

Effects of incomplete residential histories on studies of environmental exposure with application to childhood leukaemia and background radiation

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The authors have no conflicting interests to disclose.

Abstract

When evaluating environmental exposures, residential exposures are often most relevant. In most countries, it is impossible to establish full residential histories. In recent publications, childhood leukaemia and background radiation have been studied with and without full residential histories. This paper investigates the consequences of lacking such full data.

Data from a nationwide Finnish Case-Control study of Childhood Leukaemia and gamma rays were analysed. This included 1093 children diagnosed with leukaemia in Finland in 1990–2011. Each case was matched by gender and year of birth to three controls. Full residential histories were available. The dose estimates were based on outdoor background radiation measurements. The indoor dose rates were obtained with a dwelling type specific conversion coefficient and the individual time-weighted mean red bone marrow dose rates were calculated using age-specific indoor occupancy and the age and gender of the child. Radiation from Chernobyl fallout was included and a 2-year latency period assumed.

The median separation between successive dwellings was 3.4 km and median difference in red bone marrow dose 2.9 nSv/h. The Pearson correlation between the indoor red bone marrow dose rates of successive dwellings was 0.62 (95% CI 0.60, 0.64). The odds ratio for a 10 nSv/h increase in dose rate with full residential histories was 1.01 (95% CI 0.97, 1.05). Similar odds ratios were calculated with dose rates based on only the first dwelling (1.02, 95% CI 0.99, 1.05) and only the last dwelling (1.00, 95% CI 0.98, 1.03) and for subjects who had lived only in a single dwelling (1.05, 95% CI 0.98, 1.10).

Knowledge of full residential histories would always be the option of choice. However, due to the strong correlation between exposure estimates in successive dwellings and the uncertainty about the most relevant exposure period, estimation of overall exposure level from a single address is also informative. Error in dose estimation is likely to cause some degree of classical measurement error resulting in bias towards the null.

Key words

Residential history, exposure assessment, childhood leukaemia

Funding

The work of AN was supported by Väre Foundation for Pediatric Research, Finnish Foundation for Pediatric Research and Competitive State Research Financing of the Expert Responsibility are dot Tampere University Hospital (9T030 and 9U030).

The work of GMK was supported by Children with Cancer (UK) under grant number HTRVVK0.

The review of the study protocol by the local ethical committee

Scanned documents

TAMPEREEN YLIOPISTOLLISEN SAIRAALAN ERITYISVASTUUALUEEN ALUEELLINEN EETTINEN TOIMIKUNTA		OTE PÖYTÄKIRJASTA 28.5.2014	Nro 5/2014
KOKOUSTIEDOT			
Aika	27.5.2014 klo 12-13.50		
Paikka	FM 5, Tiedekeskuksen neuv. huon.		
OSALLISTUJAT			
Pasternack Amos	LKT, professori (emer.)	puheenjohtaja	
Alanen Seija	TTT, vs. yllhoitaja		
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Mattila Eina	TTT, yllhoitaja		
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Tainen Virpi	toimittaja	maalikkoköjäsen	
Korhonen Kirsi	TIM, palveluesimies	sihteeri	
Laitinen Minna	TIK, tutkimussihteeri	sihteeri	
POISSA			
Hietaharju Aki	osastonyliääkärin		
Nuolivaara Kirsi	erikoislääkärin	varajäsen	
Saari Jukka	yllääkärin		
Sipola Antti	sairaalasielunhoidon johtaja	maalikkoköjäsen	
TIEDE §			
ETL-koodi	R14074		
Tutkimus	Auvinen Anssi, uusi tutkimussuunnitelma		
Lausunto	Kyseessä ei ole lääketieteellisen tutkimuksen (488/1996) tarkoittama tutkimus. Eettinen toimikunta ei näe eettisiä esteitä tutkimuksen toteuttamiselle.		
Pöytäkirjan oiteen oikeaksi todistaa			
Kirsi Korhonen sihteeri			

