Supplementary material

Childhood cancer and residential exposure to highways: a nationwide cohort study

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Text S1: Calculating person years at risk for the incidence density analyses

For incidence density analyses, we calculated person years at risk according to a previously described method[1] for each combination of categories of predictor variables included in regression analyses: calendar year, age (in years), sex, and distance category. Let $x_t(u)$ represent the number of person years accrued by children aged *u* in year *t* with given sex and distance category. The values $x_{1990}(u)$ and $x_{2000}(u)$ were obtained from the census data for 1990 and 2000 respectively. To calculate $x_{1990}(u)$, we identified the children in 1990 census with the given combination of predictors and summed their individual person year contributions to age *u* during the 365 days preceding the census date. Person years $x_{2000}(u)$ were calculated analogously. Person years $x_t(u)$ for non-census years were then calculated as a linear extra-/interpolation from the values $x_{1990}(u)$ and $x_{2000}(u)$. To adjust for non-linear population fluctuations, we weighted the values $x_{1990}(u)$ and $x_{2000}(u)$ prior to extra-/interpolation based on age and sex specific national population levels which were obtained from the Federal Office of Statistics for all years 1985-2008. Weights for $x_{1990}(u)$ and $x_{2000}(u)$ were equal to the ratio between the sex-specific population aged *u* in year *t* and the sex-specific population aged *u* in the years 1990 and 2000 respectively. In Poisson regression, cases belonging to the given combination of predictor values were then assigned the person years $x_t(u)$.

Table S1: Characteristics of cancer cases included in analyses

		Included in time to event analysis N (%)	Included in incidence density analysis N (%)
All children		1783 (100.0)	4263 (100.0)
ICCC3 main diagnostic group	Leukaemias, myeloproliferative diseases, and myelodysplastic diseases	532 (29.8)	1367 (32.1)
	Lymphomas and reticuloendothelial neoplasms	326 (18.3)	574 (13.5)
	CNS and miscellaneous intracranial and intraspinal neoplasms	420 (23.6)	890 (20.9)
	Neuroblastoma and other peripheral nervous cell tumours	34 (1.9)	287 (6.7)
	Retinoblastoma	21 (1.2)	111 (2.6)
	Renal tumours	55 (3.1)	234 (5.5)
	Hepatic tumours	14 (0.8)	44 (1.0)
	Malignant bone tumours	128 (7.2)	209 (4.9)
	Soft tissue and other extraosseous sarcomas	125 (7.0)	291 (6.8)
	Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	48 (2.7)	117 (2.7)
	Other malignant epithelial neoplasms and malignant melanomas or unspecified malignant neoplasms	80 (4.5)	138 (3.2)
Sex	Male	994 (55.7)	2357 (55.3)
	Female	789 (44.3)	1906 (44.7)
Median age in years (IQR)		10.1 (6.1-13.2)	6.1 (2.7-11.7)

Abbreviations: ICCC3 International Classification of Childhood Cancers – 3rd Edition,[2] IQR interquartile range, CNS central nervous system

Table S2: Association between childhood cancer and highway traffic volume among children living <500 m from a highway (time to event analyses)

	All vehicles		Trucks only	
Outcome	**HR[a] (95% CI) per increase of 10,000 veh/d**	**P**	**HR[a] (95% CI) per increase of 1,000 veh/d**	**P**
Leukaemia	1.02 (0.94, 1.11)	0.603	1.01 (0.92, 1.10)	0.906
ALL	0.99 (0.90, 1.09)	0.806	1.00 (0.89, 1.11)	0.933
Lymphoma	1.14 (1.04, 1.25)	0.005	1.10 (0.99, 1.21)	0.075
CNS tumours	1.00 (0.90, 1.10)	0.950	1.01 (0.91, 1.12)	0.798
Other malignant tumours	1.07 (0.98, 1.16)	0.118	1.08 (0.98, 1.18)	0.104
All cancers	1.05 (1.01, 1.10)	0.021	1.05 (1.00, 1.10)	0.072

Abbreviations: ALL acute lymphoblastic leukaemia, CI confidence, CNS central nervous system, HR hazard ratio, veh/d vehicles per day

[a] From Cox proportional hazard models adjusting for sex, birth year and distance to highway.

