–1.37) but not for children under 5 years of age (HR 1.00, 95%-CI 0.76–1.30). Results were very similar for the subtype of ALL. For AML, the increase was more pronounced (HR 1.29, 95%-CI 0.86–1.95) (Table 5). Elevated HRs were also observed for lymphomas (HR 1.11, 95%-CI 0.90–1.39), HL (HR 1.06, 95%-CI 0.75–1.50), NHL (HR 1.14, 95%-CI 0.80–1.63), malignant bone tumors (HR 1.07, 95%-0.75–1.53), and soft-tissue sarcomas (HR 1.10, 95%-CI 0.78–1.56). By contrast, there was little indication of increased risks for CNS tumors overall (HR 0.93, 95%-CI 0.76–1.13) nor for diagnostic subtypes. Adjusting the analyses for potential confounders generally had only a

Table 5
Association between exposure to estimated annual mean ambient levels of benzene (in increments of 1 μg/m^3) at place of residence at time of diagnosis and risk of childhood cancers diagnosed in Switzerland 1990–2015.

Outcome	Cases	Crude HR (95%-CI)[1]	Adj HR (95%-CI)[2]
All cancers	**2,960**	**1.07 (0.99–1.15)**	**1.05 (0.96–1.15)**
Leukemia	**902**	**1.12 (0.98–1.28)**	**1.07 (0.92–1.26)**
Leukemia, 0-4y	314	1.05 (0.84–1.31)	1.00 (0.76–1.30)
Leukemia, 5-15y	588	1.16 (0.98–1.37)	1.12 (0.92–1.37)
ALL	710	1.08 (0.93–1.25)	1.03 (0.86–1.23)
ALL, 0-4y	273	0.98 (0.77–1.24)	0.93 (0.69–1.24)
ALL, 5-15y	437	1.15 (0.95–1.40)	1.11 (0.88–1.39)
AML	131	1.32 (0.94–1.85)	1.29 (0.86–1.95)
AML, 0-4y	30	1.51 (0.76–3.00)	1.41 (0.58–3.40)
AML, 5-15y	101	1.26 (0.86–1.86)	1.28 (0.80–2.04)
Lymphoma	**464**	**1.20 (1.00–1.44)**	**1.11 (0.90–1.39)**
HL	219	1.21 (0.91–1.60)	1.06 (0.75–1.50)
NHL	149	1.21 (0.90–1.63)	1.14 (0.80–1.63)
CNS	**669**	**0.94 (0.79–1.11)**	**0.93 (0.76–1.13)**
Astrocytoma	299	0.94 (0.73–1.21)	0.99 (0.74–1.34)
Embryonal tumors	119	1.12 (0.79–1.59)	1.02 (0.67–1.55)
Malignant bone tumors	**187**	**1.07 (0.79–1.44)**	**1.07 (0.75–1.53)**
Soft tissue sarcomas	**196**	**1.07 (0.80–1.43)**	**1.10 (0.78–1.56)**

[1] Hazard ratio and 95% confidence interval based on conditional logistic regression models using a nested case-control data set obtained by risk set sampling from the Swiss National Cohort.

[2] Hazard ratio and 95% confidence interval based on conditional logistic regression models adjusted for neighborhood socio-economic position (Swiss-SEP in quintiles) (Panczak et al., 2012), level of urbanization (urban, suburban, or rural), and background ionizing radiation (total dosage from terrestrial gamma and cosmic radiation) (Rybach et al., 2002).

Table 4
Sensitivity analysis of timing of exposure: Association between estimated annual mean ambient levels of NO_2 (in increments of 10 μg/m^3) at place of residence at time of diagnosis (0 years) and 1, 2, 3, 4, and 5 years prior to diagnosis and risk of childhood cancers diagnosed in Switzerland 1990–2015.