TAMPEREEN YLIOPISTOLLISEN SAIRAALAN ERITYISVASTUUALUEEN ALUEELLINEN EETTINEN TOIMIKUNTA		LIITE	Nro 5/2014
		27.5.2014	
TIEDE §			
R14074 Auvinen Anssi, uusi tutkimussuunnitelma			
Tutkijat	Auvinen Anssi, Erme Sini, Lohi Olli, Järvelä Laura, Pasanen Kari, Gissler Mika, Pukkala Eero, Juutilainen Jukka		
Tutkimuspaikat	Tampereen yliopisto: Anssi Auvinen, Sini Erme, Olli Lohi, Laura Järvelä Terveystieteiden ja hyvinvoinnin laitos (THL): Kari Pasanen, Mika Gissler, Eero Pukkala Itä-Suomen yliopisto: Jukka Juutilainen Tays/lastentautien vä: Sini Erme, Olli Lohi		
Tutkimus	The Riskfactors of Childhood Leukemia: a register-based case-control study Lasten leukemian riskitekijät: rekisteripohjainen tapaus-verrokkitutkimus		
Tutkimusaika	27.5.2014 - 31.12.2017		
Tutkimuksen laajuus	4400		
Toimitettu materiaali	-Lausuntohakemus (31.3.2014) -Tutkimussuunnitelma (ei päivitystä) -TVH:n lausunto eettisyydestä (1.4.2014) -Rekisteriseloste (31.3.2014)		
Lausunto	Kyseessä ei ole lääketieteellisen tutkimuksen (488/1996) tarkoittama tutkimus. Eettinen toimikunta ei näe eettisiä esteitä tutkimuksen toteuttamiselle.		
Lausuntomaksu	Ei lausuntomaksua		
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1 Introduction

Environmental exposure is often determined by location. Because children typically spend most of their time at home (UNSCEAR, 2000), residential exposures, also known as domestic exposures, are often most relevant. Examples include residential exposure to background radiation for residential radon and terrestrial gamma rays, electromagnetic fields and air pollution (Kroll et al., 2010; Raaschou-Nielsen et al., 2001; UK Childhood Cancer Study Investigators, 1999).

Children are more susceptible to the carcinogenic effects of ionizing radiation than adults, and many studies of natural radiation and cancer have focused on children (Demoury et al., 2017; Kendall et al., 2013; Nikkilä et al., 2016; Raaschou-Nielsen et al., 2008; Spix et al., 2017; Spycher et al., 2015). Such studies must include thousands of cases in order to achieve sufficient statistical power to detect the small effects expected from ambient exposures, as extrapolated from high dose levels (Little et al., 2010). However collecting information on such large samples through interview or direct measurement is expensive and prone to selection bias. In most countries, it is impossible to establish full residential histories, i.e. a list of dwellings occupied with dates of moving in and out, without individual contact with study subjects. Only few countries, including the Nordic countries, have nationwide registries that provide such data. For this reason, many such studies have limited exposure assessment to a single dwelling, for example that occupied at diagnosis (UK Childhood Cancer Study Investigators, 2002a; UK Childhood Cancer Study Investigators, 2002b; Demoury, 2017) or that at birth (Kendall et al., 2013).

Because direct measures of natural radiation are impracticable, exposure is usually estimated from models. The indoor dose rates of terrestrial gamma radiation depend on outdoor dose rates, the shielding effect of the material of the house, and the radiation emitted by the building materials. Reasonable predictions of indoor gamma-ray dose rates can be made based on location and factors such as geology and socioeconomic status of the area (Chernyavskiy et al., 2016; Kendall et al., 2016; Warnery et al., 2015). Nevertheless, considerable inter-house variation remains. In the British studies, the residual Mean Square Error (MSE) was 378 (nGy/h)^2 on a mean estimate of 96 nGy/h ; in France $\text{MSE}=407 \text{ (nSv/h)}^2$ with a mean of 76 nSv/h . Such significant uncertainties can be avoided only by direct measurement in the house in question or, potentially, by modelling using more detailed information, in particular on the radioactive content of all significant building materials used in each dwelling (European Commission, 1997). Similar considerations apply, perhaps with even more force, to indoor radon concentrations – neighbouring houses can differ greatly in a random, time varying and unpredictable way, but models can make reasonable predictions for areal averages (Miles and Appleton, 2005).