Table S3: Association between childhood cancer and highway traffic volume (incidence density analyses)

Outcome	All vehicles		Trucks only	
	IRR[a] (95% CI) per increase of 10,000 veh/d	P	IRR[a] (95% CI) per increase of 1,000 veh/d	P
Analysis including children living <500 m from a highway				
Leukaemia	1.02 (0.96, 1.07)	0.522	1.02 (0.97, 1.09)	0.413
ALL	1.01 (0.95, 1.07)	0.709	1.02 (0.96, 1.09)	0.528
Lymphoma	1.06 (0.98, 1.14)	0.171	1.04 (0.95, 1.13)	0.427
CNS tumours	1.01 (0.94, 1.08)	0.801	0.97 (0.90, 1.04)	0.362
Other malignant tumours	1.04 (0.99, 1.09)	0.164	1.04 (0.98, 1.10)	0.162
All cancers	1.03 (1.00, 1.06)	0.074	1.02 (0.99, 1.05)	0.258
Analysis including children living <250 m from a highway[b]				
Leukaemia	1.02 (0.94, 1.11)	0.591	1.04 (0.96, 1.14)	0.355
ALL	1.02 (0.93, 1.11)	0.656	1.05 (0.95, 1.15)	0.331
CNS tumours	0.94 (0.83, 1.07)	0.341	0.90 (0.77, 1.05)	0.167
Other malignant tumours	1.02 (0.94, 1.11)	0.606	0.99 (0.90, 1.09)	0.892
All cancers	1.01 (0.96, 1.06)	0.699	0.99 (0.94, 1.05)	0.851
Analysis including children living <100 m from a highway[b]				
Leukaemia	1.03 (0.91, 1.17)	0.638	1.03 (0.88, 1.20)	0.741
ALL	1.04 (0.90, 1.19)	0.629	1.03 (0.87, 1.22)	0.756
CNS tumours	0.92 (0.74, 1.14)	0.446	0.81 (0.60, 1.09)	0.171
Other malignant tumours	1.07 (0.94, 1.23)	0.296	1.12 (0.96, 1.30)	0.143
All cancers	1.03 (0.95, 1.12)	0.509	1.02 (0.93, 1.13)	0.630

Abbreviations: ALL acute lymphoblastic leukaemia, CI confidence, CNS central nervous system, IRR incidence rate ratio, veh/d vehicles per day

[a] From Poisson regression models adjusting for sex, age, year of diagnosis, and distance to highway.

[b] Lymphoma were not considered in these analyses due to the small number of cases.

Table S4: Association between childhood cancer and quartiles of highway traffic volume (incidence density analyses)

Outcome	Traffic density quartile	IRR[a] (95% CI)	P-value[b]
Any cancer	1st Q	1.00	0.44
	2nd-3rd Q	0.99 (0.80,1.23)	
	4th Q	1.19 (0.94,1.50)	
Leukaemia	1st Q	1.00	1.00
	2nd-3rd Q	1.04 (0.71,1.52)	
	4th Q	1.09 (0.71,1.66)	
ALL	1st Q	1.00	1.00
	2nd-3rd Q	0.93 (0.62,1.41)	
	4th Q	0.99 (0.62,1.57)	
Lymphoma	1st Q	1.00	0.10
	2nd-3rd Q	0.59 (0.33,1.06)	
	4th Q	1.22 (0.69,2.17)	
CNS tumours	1st Q	1.00	1.00
	2nd-3rd Q	1.01 (0.65,1.58)	
	4th Q	1.03 (0.62,1.70)	
Other malignant tumours	1st Q	1.00	0.59
	2nd-3rd Q	1.14 (0.78,1.66)	
	4th Q	1.39 (0.93,2.09)	

Q Quartile

[a] From Poisson regression models adjusting for sex, age, year of diagnosis, and distance to highway

[b] P-value from likelihood ratio test

References

1. Spycher BD, Feller M, Zwahlen M, Roosli M, von der Weid NX, Hengartner H et al. Childhood cancer and nuclear power plants in Switzerland: a census-based cohort study. Int J Epidemiol. 2011;40:1247-60.

2. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer. 2005;103:1457-67.