	0 years		1 year		2 years		3 years		4 years		5 years	
	Cases	Adj HR (95%-CI)[1]	Cases	Adj HR (95%-CI)[1]	Cases	Adj HR (95%-CI)[1]	Cases	Adj HR (95%-CI)[1]	Cases	Adj HR (95%-CI)[1]	Cases	Adj HR (95%-CI)[1]
All cancers	**2,959**	**1.02 (0.96–1.08)**	**2,905**	**1.01 (0.95–1.07)**	**2,663**	**1.00 (0.94–1.06)**	**2,408**	**1.00 (0.94–1.07)**	**2,172**	**0.99 (0.93–1.06)**	**1,950**	**0.96 (0.89–1.03)**
Leukemia	**902**	**1.06 (0.95–1.18)**	**893**	**1.02 (0.92–1.13)**	**806**	**1.04 (0.93–1.17)**	**693**	**0.99 (0.88–1.11)**	**586**	**1.08 (0.95–1.23)**	**503**	**0.99 (0.86–1.14)**
ALL	710	1.00 (0.88–1.13)	707	0.97 (0.86–1.09)	645	0.99 (0.87–1.12)	544	0.95 (0.83–1.09)	445	1.06 (0.92–1.23)	374	0.96 (0.81–1.13)
AML	131	1.31 (1.00–1.71)	126	1.21 (0.94–1.55)	108	1.31 (0.98–1.74)	99	1.18 (0.88–1.59)	94	1.18 (0.87–1.59)	85	1.12 (0.81–1.55)
Lymphoma	**464**	**1.03 (0.89–1.19)**	**462**	**1.02 (0.88–1.18)**	**439**	**1.00 (0.86–1.16)**	**422**	**1.00 (0.86–1.17)**	**398**	**0.99 (0.85–1.16)**	**368**	**0.96 (0.82–1.13)**
HL	219	0.99 (0.79–1.23)	219	0.99 (0.79–1.23)	212	1.02 (0.82–1.28)	203	1.06 (0.85–1.33)	199	1.03 (0.83–1.29)	189	0.99 (0.78–1.24)
NHL	149	1.11 (0.87–1.43)	147	1.08 (0.84–1.38)	139	1.00 (0.78–1.30)	136	0.96 (0.74–1.24)	123	0.90 (0.68–1.19)	112	0.80 (0.59–1.07)
CNS	**668**	**0.96 (0.84–1.09)**	**662**	**0.96 (0.84–1.09)**	**619**	**0.92 (0.80–1.05)**	**572**	**0.97 (0.85–1.11)**	**521**	**0.88 (0.76–1.01)**	**471**	**0.82 (0.71–0.96)**
Astrocytoma	299	0.93 (0.76–1.13)	296	0.97 (0.80–1.18)	281	0.92 (0.75–1.12)	256	0.95 (0.78–1.17)	229	0.89 (0.72–1.11)	207	0.81 (0.64–1.03)
Embryonal tumors	119	1.10 (0.83–1.47)	117	1.14 (0.87–1.49)	110	1.02 (0.76–1.35)	101	0.93 (0.69–1.25)	90	0.73 (0.52–1.02)	78	0.72 (0.50–1.05)
Bone tumors	**187**	**0.94 (0.74–1.20)**	**187**	**0.95 (0.74–1.21)**	**178**	**1.06 (0.83–1.35)**	**170**	**1.06 (0.83–1.36)**	**164**	**0.97 (0.75–1.25)**	**157**	**0.97 (0.75–1.25)**
Soft tissue sarcomas	**196**	**1.05 (0.83–1.33)**	**193**	**1.06 (0.84–1.33)**	**176**	**0.94 (0.73–1.22)**	**167**	**0.89 (0.68–1.16)**	**158**	**1.01 (0.78–1.31)**	**146**	**0.97 (0.74–1.26)**

[1] Hazard ratio and 95% confidence interval based on conditional logistic regression models using a nested case-control data set obtained by risk set sampling from the Swiss National Cohort adjusted for neighborhood socio-economic position (Swiss-SEP in quintiles) (Panczak et al., 2012), level of urbanization (urban, suburban, or rural), and background ionizing radiation (total dosage from terrestrial gamma and cosmic radiation) (Rybach et al., 2002).

