Radon exposure and socioeconomic status in relation to childhood leukemia and cancer in the central nervous system.

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Preface and acknowledgements

After several years of working as health monitoring adviser at the Agency for Health in the City of Oslo I found it very inspiring to have the opportunity to work with the present project. Oslo city has through regulations on environmental health the responsibility to promote public health, contribute to good environmental conditions, and to secure the population against environmental factors, including biological, chemical, physical and social, that can have a negative impact on health. This study has been carried out at The University of Oslo in the period 2011-2015 in part time. The project was funded by the Agency for Health in the City of Oslo.

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When working with public health topics for the City of Oslo, I got the idea to study radon and the possible association with childhood cancer. I was responsible for design, analysis and interpretation of the results and writing of the three papers included in this thesis.

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Abstract

This thesis is investigating if the risk of childhood leukemia and cancer in the central nervous system (CNS) increases in relation to high levels of indoor radon concentrations at home or low parental socioeconomic status. For assigning indoor radon exposure in dwellings lacking on-site measurements, we developed a new buffer model based on the distance to the nearest measured houses.

All 712,674 children born alive in the Oslo region in the period 1967-2009 identified from The Norwegian Population Register were included. Through geographical information systems the residence of every child was geo-coded and assigned a radon exposure value for each household. The model was based on 41,515 indoor radon measurements. We had on-site indoor radon measurements for only for 6% of the residences in the study region and therefore, we used a buffer model with different radius sizes to estimate radon exposure to the rest of the cohort. The model was validated against two datasets, the indoor radon measurements available in the study, and results from a regression model constructed with radiometric data and bedrock geology.

We took into account residential history for every child. Exposure was estimated for each year from birth to whatever came first: the age of 15 years, the date of diagnosis of leukaemia or cancer in the CNS, emigration, death or the end of the follow-up period in 2009. A total of 437 children got leukaemia and 427 got cancer in the CNS.

From The Medical Birth Register of Norway, we obtained several risk factors associated in earlier studies with the risk of childhood cancer, date of birth, sex, birth weight, gestational age and congenital malformations. For the mother, we had year of birth, parity, and complications during pregnancy, including haemorrhage and hypertensive conditions. Parents’ highest educational level and annual family income data were obtained from Statistics Norway.

Family income was categorized into quartiles and grouped into three categories, below the official poverty line (OECD-50 limit, medium income, and high income. We included information on marital status and others birth characteristics. Parents’ educational level was categorized in three subgroups, less than 10 years, 10-12 years and 13 or more years.
We used radon mean concentrations to analyze the radon exposure for each child at different points in times, during the first year of life, between birth and four years of age and in the whole study period (0-15 years).

**Results**

We found a reasonable good agreement between radon values from buffers compared to radon values from a regression model constructed with radiometric data. The level of agreement varied between 0.54 and 0.67. Comparing estimates from the buffer method with indoor radon values from measured houses had a level of agreement between 0.63 and 0.68. (Paper I).

No association was observed between radon exposures at home and the risk for leukemia (HR=1.00, 95% CI=0.87–1.15) or cancer in the CNS (HR=1.13, 95% CI=1.00–1.28) (Paper II).

An elevated risk of lymphoid leukemia among children in the lowest income category during the first two years of life was observed (OR=1.72, 95% CI=1.11-2.64). For cancer in the CNS we found no increased risk related to family income (Paper III).

**Conclusions**

The buffer method of estimating indoor radon exposure is suitable for use in epidemiological studies.

No association between radon exposure at home and the risk for leukemia or cancer in the CNS among children younger than 15 years of age living in the Oslo area was observed.

Being born into a household of low family income the first two years of life might be a risk factor for lymphoid leukemia.
List of papers

This thesis is based on the following papers, referred to in the text by Roman numerals:

Paper I

Paper II

Paper III

Ethics
The project was approved by The Norwegian Data Protection Authority and The Regional Committee for Medical and Health Research Ethics and followed The Helsinki Declaration.
Aims

The aim of the studies was to describe and test these hypotheses:

1) To investigate if it is possible to assess radon occurrence in all homes in the Oslo region where children under 16 years were living during the period 1967 to 2009.