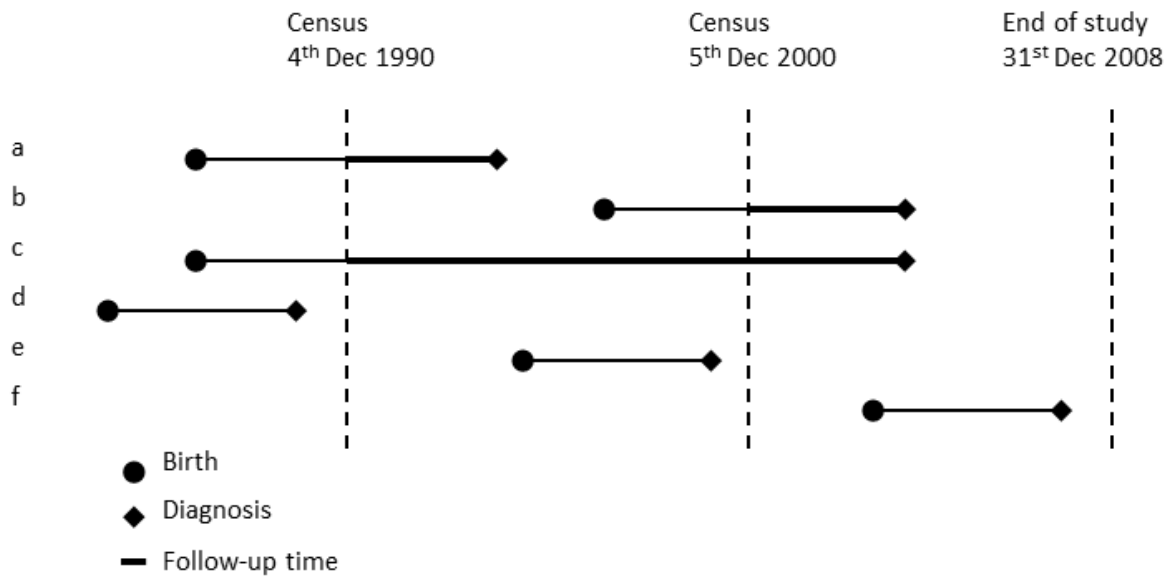

Fig. S1: Eligibility of incident cases. Eligible cases (a, b, c) are those that contribute follow-up time to the study if linked to the Swiss National Cohort (SNC). Non-eligible cases (d, e, f) cannot contribute follow-up time and were excluded from the SNC if linked (only d and e are linkable).