minor effect on the results, although hazard ratios for lymphomas and intracranial and intraspinal embryonal tumors were again somewhat attenuated (Table 5). Conditional logistic regression models including benzene as a categorical variable produced no evidence of increased risks for any diagnostic group but adjusted HRs were elevated for AML (HR 1.63, 95%-CI 0.57–4.64) when comparing children with the highest levels of exposure (≥2.5 μg/m^3) to the reference category of below median concentration (<0.977 μg/m^3). Similarly, there was an indication of increased risks for lymphomas (HR 1.39, 95%-CI 0.80–2.41) and the subtypes HL and NHL (Table S5).

4. Discussion

4.1. Main findings

This nationwide census-based cohort study found evidence of an increased risk of childhood leukemia from exposure to traffic-related outdoor air pollution at children's place of residence. For NO_2, this association appeared to be limited to the subtype of AML. Hazard ratios gradually diminished for lagged exposure but elevated risks were observed for exposure levels at place of residence up to 5 years preceding diagnosis. For benzene, we found weak evidence of an association for AML, and some indication of increased risks for ALL (in 5–15 year-olds). We also observed increased risks for lymphomas, particularly NHL, and, to a lesser extent, soft-tissue sarcomas, and malignant bone tumors but only for exposure to benzene. By contrast, there was little indication of an association for CNS tumors overall or subtypes, except for intracranial and intraspinal embryonal tumors with exposure to NO_2. Adjusting for potential confounders generally had little impact on results.

4.2. Results in the context of previous studies

Our results on childhood leukemia are congruent with previous systematic reviews, most of which were suggestive of an increased risk in relation to traffic-related outdoor air pollution (Filippini et al., 2019; Boothe et al., 2014; Carlos-Wallace et al., 2016; Filippini et al., 2015). The estimated hazard ratio for childhood leukemia for exposure to NO_2 (HR 1.06, 95%-CI 0.95–1.18) in our study were similar to the summary relative risk estimate of a recent systematic review and *meta*-analysis (Filippini et al., 2019) (HR 1.04, 95%-CI 0.90–1.19). Results were also closely similar for preschool children (diagnosed under the age of five or six years). For benzene, however, estimated HR were lower than in the review, particularly for preschool children. Regarding the subtype of ALL, both the systematic review and our analysis reported little evidence of an increased risk from exposure to NO_2 but were suggestive of a weak positive association for benzene, even though results stratified by age group did not concur. For AML, our analysis found clearly increased risks for exposure to both benzene and NO_2, whereas in the systematic review summary relative risks were elevated only for the former (1.84, 1.31–2.59) but not for the latter (0.97, 0.79–1.19) (Filippini et al., 2019).

Our findings of increased hazard ratios for NHL and, in the case of benzene, also for HL and lymphomas overall, are in accord with some previous reports in the literature, but the evidence base remains inconclusive. Studies analyzing lymphoma overall reported mixed results; our previous study (Spycher et al., 2015) as well as a recent register-based case-control study from Denmark (Hvidtfeldt et al., 2020) reported little evidence of an association, whereas an earlier register-based Danish case-control study reported increased risks for lymphoma for exposure to NO_2 but not for benzene (Raaschou-Nielsen et al., 2001). The few studies that analyzed lymphoma subtypes separately produced inconsistent results on HL. An ecological study from Texas (Whitworth et al., 2008) reported some indication of an increased risk of HL from exposure to benzene, while a recent ecological study from São Paulo, Brazil (Ribeiro et al., 2021) found evidence of an association with exposure to NO_2. On the other hand, the two register-based studies from Denmark found little evidence of an association for exposure during childhood to NO_2 or benzene, although the earlier study did observe an effect for *in utero* exposure to both NO_2 and benzene (Raaschou-Nielsen et al., 2001; Hvidtfeldt et al., 2020). By contrast, analyses of NHL generally reported no or little evidence of an association with exposure to either NO_2 or benzene (Raaschou-Nielsen et al., 2001; Lavigne et al., 2017; Raaschou-Nielsen et al., 2018; Ghosh et al., 2013; Whitworth et al., 2008), except for the recent register-based study from Denmark which found evidence of an increased risk from exposure to $PM_{2.5}$ and black carbon but a much weaker association for NO_2 (Hvidtfeldt et al., 2020), rather similar to our effect estimate.