2) To investigate if exposures to indoor radon increases the risk of leukemia and cancer in the central nervous system among children (0-15 years) in the Oslo region.

3) To investigate if low socioeconomic status, measured as family income and parents’ educational level increases the risk of leukemia and cancer in the central nervous system among children (0-15 years) in the Oslo region.
1. Introduction

Worldwide, the yearly number of children being diagnosed with cancer before the age of 15 exceeds 175,300.\(^1\) Since the 1970’s the overall incidence of childhood cancer has been increasing over time in all ages with an increase of 1-1.5% per year; notable for carcinomas, lymphomas, and germ-cell tumours. Norway is one of the countries with the highest incidence of childhood cancer in the world with an incidence of 167.6 per million.\(^2\)\(^3\) The highest incidence for both leukemia and cancer in the central nervous system (CNS) is found in the Oslo region.\(^4\)

Leukemia constitute approximately one-third of cancers in children (age 0–14 years) and 10% in adolescents (age 15–19 years). In Europe during 1988–1997, the overall incidence rate of leukemia in children was 44 per million person-years. Lymphoid leukemia accounted for 81%, acute non-lymphocytic leukemia for 15%, chronic myeloid leukemia for 1.5% and unspecified leukemia for 1.3% of cases.\(^5\) In the same period overall age-standardized incidence rate of CNS tumours in Europe was 29.9 per million, with the highest rates in the North of Europe. Astrocytoma, primitive neuroectodermal tumours and ependymoma were the most frequent types.\(^6\)

Some observed geographical differences or temporal changes in incidence rates found in the European studies may have been influenced by diagnostic improvements, which besides incrementing the number of diagnosed cases contributed to the improvement of classification of CNS tumours. Moreover, the development of the system of care provision through regional or national pediatric haematological networks, and also variations in risk factors may have contributed to the increased incidences.

1.1 Background

The process that leads to the onset of a childhood leukemia is likely to involve both genetic predisposition and one or more environmental exposures. Overall, there is a wide body of literature regarding environmental risk factors for childhood leukemia and cancer in the CNS. However, apart from a few notable exceptions, there are few risk factors where exposure to which either increase the risk greatly or can account for a sizeable number of cases. An
alternative explanation for the limited associations is the belief of some cancer investigators that most paediatric tumors reflect the inherent risk associated with the complex process of normal development rather than a response to an external toxic insult.\(^7,8\)

Several environmental factors have been investigated with regard to childhood leukemia and cancer in the CNS. They include ionizing radiation, electromagnetic fields, chemical exposures (solvents, benzene and other hydrocarbons, pesticides) parental smoking, parental alcohol consumption, diet and vitamin supplementation, iron or folate supplementation, medications, infections, breast feeding, birth weight and allergies.

The risk of developing childhood leukemia has been shown to be significantly higher among children of older mothers, especially mothers above 35 years.\(^9,10\) The child's sex, birth weight and congenital malformations are well known risk factors for both leukemia and cancer in the CNS. Boys have higher cancer incidence compared with girls.\(^11\) Several studies have found that heavy new-born babies have higher risk for developing leukemia and cancer in the CNS.\(^12,13\) Children with congenital malformations have higher risk for developing both leukemia and cancer in the CNS.\(^14\) Children with Down syndrome have a 10- to 20- fold increased risk of the disease.\(^15\) Maternal birth history, complications during pregnancy, including, haemorrhage and hypertensive conditions are also factors that may increase the development of cancer in children.\(^16,17,18,19\) Exposure to radiation from medical diagnostic use are also linked to the risk of childhood cancer.\(^20\)