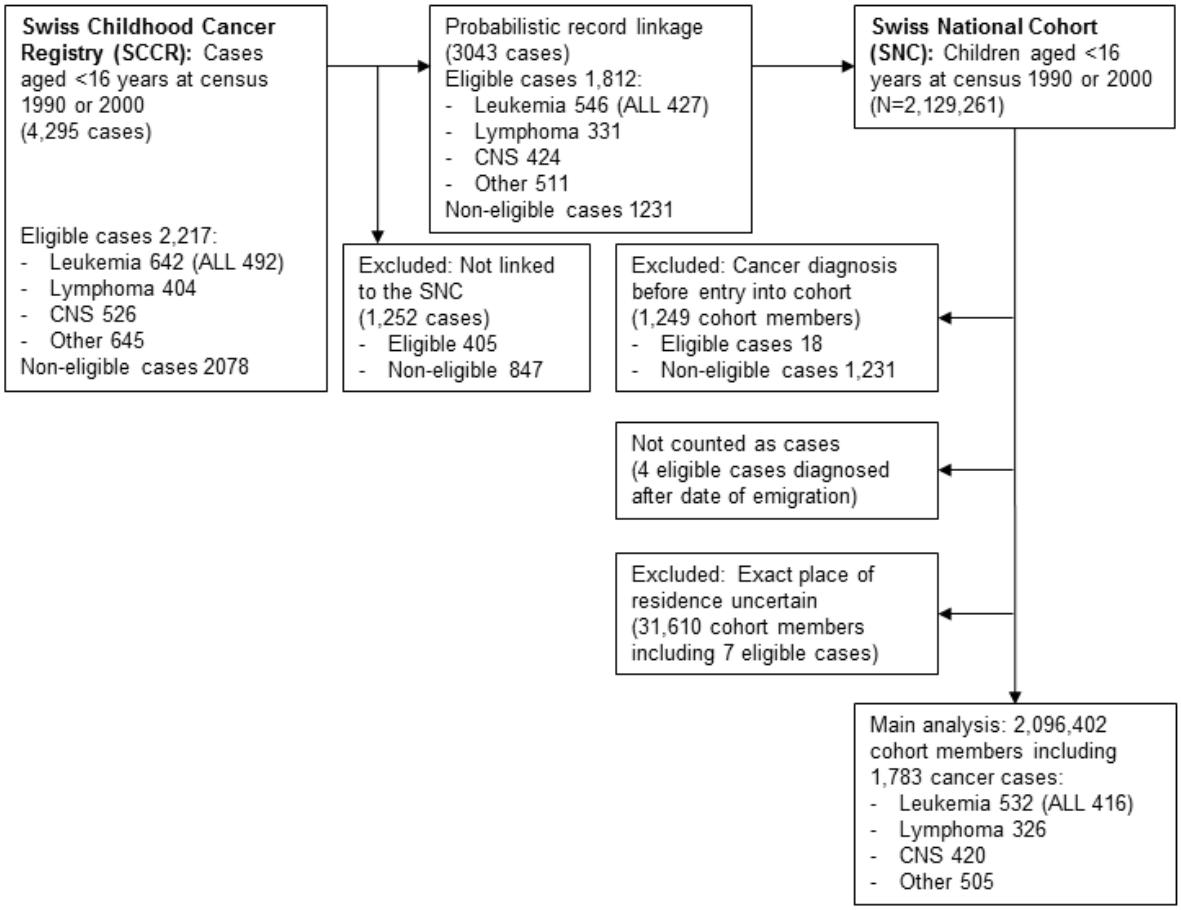

Fig. S2: Flow chart of study population. Both eligible and non-eligible cases (See Figure 1) were linked to the Swiss National Cohort. Non-eligible cases were subsequently excluded because they were diagnosed before entry into the cohort.

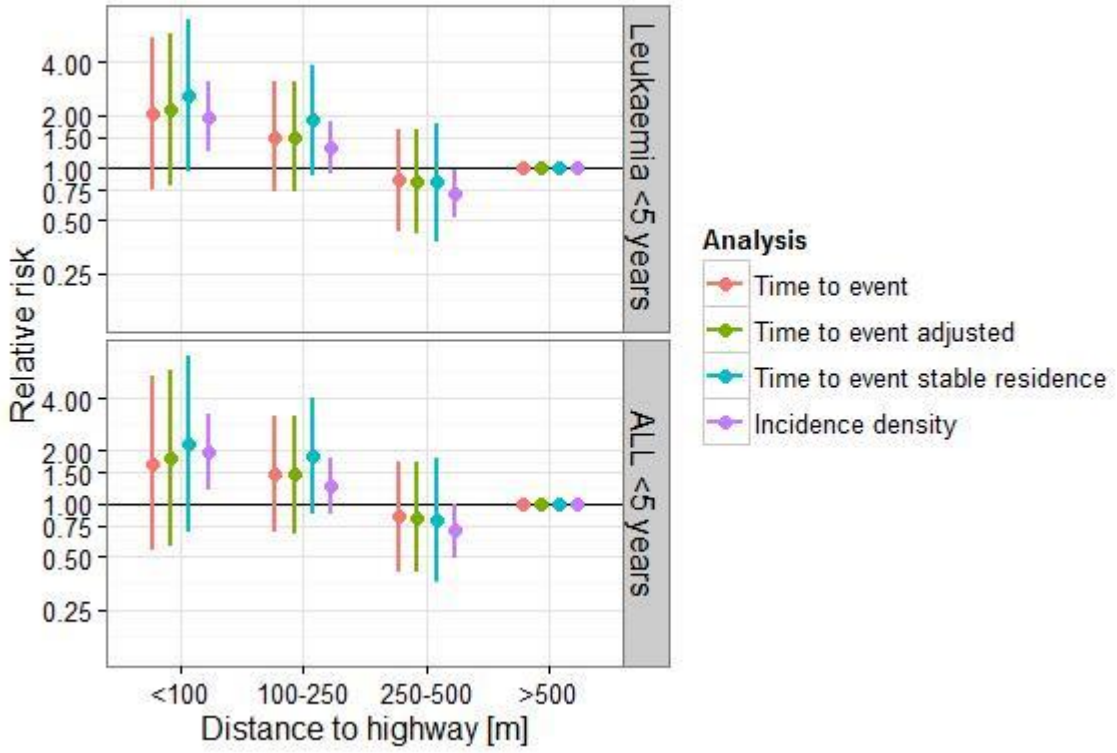

Fig. S3: Associations between leukaemia in children aged <5 years and distance of residence to nearest highway. Results from time-to-event analysis adjusting sex and birth year; time-to-event analysis adjusting for sex, birth year and other potential confounders; time-to-event analysis adjusting for sex and birth year in a subsample with stable place of residence 5 years preceding entry into cohort; incidence density analysis adjusting for sex, age and calendar year. Reference category is residence >500 m.