In studies of the effects of protracted exposures to ionising radiation (or other agents) it is necessary to consider how susceptibility varies over the exposure period. This is particularly important in the context of background radiation, as doses are accumulated throughout life and children are known to be more susceptible (UNSCEAR, 2008a). The extent to which susceptibility varies throughout childhood is unknown though there is evidence that susceptibility is greatest at younger ages (National Research Council (NRC), 2006; UNSCEAR, 2008a; UNSCEAR, 2013). A reasonable approach is to use total cumulative dose or time-integrated dose rates from

birth or conception to diagnosis as exposure measure. However, it is possible that, for example, exposures around the time of birth or during pregnancy are disproportionately important (ICRP: International Commission on Radiological Protection, 2003; National Research Council (NRC), 2006; UNSCEAR, 2013).

A recent publication from the Finnish Register-based Case-Control study of Childhood Leukemia (FRECCLE) (Nikkilä et al., 2016), on the effect of natural gamma rays on risk of childhood leukaemia made use of a nationwide population registry in order to obtain complete residential histories for the study subjects. The present paper analyses these data in more detail to obtain insights for the interpretation of similar epidemiological studies, which lack the richness of the data available in Finland.

It is the aim of this paper

- i) to investigate patterns of residential mobility, or migration, in families with young children,
- ii) to investigate the extent to which doses in successive dwellings vary and
- iii) to examine the implications of residential mobility for epidemiological studies of natural gamma rays and childhood cancers in general and leukaemia in particular.

2 Materials and Methods

FRECCLE includes 1093 children diagnosed with leukaemia in Finland in 1990–2011, identified from the Finnish Cancer Registry. Each case was matched by gender and year of birth to three controls at the Population Register Centre. For the matched

cases and controls, the Population Register Centre provided complete residential histories from birth to the reference date (date of diagnosis for cases; for controls, date when an exposure period of similar length is reached). These residential histories included moving dates and municipalities of residence, as well as coordinates, building type and identification codes for each residence.

The ambient dose estimates are based on an 8x8 km gridded map of outdoor natural background radiation from the Finnish Radiation and Nuclear Safety Authority. This map is based on the measurements from a mobile survey carried out between 1978–1980 in Finland (Arvela et al. 1995). The indoor dose rates were obtained with a conversion coefficient specific to the dwelling type and the individual time-weighted red bone marrow dose rate averages were calculated using age-specific indoor occupancy coefficients and the age and gender of the child (Arvela et al. 1995; Kendall et al. 2009; Mäkeläinen et al. 2005). Radiation from Chernobyl fallout was also modelled, though its contribution to the total dose estimates was small (~3%) (Nikkilä et al. 2016). The median dose rate to red bone marrow (Chernobyl and natural background radiation) was 67.2 nSv/h for cases and 66.4 nSv/h for controls.

Based on previous studies, Nikkilä et al (2016) assumed a 2-year minimum latency period in their main analysis resulting in zero exposure for subjects younger than 2 years at the reference date (in utero exposure was ignored) (UNSCEAR, 2008; Shu et al. 2002). The odds ratio (OR) of childhood leukaemia was calculated for every 10 nSv/h increase in time-weighted average indoor gamma-ray dose-rate over the period from birth to the reference date. For the present work other measures of exposure were investigated as described in the Results section.

Statistical analyses were done using R (3.4.0) and conditional logistic regression was used for matched case-control data. The ethical committee of Pirkanmaa Hospital district reviewed the study protocol (tracking number R14074). According to Finnish regulations, no informed consent was required for a register-based study.

3 Results

Table 1 shows the number of dwellings occupied by cases and by controls in the Finnish study (Nikkilä et al., 2016). These numbers take into account the two-year latency period, so that subjects aged less than 2 years at their reference date (156 cases and 468 controls) were excluded, leaving 937 cases and 2811 controls for analysis. About 48% of both cases and controls had lived at only one address between birth and the reference date. Five percent of both cases and controls had lived in five or more dwellings during the exposure period. The mean number of addresses occupied between birth and the reference date was approximately 1.9 for both cases and controls. In total, there were 63 (0.8%) residencies abroad. The percentage of cases who moved during the two-year latency period preceding the reference date was 26.0% and 26.2% for controls.