Since we do not know the aetiology of childhood cancer, earlier studies have studied parental exposures to environmental factors and carcinogenesis in different periods of the child’s development, including parental exposures in utero and early life. Several authors have considered the importance of critical periods of vulnerability in the developing organism.\(^21\) Cancer in children may be caused by genetics and environmental exposures. However, because epidemiological studies are not conducted in laboratories, specific questions about critical time windows in relation to childhood cancer are not easily answered. Studies with exposures at different times of the child’s life may help to identify periods of more vulnerability. In our study we explore the effect of childhood poverty in the first two years of life and the risk of developing cancer in the later ages. Most case control and cohort studies have concentrated on single risk factors. If the process that leads to the onset of leukemia or cancer in the CNS involves a number of environmental factors then such studies are less
likely to discover to increased risk. The risk conferred by a single factor so far appears to be small. This is one of the reasons that future studies should include exposure to a number of potential environmental risk factors together.

1.2 The role of socioeconomic status and childhood cancer

Parental SES may impact both parents’ own health and the health of their children. Assessing SES as a risk factor for childhood cancer is of public health importance, and may increase the understanding of the etiology of the disease. In epidemiological studies, SES has usually been measured by three different indicators, taken either separately or in combination, educational attainment, income, and occupational status.

**Parental education** includes the acquisition of knowledge and skills among parents that promote health such as the adoption of healthier behaviors. Parents with more schooling smoke less, drink less alcohol, exercise more and work less often in dangerous occupations. They also adhere more carefully to prescribed medical therapies and are more likely to use newer medical technologies to address health problems. These tendencies may be caused by education, or they may indicate that people who plan for the future better tend both to pursue more schooling and to behave in healthier ways. In other words, they treat health inputs that impact their children, like cigarettes and alcohol, differently than do less educated mothers.

Mothers may be more involved in the day-to-day decisions on general hygiene and nutritional intake of a child than the fathers. Another way through which maternal education may act on child health is through increasing the probability of maternal labour force participation. This relationship is complex because on the one hand a child may suffer through lack of attention (in the case of infants this may mean they forgo the benefits of breast feeding for example) while on the other hand, participating in the labour force may increase the family income and lead mothers to gain external information on healthy practices enhancing their propensity to use preventive and curative medicines and treat childhood illnesses.

The causal mechanisms underlying the relationship between **parental income** and child’s health may be linked to the ability to access material goods and services necessary for the maintenance of themselves and child’s health. In the same way wealthier parents may be better able to provide safer environments for their children. Size of income influences
freedom of choice concerning food and leisure activities. A study from the Nordics country shows that there is a social inequality in obesity with higher prevalence in groups of the lowest socioeconomic position.\textsuperscript{25} They point out that in the Nordic region as well as in other countries in the Western world, access to healthy food is limited for those with low income. Food with high energy density has become cheaper and thus easily available for people with low assets, making food with low energy density relatively more expensive.

Children’ health may also be affected by the health status of their parents, possibly through an inherited susceptibility to different diseases, a less healthy uterine environment or lower quality care by sick parents. In addition, the health of parents and children might be affected by common but unmeasured environmental factors, resulting in a correlation between their health levels.\textsuperscript{26} Poorer parents may also smoke to buffer themselves from poverty-related stress and depression.

Other measures of SES such as occupational class have also been linked to several cancer subtypes in children. Exposure of the mother may be relevant during the intrauterine period. There is also the possibility that paternal exposure to certain chemicals or radiation could cause genetic changes in the sperm, which could predispose a child to cancer.\textsuperscript{27}

### 1.3 Ionizing radiation and childhood cancer

It is has not been possible to provide a definite answer to if low radiation coming from indoor radon exposures are a risk factor for childhood leukemia and cancer in the CNS. Leukemia was the first malignant disease recognized to be in excess among the Japanese survivors of the atomic-bomb explosions over Hiroshima and Nagasaki in 1945. However, the results could not support differences in leukemia incidence in the youngest group (0-14).\textsuperscript{28} Richardson et al, 2009\textsuperscript{29} in a later study examined leukemia mortality. Their results demonstrated variation of excess relative risk with age at exposure, with the risk being notably higher at younger ages at exposure. It have also been suggested that populations whose parents were exposed to substantial amounts of radiation before conception may have a higher risk to developing cancer than those not exposed. Nevertheless, these findings have no support in recent studies.\textsuperscript{30} Actually there is consensus that cancer risk increases after exposure to moderate and high doses of radiation. However, whether cancer risk is increased by acute low doses rates are unclear.\textsuperscript{31} \textsuperscript{32}
Moderate doses of radiation can produce catastrophic effects on the developing embryo and fetus. The effects depend on the stage of gestation and the dose. Radiation on the developing embryo and fetus may also cause congenital malformations; growth retardation; and functional impairment, such as mental retardation.