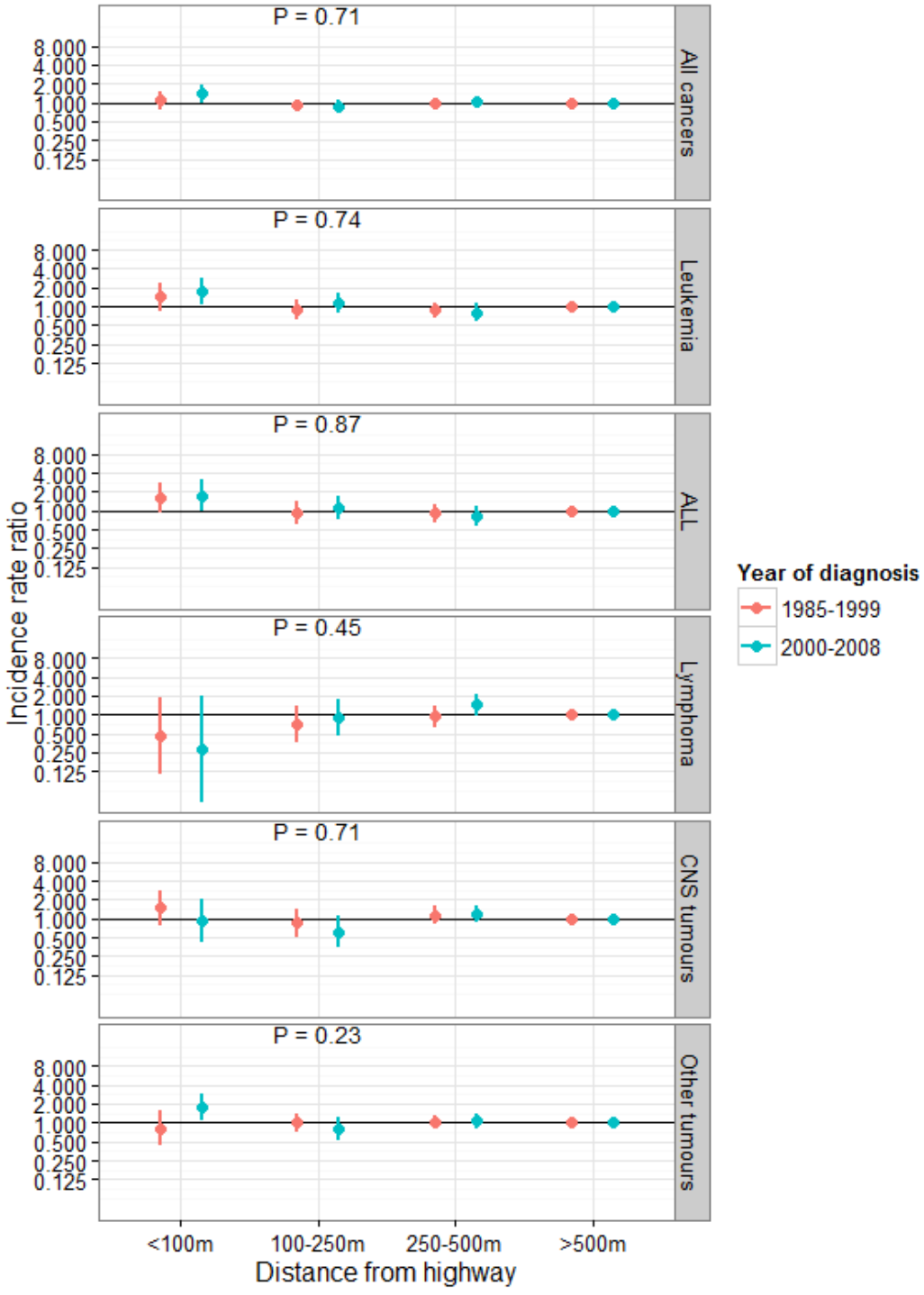

Fig S4: Interaction between time period of diagnosis and distance to nearest highway. Results from incidence density analyses including interaction terms between distance and time periods (1985-1999, 2000-2008) adjusting for sex, age at diagnosis and year of diagnosis. The reference category is residence >500 m in each calendar period respectively. P-values of likelihood ratio tests for interaction are shown.