Table 2 shows the separation (km) and mean difference in dose rate for different pairs of addresses for cases and controls separately. The first of these is equivalent to the separation of two randomly chosen dwellings in our Finnish dataset; the median is similar to the mean for cases and controls (cases: 233 km vs. 267 km, controls: 230 km vs. 264 km). Successive homes of the same family are, on average, much closer

together, with a median separation of only 3.4 km (cases: 3.6km, controls: 3.3km). The mean distance between successive dwellings of the same family is an order of magnitude larger than the median, because of the influence of relatively uncommon long-distance moves (i.e. the distribution is highly skewed). The separation of the first and last dwellings occupied by a family is a little larger than the separation of successive homes, but broadly similar. The dose rates varied as might be expected, with successive dwellings of the same family having the lowest changes in dose rate.

The Pearson correlation coefficients with their 95% confidence intervals for four selected pairs of dose-rate variables (“scenarios”) are presented in the Table 3. For all scenarios, the indoor and outdoor dose rates for all study subjects were analysed separately. The correlation coefficient between indoor gamma dose rates for two successive dwellings occupied by study subjects was 0.62 (95% CI 0.60, 0.64). The correlation between the dose rates at the first and the last dwelling occupied by the study subjects was 0.67 (95% CI 0.65, 0.70). The correlation between the indoor dose rate averaged over all the subject's dwellings and the dose rate inside the first dwelling was 0.78 (95% CI 0.76, 0.80). The respective values of these correlation coefficients for outdoor dose rates were higher. The Pearson correlation between the separation and difference in the indoor effective dose rate for pairs of successive dwellings was quite low (0.32, 95% CI 0.29, 0.35). In all these analyses, results for cases were similar to those for controls.

Nikkilä et al (2016) reported that the odds ratio of childhood leukaemia for every 10 nSv/h increase in dose rate based on the time-weighted average indoor gamma-ray dose rate over all residences in the time window was 1.01 (95% CI 0.97, 1.05). The

corresponding OR, based on the dose rate in only the first and the last dwelling, are 1.02 (95% CI 0.99, 1.05) and 1.00 (95% CI 0.98, 1.03), respectively, for every 10 nSv/h increase. When the subgroup of subjects with only one residence in their history (488 cases and 1458 controls) was analysed, we observed an OR of 1.05 (95% CI 0.98, 1.11) for every 10 nSv/h increase. When we modelled the indoor dose rates naively as the outdoor dose rates, neglecting the effects of the dwelling type, we observed an OR of 1.04 (95% CI 1.00, 1.08) for every 10 nSv/h increase using the full residential histories.

When the cumulative RBM dose is considered, with full residential histories an OR of 0.97 (95% CI 0.89, 1.06) per 1 mSv was previously reported (Nikkilä et al. 2016). In analyses considering only the first and only the last dwelling the ORs per 1 mSv were respectively: 1.04 (95% CI 0.99, 1.10) and 1.00 (95% CI 0.95, 1.06). For the subset of subjects with only one dwelling in their history we observed OR of 1.20 (95% CI 0.94, 1.52) and if the analysis is completed based on outdoor dose rates with full residential histories an OR of 0.98 (95% CI 0.90, 1.08) was observed. The results based on average dose rate and cumulative RBM dose with a two-year latency period are presented in Figure 1.

When the more mobile subjects, with at least two dwellings in their residential history (425 cases and 1304 controls), were analysed separately we observed an OR of 0.97 (95% CI 0.90, 1.05) for every 10nSv/h increase. To explore the effect of our chosen latency period, we calculated odds ratios for cumulative RBM for no latency period and for a latency period of five years (Supplementary table 1).

4 Discussion

Residential mobility, that is the movement of study subjects from one residential address to another, is a challenge for epidemiological studies, where exposure to the agent of interest depends on place of residence. The data of the Finnish study (Nikkilä et al., 2016) demonstrate that, in their study subjects, about half the children diagnosed with leukaemia had not moved from the birth address by the time of diagnosis. Those who had moved generally had not moved far; the median separation of successive dwellings being 3.4 km.

A recent paper (Kendall et al., 2015) examined residential mobility in a case-control study, in which addresses were available for both the residence at birth and the residence at diagnosis of cases. Kendall et al reported that 44% of all cases of childhood cancer had not moved by the time of diagnosis. For leukaemias, the figure was 45%. Those who had moved to a new house did not, on average, move far: median distance 3.1 km for both childhood leukaemia and all childhood cancers. In consequence, the estimated indoor gamma ray dose rates in the house at birth were strongly correlated with those in the house at diagnosis. These results are consistent with those from the Finnish data.