1.3.1 The latent period
The time interval between irradiation and the appearance of malignancy is known as the latent period. Leukemia has a short latent period. Excess cases began to appear in the survivors of Hiroshima and Nagasaki a few years after irradiation and reached a peak by 5 to 7 years; most cases occurred in the first 15 years. Solid tumors show a longer latency than the leukemia, in the order of anything from 10 to 60 years or more. Although the studies of the Japanese atomic-bomb survivors give detailed information on radiation risks, they cannot generate direct information on all aspects of radiation-induced risks since the bomb survivors received mainly doses of external radiation, and some of the dose estimates remain uncertain due to retrospective calculation. Further, data for the period before October 1950 were not collected systematically, making it difficult to determine the minimum latent period for leukemia. The age at which exposure occurs appears to be relevant, the lower the age at the time of exposure, the higher the lifetime risk. For leukemia, the exposure of the lymphatic system, and in particular the red bone marrow, is assumed to be especially relevant. The exposure quantity is therefore usually established to be the equivalent dose to the red bone marrow. The contribution of the inhalation of radon and radon decay products to bone marrow dose is quite uncertain. Thus, the present study aims to contribute to the understanding of the possible association between radon exposure and the risk of childhood cancer among children, focusing on leukemia and cancer in the CNS.

1.3.2 Radon
Natural radiation is the main source of human exposure to ionizing radiation, and the largest component of the effective dose comes from inhalation of radon (Rn-222) and its daughters (Rn-219, Rn-220 and Rn-222). Radon-222 is a naturally radioactive gas resulting from the decay of uranium-238. It is the most common naturally occurring uranium isotope. Uranium is found in small quantities in all soils and rocks, but the concentration varies. Rn-222 is formed when radium-226 dissolves in accordance with the uranium-238 series. Rn-220 is
formed when radium-224 decays according to the thorium-232 series. Therefore, in areas where there is uranium or thorium, is it likely to be airborne radon or thoron in air. If there is insufficient ventilation in a dwelling, the concentration of radon and their daughters in the dwelling will increase. Rn-222 has a half-life of 3.82 days, and provides about 50% of the total radiation dose for an average person in Europe.\(^{34}\)

Permeability in the ground is also an important factor for the occurrence of radon in the air. Areas of high permeability are therefore radon exposed,\(^{35}\) while areas with low permeability, such as clay, may have lower radon exposure even if the bedrock below contains uranium.\(^{36}\)

Measurements of gamma radiation from airplanes and helicopters make it possible to map the near-surface concentration of the isotopes 232-thorium, uranium-238 and potassium-40, which are responsible for most of the naturally occurring radioactivity.

Indoor radon concentrations vary and might be influenced by several factors, including the properties of the underlying geology, the permeability of the soil, building materials and residents’ lifestyles.\(^{37,38}\) Several authors point out geology as a useful, but not sufficient indicator for estimating radon in buildings.\(^{39,40,41}\) Indoor radon concentrations are extremely variable, even for houses in identical geological areas. There might also be some uncertainty arising from the use of geological maps regarding the coordinates of geological boundaries. Geological conditions such as rocks containing high levels of uranium and high permeability of soils and rocks for gases are some of the main parameters for radon risk classification of buildings. Even areas with low radon concentration in the soil can cause significant indoor radon concentrations in cases of high permeability in the contact area between the building and the soil environment.\(^{42}\) Radon exposure can occur from some building materials if they are made of radon-containing substances, such as concrete. In most cases these levels are very low. In Norway, geology, ventilation systems, ventilation habits and floor materials are found to have the strongest correlation with indoor radon levels.\(^{35}\) Building materials are less important because of a large percentage of the homes in Norway are built of wood. Radon levels generally decrease with height of the building, and the possibility to find high radon levels are therefore less probable at higher floors.