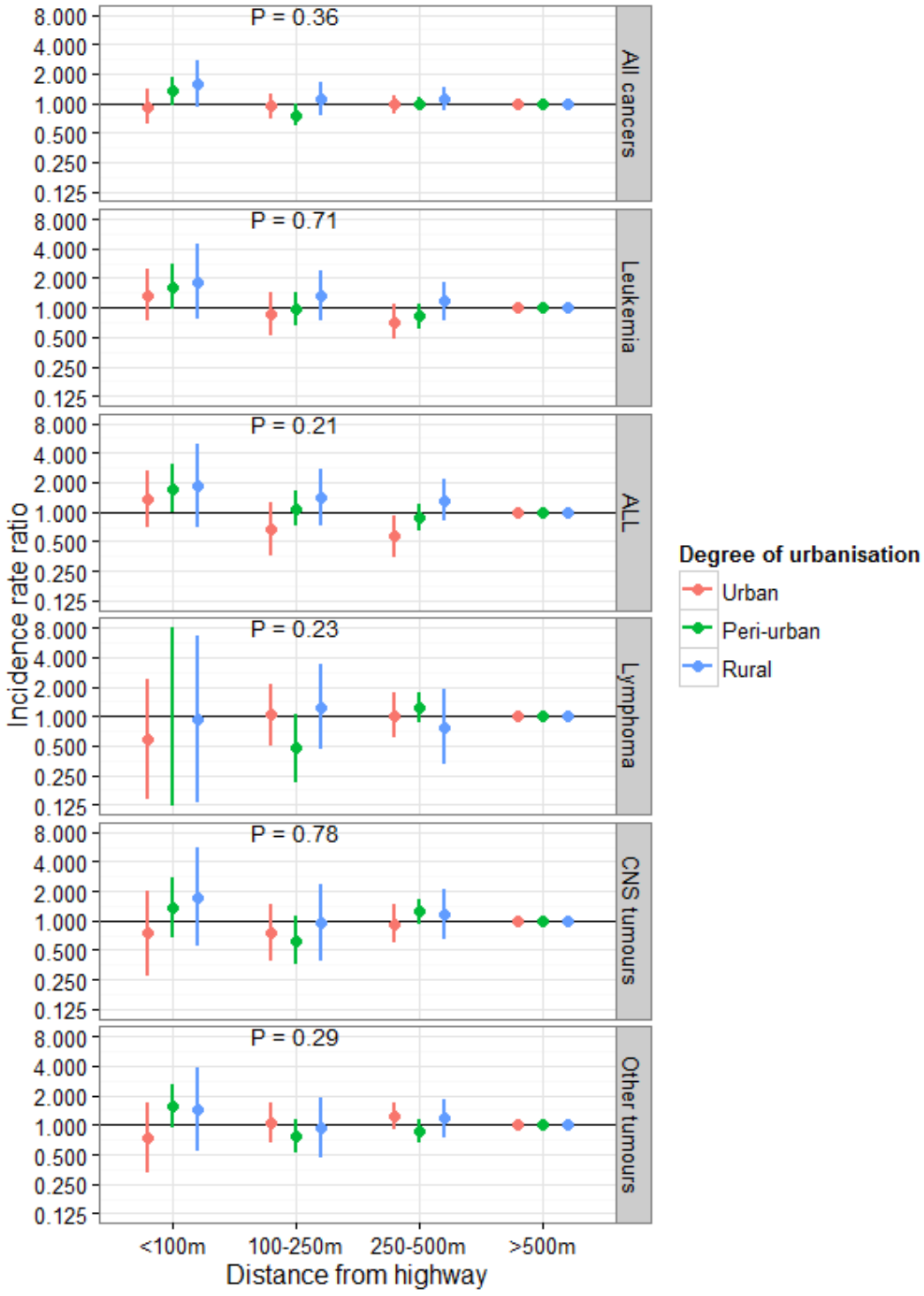

Fig S5: Interaction between degree of urbanisation and distance to nearest highway. Results from incidence density analyses including interaction terms between distance and degree of urbanisation adjusting for sex, age at diagnosis and year of diagnosis. The reference category is residence >500 m in each stratum. P-values of likelihood ratio tests for interaction are shown. There were no observed cases of lymphoma for distance category <100 m in peri-urban areas resulting in an estimate outside the range of the y-axis.