In a recent nationwide study on childhood cancer and background radiation in Switzerland (Spycher et al., 2015), residential locations were available for all children at the time of national censuses. In analyses using cumulative doses since birth, the hazard ratio for childhood leukaemia was higher in a sub-cohort with stable place of residence for at least 5 years before census (excess relative risk per mSv: 4.6%, 95%

CI: -0.1% to 9.6%) compared to the full cohort (3.6%, -0.3% to 7.7%), in which mobility was more common. For cases, full residential histories were available from the national childhood cancer registry. These data show that 34% of leukaemia cases moved house at least once between birth and diagnosis (Kreis et al., 2016), somewhat fewer than in the present study.

Demoury et al (2017) note that in the ESCALE interview-based study of childhood cancers and leukaemia in France, 66% of the children had been living in the same municipality (Commune) since birth. The correlations between exposure estimates at birth and at diagnosis (cases) or inclusion (controls) were 0.86 for radon exposure and 0.89 for gamma radiation exposure. A Danish study by Raaschou-Nielsen et al (2008) reported that in their data 58% of the families had lived in a single-family dwelling throughout their childhood.

In their published paper, Nikkilä et al (2016) chose as their principal exposure measure the indoor gamma-ray dose rate averaged over all dwellings. Here, the effect of not having complete residential histories is explored by using several other exposure indicators (based on only first dwelling, only last dwelling, subgroup of subjects with only one dwelling and dose-rate estimated neglecting the dwelling type). The confidence intervals of the ORs overlap markedly with results for the average dose rate, though the central estimates ranged from 1.00 to 1.05, while the published result was 1.01. A similar picture is seen for results based on cumulative dose for which the point estimates were more dispersed: from 0.97 to 1.20. The sensitivity analyses with differing length latency periods reflected the previously reported results

– in our material, the age of the subject appears to be an effect modifier (higher ORs were observed for younger children).

Patterns of migration may vary from country to country and from time to time.

Further, exposure difference between successive homes may depend on the size of the country and spatial variation of dose rates. Childhood leukaemia peaks at a younger age than most other paediatric cancers and therefore residential histories are likely to be somewhat shorter and involve fewer residencies (although Kendall et al (2015) reported that such differences were not great). Hence, there will always be uncertainties in extrapolating from one set of circumstances to others.

Interestingly, it has been hypothesized that a particular migration pattern characterised by rapid population influx into isolated rural areas might play a role in the aetiology of childhood leukaemia (Kinlen et al., 2012). Hence, in such specific instances, moving might not only induce exposure measurement error, but also confounding. Thus, having complete residential histories might enhance control of confounding besides producing more accurate estimates of exposure.

Considerable uncertainty remains about the most important time window for leukaemogenesis in childhood. If study subjects move house between birth and the start of the latency period then adequate residential histories are needed to establish the precise mean dose rate or integrated dose over this exposure period. However, if susceptibility varies with age, such time-weighted averages based on subjects' whole residential histories are not necessarily the most relevant. Different weights should perhaps be given to the birth address for example (ICRP: International Commission

on Radiological Protection, 2003; National Research Council (NRC), 2006; UNSCEAR, 2013). If latency plays an important role, modelling exposure by the dwelling at diagnosis is not optimal. That is because a proportion (in our dataset a fourth, assuming two-year latency) of study subjects will have moved during their latency period. For these subjects, there would be no relevant information available about their exposure during the (presumed) etiologically relevant time window. Of course, with full residential histories it is theoretically possible to explore sensitivity during different time windows using the data themselves. However, this would require a larger study with greatly increased statistical power.

The ORs observed in the present study were somewhat higher for cases who had lived in only a single dwelling in history compared to those with two or more. This reflects the previously reported difference in leukaemia risk by age group as the mean number of dwellings increases with age.

With dose metrics averaged over the exposure periods of subjects, such as the average dose rate, regression towards mean with an increasing number of dwellings in history will occur, and it is likely to decrease variation between subjects and hence diminish exposure contrast and dilute the extremes. The extent of regression toward mean depends correlation between successive dwellings which was found to be high.