Norway has some of the highest concentrations of indoor radon in the world because of geologic conditions.\(^{43,44}\) A representative survey shows that Norwegian homes have an
average radon concentration of 88 Bq/m³, and that 27% of the population is exposed to levels higher than 100 Bq/m³. On a national basis, the bulk of high radon values are in the areas around Oslo. This includes both average concentrations and proportion of homes with elevated concentrations. In accordance with international recommendations measures in Norwegian homes are recommended if the annual mean concentration in living rooms exceeds 100 Bq/m³. The Norwegian authorities have set 200 Bq/m³ as a maximum limit in a residence. The term maximum limit is defined as the threshold which Norwegian authorities consider that all residential buildings should satisfy. If the radon concentration exceeds the national upper recommended reference level, remedial measures like increasing ventilation in the building should be taken to reduce radon levels, preferably to a level below 100 Bq/m³.

1.4 Studies on radon exposure and childhood cancer
A recent meta-analysis summarized data from ecological and case-control studies on radon exposure and childhood leukemia. Since 1987 eight case-control studies regarding childhood cancer, in particular leukemia and radon exposure have been reported. Studies from USA/Canada, Germany, Japan and UK found no association with childhood leukemia. Contrary to this, studies from Egypt and Denmark found an association with childhood leukemia. An even more recent cohort study did not find association between radon exposure and leukemia and CNS cancers.

The next section describes some strength and limitations in nine of the most recent studies regarding childhood cancer and radon and studies where radon exposure is measured at home:

Case-control study of childhood acute lymphoblastic leukemia and residential radon exposure. This is a case-control study including 505 leukemia cases children younger than 15 years. Radon detectors were placed in current and previous homes of children where they resided for 6 months or longer. Children were included in the analyses if radon measurements covered 70% or more of the 5-year period prior to diagnosis for case subjects (or from birth for case subjects under age 5 years) and the corresponding reference dates for control subjects. Mean radon concentration was 65.4 Bq/m³ for cases and 79.1 Bq/m³ for controls.
As covariates were included age at the time of diagnosis, total household income, birth order, birth weight, sex, type of residence, and the time weighted average magnetic field measurement. One of the limitations reported in the study was missing radon exposure data for the subjects. The participation rate was of 79%.

Results of the study found no association between acute lymphoblastic leukemia and residential radon.

*Indoor residential radon exposure and risk of childhood acute myeloid leukemia.*

This was an interview-based case–control study including children younger than 18 years from USA and Canada. The study included 173 cases of acute myeloid leukemia and 254 controls.

Two alpha-track radon detectors were used in the residence of the child at the time of the diagnosis. One criterion was that the child lived in the residence a minimum of five years prior to the cancer diagnosis. Detectors were placed for a period of one year. One detector was located in the child’s bedroom, and the other in a room on which the child spent more time during the day. The arithmetic mean of the time-weighted radon concentrations for cases and controls were 49.8 and 56.0 Bq/m$^3$ respectively.

The models were adjusted for maternal race, maternal education, family income and age of the child. Nineteen cases with Down’s syndrome were excluded from the study due to their higher risk of leukemia. Some limitations were pointed out in the study such as the small size of the study limiting the possibility for subanalysis. There was no available residential history making it difficult to calculate life time radon exposure. The participation rate was of 27%.

The study found no association between residential radon and risk of childhood acute myeloid leukemia.

*Childhood cancer and residential radon exposure - results of a population-based case-control study in Lower Saxony (Germany).*
This is a population-based case-control study. Cases were children younger than 15 years diagnosed with leukemia and common solid tumours (nephroblastoma, neuroblastoma, rhabdomyosarcoma and CNS tumours. A total of 82 leukaemia, 82 solid tumours and 209 controls were included.