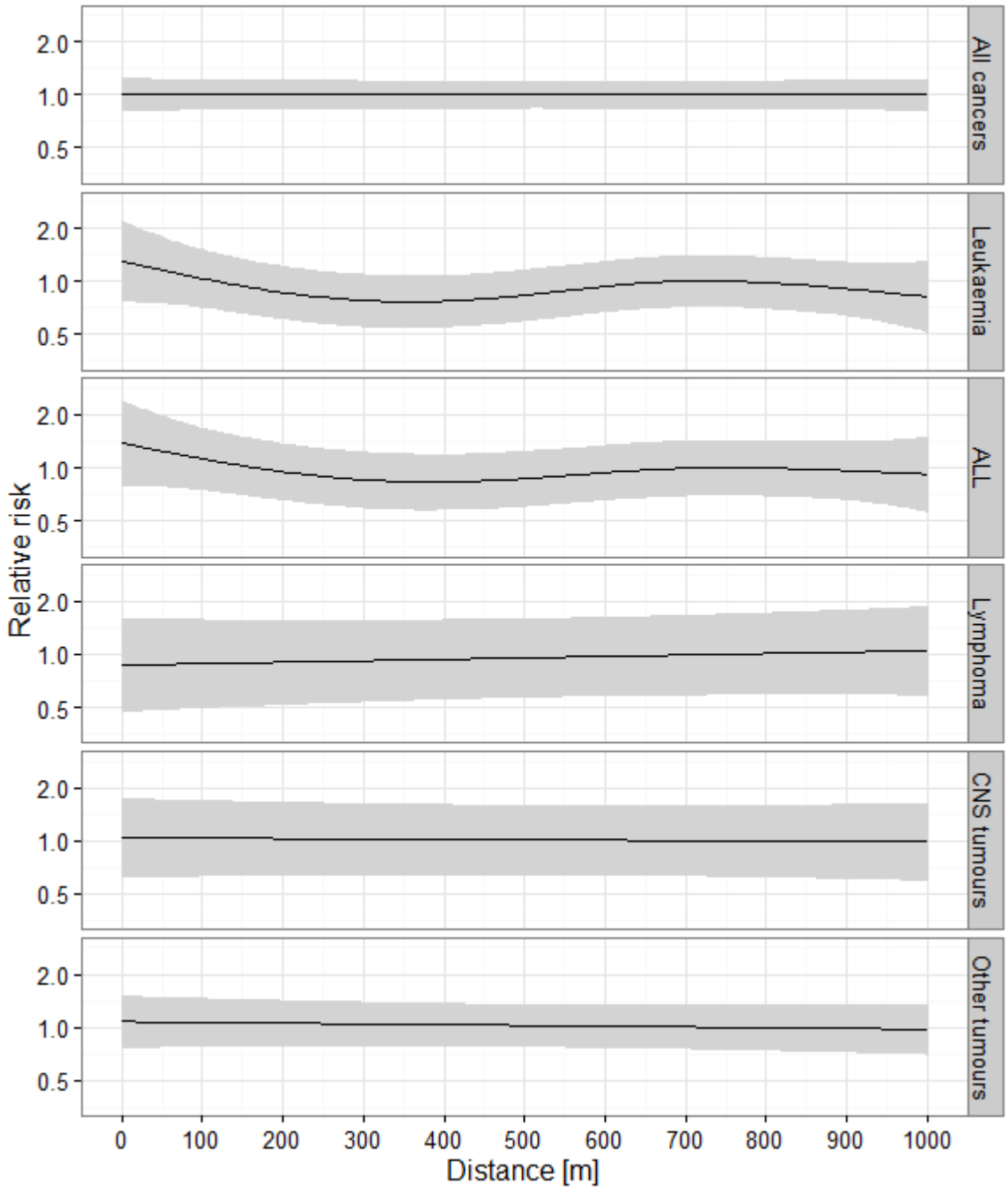

Fig S6: Smoothed relative risks for childhood cancer by distance from nearest highway. Results from incidence density analysis with distance as a continuous exposure variable adjusting for sex, age and calendar year and restricting to children living <1 km from a highway. Penalised cubic regression splines were used to model the association with distance and estimated risk. The estimated risk at 750 m was used as reference value (relative risk = 1). The shaded area represents point-wise 95% confidence intervals.