The lack of association between CNS tumors and ambient levels of NO_2 or benzene in our study is congruent with the majority of reports in the literature. Studies analyzing all CNS tumors combined mostly reported no (Raaschou-Nielsen et al., 2001; Hvidtfeldt et al., 2020; Reynolds et al., 2004) or only weak (Savitz and Feingold, 1989) evidence of such an association. Some supportive evidence comes from two population-based studies from Texas (Danysh et al., 2016) and Switzerland (Spycher et al., 2015) that used proximity of place of residence to major roads or highways as exposure metric and an ecological study from Texas (Danysh et al., 2015) that found an effect for exposure to diesel particulate matter but not for 1,3-butadiene nor for benzene. Similarly, the absence of any indication of an excess risk for astrocytoma from exposure to NO_2 or benzene is also consistent with the majority of previous studies, most of which found no evidence of an association (Raaschou-Nielsen et al., 2001; Hvidtfeldt et al., 2020; von Ehrenstein et al., 2016; Ghosh et al., 2013; Heck et al., 2013). Reports of a positive association came from a case-control study from Denmark for benzene (Raaschou-Nielsen et al., 2018), and a cohort study from Ontario, Canada, that found evidence of an effect from exposure to NO_2 during the third trimester of pregnancy but not for exposure over the entire gestation period (Lavigne et al., 2017). Two Texan studies indicated associations between childhood astrocytoma and exposure to 1,3-butadiene and diesel particulate matter (Danysh et al., 2015) and proximity to roads (Danysh et al., 2016). Finally, a recent Danish (Hvidtfeldt et al., 2020) and a Californian study (Ghosh et al., 2013) found no indication of an association between the risk of intracranial and intraspinal embryonal tumors and NO_2 exposure, unlike in our study.

The absence of any indication of an increased risk for malignant bone tumors from exposure to NO_2 is in accord with the findings of a recent population-based case control study from Denmark (Hvidtfeldt et al., 2020). Two previous studies that did find an association with outdoor air exposure to benzene analyzed the risk of malignant bone tumors in relation to distance to nearby industrial plants emitting specific pollutants (Pan et al., 1994; García-Pérez et al., 2017). Finally, the lack of any clear association between exposure to NO_2 and soft tissue sarcomas in our study is in line with the results of the recent Danish study that also found little evidence of such an association (Hvidtfeldt et al., 2020).

We are not aware of any previous study that looked at the effects of lagged exposure to traffic-related air pollution on childhood cancer risks.

4.3. Limitations and strengths

Our study was based entirely on national routine datasets resulting in both strengths and limitations. The record linkage between the SCCR and the SNC was done probabilistically, which may have resulted in some degree of misclassification of the outcome. Of the eligible cases who were diagnosed after their entry into the cohort and who were thus assumed to be linkable to a record of the SNC, 13% could not be linked and had to be dropped from the analysis. Another 4% of eligible cases had to be excluded because of missing geo-information on their place of residence. We had no indication that misclassification or under-ascertainment of the outcome were differential by exposure, but cannot rule out possible bias from this. Moreover, there was no