Long-term (one year) radon measurements were performed in those homes where the children had been living for at least one year, with particular attention being paid to those rooms where they had stayed most of the time. One radon detector was placed in the child’s bedroom, the second one in another room and the third one in the basement. The mean radon concentrations were 26.4 Bq/m\(^3\) for leukemia patients, 33.1 Bq/m\(^3\) for tumour patients, and 28.5 Bq/m\(^3\) for controls.

The models were adjusted by age, gender, urbanization, cohabitants and socioeconomic level. The study had some limitations. The participation rate was 36%. The study had high probability of bias due to losses in radon measurements and due to selection of controls (selection bias).

The study found no evidence for an association between indoor radon and childhood leukemia or CNS tumours.

4) Maged et al, 2000

*Domestic radon concentration and childhood cancer study in Cairo, Egypt.*

This is a case-control study including 50 children younger than 15 years diagnosed with acute lymphoblastic leukemia and 110 controls.

Radon exposure was measured with radon detectors with an exposure time of three months. The study did not report use of residential history or adjustment for possible confounders. One criterion for inclusion in the study was that the children must be living in their houses in Cairo since they were born. A total of 500 cases of lymphoblastic leukemia were enrolled in the study. Only 50 out of 240 cases who met the eligibility criteria for selection agreed to participate. The participation rate was 10%.

The mean radon concentration was markedly higher for cancer cases than for controls.
The mean indoor radon concentration in the houses of patients was 75 Bq/m$^3$ while it was 55 Bq/m$^3$ in houses of controls.

The study found an association between acute lymphoblastic leukemia and radon exposure.

5) UK Childhood Cancer investigators, 2002

*The United Kingdom Childhood Cancer Study of exposure to domestic sources of ionising radiation: 1: radon gas.*

This national case-control study conducted in UK included 2226 cancer cases, 951 cases of leukemia and 404 tumours in the CNS. Indoor radon exposure was evaluated at the time of the diagnosis of cancer and for at least six months before. The participation rate was 52%. Socioeconomic status (SES) and some factors associated with indoor radon concentration such as window glazing and central heating was taken into account. Average radon concentration in this study was 24 Bq/m$^3$.

The study found no evidence of an association between indoor radon and the risk of any of the childhood cancers.


*Childhood leukemia in areas with different radon levels: a spatial and temporal analysis using GIS.*

This study is an ecological study conducted in Östergötland, Sweden, following up 53,146 children. 90 cancer cases were included in the analysis and the residential history was available. It is based on radon exposure from radon maps including geology. The authors also discuss that radon exposure in the living area may be a better measure of the average exposure of the child than just measurements at home.

The study found evidence that children born in and continuously living in areas classified as high and normal risk of background radiation from radon have higher incidence of acute lymphatic leukemia compared with low areas.


*Domestic radon and childhood cancer in Denmark.*
This case-control study included 2400 cancer cases, 1,153 cases were leukemia and 922 cases were cancer in the CNS. They used residential history and calculated cumulated radon exposure for each child. Birth order, mother’s age, traffic density and electromagnetic fields were adjusted for. The radon exposure was based on a mathematical model of radon exposure where the authors used 3,120 radon measurements to calculate exposure in 21,338 dwellings distributed throughout whole Denmark. The model included several predict variables such as house type, floor, basement, geology, geographic region, type of house and building materials. The model explained 40% overall of the variability of radon. Average indoor radon concentration in Denmark is 59 Bq/m³.

The study found an association between indoor radon exposure and the risk of acute lymphatic leukemia but not for other childhood cancers.

8) Kendal et al, 2013
_A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980-2006._

This is large population-based study including 36,793 cancer cases, 7,267 of these were lymphoid leukemia and 6,585 were CNS tumours. Doses of radon exposure to the red bone marrow were calculated. Radiation exposures were estimated for mother’s residence at the child’s birth from national databases, using the county district mean for gamma rays and a predictive model based on measurements of radon in 460,000 dwellings. The radon results were grouped first by geological boundaries, and then by one km grid squares. Results were adjusted for SES. The study was lacking information of residential histories. The arithmetic mean of radon concentration was 21.3 Bq/m³.