How much will exposures in successive dwellings vary? Clearly this depends on the agent in question. However, for natural gamma rays there is good evidence that dose rates in adjacent locations tend to be similar. In consequence, indoor gamma-ray doses in successive dwellings are highly correlated. This is supported by the present

study and by Kendall et al (2015) who reported, for Great Britain, a correlation in estimated indoor gamma rate between birth and diagnosis locations of 0.48 for cases who had moved County District and of 0.90 for all cases (Kendall et al., 2015). However, the reasons for this correlation may be complex; the data of Table 3 suggest that it is not just a proximity effect as the correlation between separation and difference in effective indoor dose rate was not as high as was expected.

So far as other exposures are concerned, our results should be generalised only with caution. It will remain true that successive family dwellings will tend to be close together. It is plausible that exposures to many agents of interest will therefore tend to be similar, but this judgement must be made on a case-by-case basis.

Summary

Knowledge of full residential histories would always be the option of choice. If dose estimates are constructed for the full exposure periods, having full residential histories results in less exposure misclassification. However, there is considerable evidence that families with young children who move house generally do not move far. In consequence exposures to indoor gamma rays (and possibly to other agents) in successive homes are correlated. Given this strong correlation between exposure estimates in successive dwellings and the uncertainty about the most relevant exposure period, estimation of overall exposure level from a single address, in particular that at birth, will also be informative. It remains true that comparisons of results across studies using different time points of exposure (e.g. birth and diagnosis) could indicate periods of increased susceptibility provided that the studies have adequate power. As noted in the introduction there is often substantial random

variation between practical dose estimates from modelling and the (unknown) true residential doses. Thus, there is likely to be a degree of classical measurement error in the dose estimates, which will bias risk estimates towards the null.

Acknowledgements

We thank Hannu Arvela for his contributions in collecting the Finnish background radiation data and helping with the dose estimation. We are grateful to John Harrison and Richard Wakeford for helpful discussions.

Table 1: Number of dwellings occupied by study subjects

	1	2	3	4	5	≥ 6	Total	max
Controls	1459 (52%)	721 (26%)	342 (12%)	150 (5%)	72 (3%)	67 (2%)	2811	11
Cases	488 (52%)	257 (27%)	103 (11%)	44 (5%)	25 (3%)	20 (2%)	937	16

Note that account has been taken of a two year latency period in these figures

Note that the data of table 1 are reproduced by permission from the International Journal of Cancer

Table 2: Mean separation (km) and mean absolute difference in dose rate (nSv/h) between two random addresses and between addresses for the same family for cases and controls

	Median	Mean	Q1	Q3	Max
Any two addresses [†]					
Separation (km)					
<i>Cases</i>	233	267	135	371	1144
<i>Controls</i>	230	264	133	370	1179
Absolute difference in dose rate (nSv/h)					
<i>Cases</i>	14.5	17.2	6.2	25.5	102
<i>Controls</i>	14.4	17.4	6.1	26.0	102
Successive addresses					
Separation (km)					
<i>Cases</i>	3.6	36.0	1.0	12.1	792
<i>Controls</i>	3.3	29.9	0.9	13.6	760
Absolute difference in dose rate (nSv/h)					
<i>Cases</i>	2.4	8.7	0	16.5	96.1
<i>Controls</i>	3.3	9.2	0	17.7	78.7
First and last address					
Separation (km)					
<i>Cases</i>	4.3	37.2	1.16	15.0	713
<i>Controls</i>	4.2	33.3	1.19	16.3	760
Absolute difference in dose rate (nSv/h)					
<i>Cases</i>	4.7	8.9	0	17.0	39.7
<i>Controls</i>	3.8	9.0	0	17.4	74.5
Difference in dose rate (nSv/h) [‡]					
<i>Cases</i>	-0.1	-4.6	-14.5	0	39.5
<i>Controls</i>	-0.1	-5.1	-15.3	0	47.1