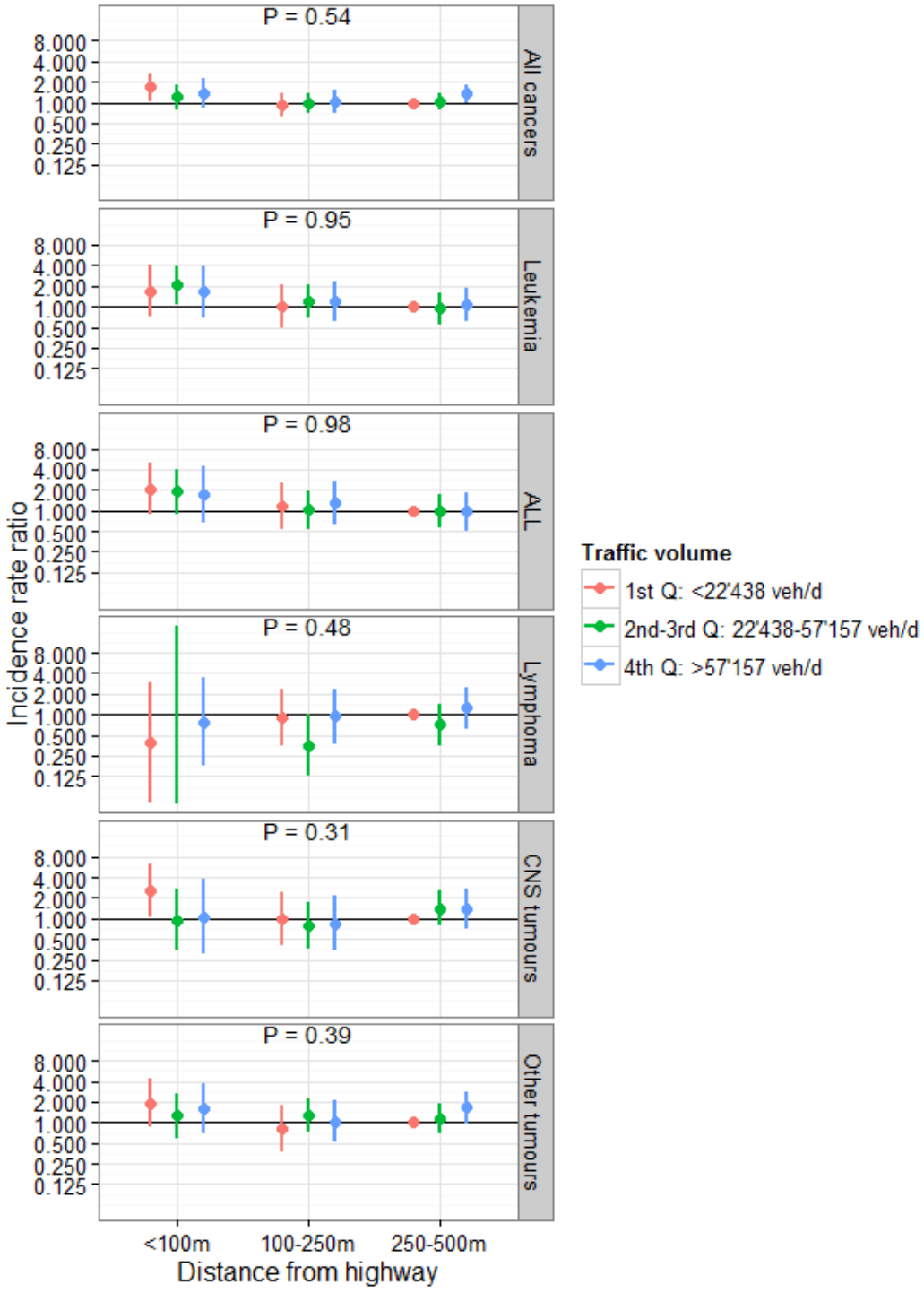

Fig S7: Interaction between quartiles (Q) of traffic volume and distance to nearest highway. Results from incidence density analyses including interaction terms between distance and traffic volume adjusting for sex, age at diagnosis and year of diagnosis. Reference category is 250-500 m from the nearest highway and 1st quartile of traffic volume. Analyses are restricted to children living <500 m from a highway. P-values of likelihood ratio tests for interaction are shown. There were no observed cases of lymphoma for the distance category <100 m and traffic volume quartiles 2-3 resulting in an estimate outside the range of the y-axis.