continuous tracking of address histories between the censuses in 1990 and 2000 and between 2000 and 2010, and at most one relocation was recorded during these periods. This will have resulted in some degree of exposure misclassification. In our annual LUR models for NO_2, only the PolluMap dispersion model estimate of air pollution was time-updated annually; for the other spatial covariates we used data from the mid-2000s for the entire study period, and time-varying covariates such as traffic volume may thus have been over- or underestimated during the early or later years of the study period, respectively. However, this should have been compensated at least partially by the model coefficient estimates in our annual models. For benzene, there were too few monitoring sites, which precluded us from building a LUR model to refine the PolluMap estimates, let alone yearly ones, resulting in lower accuracy compared to our model for NO_2. Exposure misclassification in our study is unlikely to be differential between cases and controls obtained through risk set sampling as these were matched on age and year of birth, and all residential information used was from a single source (the SNC). Non-differential exposure misclassification may thus have attenuated HRs towards one.

The main strength of our study was the availability of a cohort of the child population of the entire country with individual data on precise locations of residence. The follow-up period of 2.5 decades allowed us to assess the association between air pollution and childhood cancer risk using time-varying exposure data during a time when ambient concentrations of many air toxins including NO_2 and benzene have fallen in Switzerland. The study relies entirely on population-based routine data sets, which allowed us to obtain a relatively large sample size while minimizing the risk of selection bias. Exposure assessments for NO_2 were based on annual LUR models for each year of the study period that predicted ambient levels of air pollution as measured by monitoring sites with high accuracy. The PolluMap dispersion model for benzene was less precise, but both exposure models captured the decline in ambient levels of these pollutants over the study period. Coupled with reasonably accurate information on residential histories, this temporal variation allowed us to investigate the effect of lagged exposure on cancer risk. The availability of precise geocodes of place of residence allowed us to capture exposure contrasts in ambient levels of air pollution at a small spatial scale. Finally, we were able to account for some potentially important confounders, although we lacked information on lifestyle factors such as nutrition or smoking.

4.4. Interpretation of results

The clearest indications of an association between exposure to traffic-related outdoor air pollution and childhood cancer in our study was for leukemia, in particular the subtype of AML. These results are consistent with the literature and the findings of our own previous study, which used a cruder exposure measure, namely distance to highways. The established carcinogenic effects of outdoor air pollution are a plausible explanation of these observed effects. Traffic exhaust contains a number of recognized carcinogens including benzene, which is known to cause hematological malignancies, in particular AML, in occupationally exposed adults (Vlaanderen et al., 2012; Vlaanderen et al., 2011). The association is also biologically plausible as benzene is easily absorbed and extensively metabolized and is known to be genotoxic and to cause hematologic toxicity (Loomis et al., 2017). The current evidence also suggests that there may be no safe level of exposure and that ambient environmental benzene may be responsible for many cases of *de novo* AML, i.e. not arising out of germline predispositions, among adults (Shallis et al., 2021).

The evidence of an association with leukemia, and AML in particular, was stronger for NO_2 than for benzene. This might be due to the lower accuracy of our benzene exposure model. NO_2, contrary to benzene, is not an established carcinogen but was used here because it is a frequently monitored surrogate for traffic-related air pollution. The two most recent systematic reviews (Filippini et al., 2019; Wei et al., 2021) both found stronger evidence for increased leukemia risks associated with exposure to benzene than for NO_2. This does not exclude the possibility that traffic-related pollutants, other than benzene, contributed to the observed associations for NO_2 and benzene.

In our analyses, we found no indication of major confounding. The potential confounders considered had only a minimal effect on the observed exposure-outcome associations, including background ionizing radiation, which as in our previous study (Spycher et al., 2015) was found to be associated with leukemia and CNS risks. In an observational study, we cannot exclude possible residual confounding. However, given the pronounced associations found specifically for AML in consistency with the literature, the known leukemogenicity of benzene offers a more plausible explanation.

In conclusion, this nationwide census-based cohort study adds to the existing evidence that exposure to traffic-related air pollution is associated with an increased risk of leukemia in children. The pronounced association observed between benzene and AML is consistent with previous studies and adds support to the hypothesis that exposure to ambient levels of benzene can cause AML in children.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107380.

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