[†] All pairs of addresses in the dataset, not necessarily from the same subject

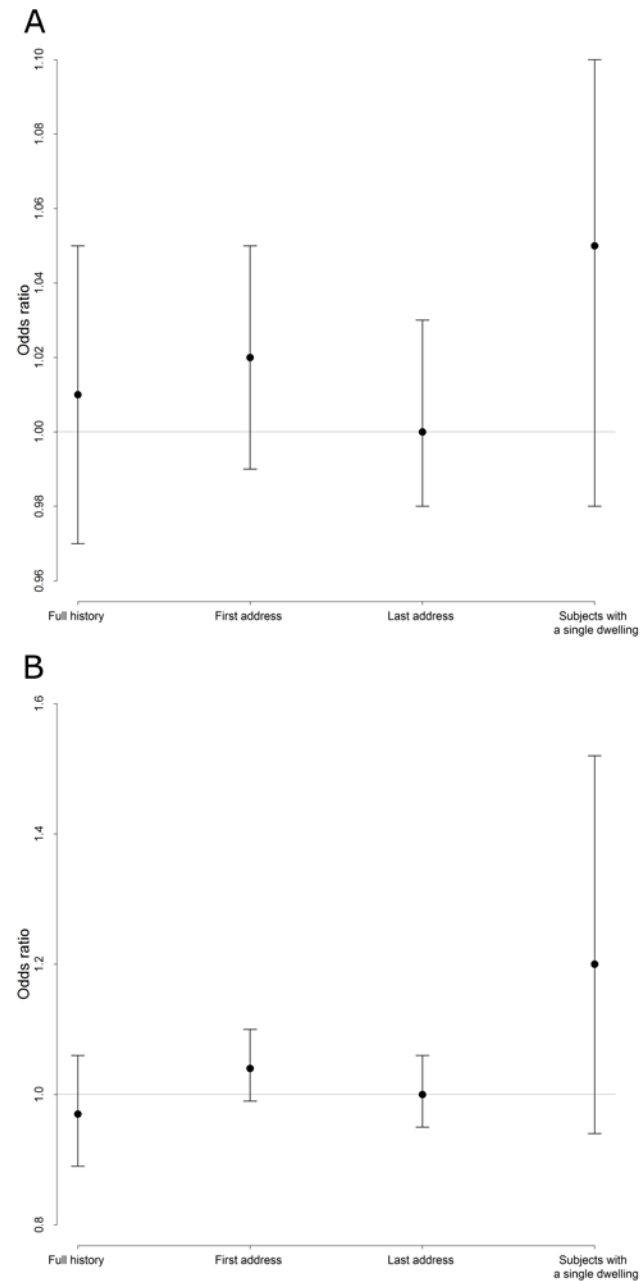
[‡] The difference is calculated by subtracting the dose rate in the last dwelling from the dose rate in the first dwelling

Table 3: Pearson correlation coefficients with 95 % confidence intervals between various In- and Outdoor gamma-ray dose rate quantities

	<i>Indoors</i>		<i>Outdoors</i>	
	<i>r</i>	<i>95% CI</i>	<i>r</i>	<i>95% CI</i>
Dose rates in successive dwellings				
<i>Cases</i>	0.59	0.55-0.64	0.85	0.83-0.87
<i>Controls</i>	0.64	0.62-0.67	0.89	0.88-0.89
Dose rates in first and last dwelling [†]				
<i>Cases</i>	0.67	0.61-0.71	0.91	0.89-0.92
<i>Controls</i>	0.67	0.64-0.70	0.88	0.87-0.89
Dose rate in first vs mean for all dwellings				
<i>Cases</i>	0.77	0.73-0.81	0.99	0.98-0.99
<i>Controls</i>	0.78	0.76-0.80	0.98	0.98-0.98
Change in dose rate vs separation of successive dwellings				
<i>Cases</i>	0.31	0.24-0.37	0.68	0.63-0.71
<i>Controls</i>	0.22	0.18-0.26	0.60	0.58-0.63

[†] If only subjects with three or more dwellings are included, the correlation for indoor values lower for cases (0.54, (0.43, 0.63)) than for controls (0.63 (0.58, 0.68)).

Fig 1: Odds ratios for 10 nSv/h increase in average red bone marrow dose rate (A) and for 1mSv increase in cumulative red bone marrow dose (B) for childhood leukaemia and terrestrial background radiation (width: 1 column)



Different scenarios were chosen to approximate exposure assessment based on residential histories

Full history: Full residential histories

First address: Only first dwelling was included

Last address: Only last dwelling was included

Subjects with a single dwelling: Only subjects with one residence in their history were included

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