The study found no association between childhood leukemia or cancer in the CNS and indoor radon exposures.

9) Hauri et al, 2013
_Domestic radon exposure and risk of childhood cancer: a prospective census-based cohort study._

This is the first cohort study investigating indoor radon exposures and the risk of childhood cancer. It was conducted in Switzerland and including 1,332,944 children. In the study period a total of 997 children developed cancer, 283 cases of leukemia and 258 cases of cancer in the
CNS. Radon exposure in this study was estimated for each child’s home address using a nationwide radon prediction model for Switzerland based on 35,706 radon measurements. Relevant predictors in the model were tectonic units, building age, building type, soil texture, degree of urbanization, and floor level. The model explained 20% overall of the variability of radon. The authors report that random exposure misclassification was relatively high due to complexity of the geology and the tectonic categories used in the prediction model. In the study there was available data on residential history from a census in 2005. The study was lacking residential history for children in the cohort born before this year. The arithmetic mean of radon concentration for all cohort members was 77.7Bq/m³.

The study found no evidence of any association between indoor radon exposure and the risk of childhood cancer.

In summary, five case-control studies (Lubin et al, 1998; Kaletsch et al, 1999; Steinbuch et al, 1999; UK Childhood Cancer Study Investigators, 2002 and Kendall et al, 2013), and a cohort study (Hauri et al, 2013) found no association between radon exposure and the risk of childhood leukemia and cancer in the CNS.

In the studies of Lubin et al (1998), Kaletsch et al (1999), Steinbuch et al (1999) and UK Childhood Cancer Study Investigators (2002), the radon exposure was assessed through radon gas measurements in the dwelling environment. This allowed exposure to be reconstructed taking into the account the years and time spent by each child in the various rooms of the occupied dwellings. Even when analysis was restricted to children who had spent their whole lives in homes with on-site radon measurements, no significant association was observed in any of these studies.

Two of the three studies using radon prediction models and individual data (Kendall et al, 2013 and Hauri et al, 2013) found no association between radon exposure and the risk of leukemia and cancer in the CNS. Incorporating predictions models allow inclusion of more children, and thus, making the risk for selection bias less likely.
Radon mean concentrations varied across the studies. The lowest mean radon concentration was found in the UK, varying between 21.3 Bq/m³ and 24.0 Bq/m³ and the highest concentration was found in Lubin’s study, with a mean radon concentration of 79.1 Bq/m³.

Kohli et al., 2000; Raasschou-Nielsen et al., 2008 and Maged et al., 2000 found an association between childhood leukemia and radon exposure. The study of Kohli et al. is an ecological study in which data on radon exposure have been aggregated on the basis of geographic units and do not have information on exposure at individual level. Since ecological studies are subject to important methodological limitations, such as “ecological bias”, and since the other previous studies analyzed radon exposure at individual levels we will only focus on the studies of Raasschou-Nielsen et al., 2008 and Maged et al., 2000 in the discussion section.

1.5 Studies on socioeconomic status and childhood cancer

Poole and colleagues reviewed 74 studies of the relationship between childhood leukemia and SES. They found more positive associations in older studies and negative associations in newer ones. The authors pointed out that many of the studies involved incidences of cancer and area-based measures of SES. Other methodological limitations in early studies were participation bias, small effect size and the type SES measures used, such as type of income, social class, occupation, unemployment and education. Despite evidence of great variation in the family’s income level over time, most studies examined the effect of income only at one single point in time. Even in families who are consistently poor, income may fluctuate from year to year; thus static measures of the economic recourses available to children may be inadequate.

The systematic review by Poole concluded that the results of these studies were heterogeneous and varied by place, time, study design and measure of SES utilized. They concluded that validation studies are needed to estimate SES-related selection and participation in case–control studies. Because different socioeconomic measures (such as income and education) and individual-level and ecological level measures may represent different risk factors, they advised researchers to report these measures separately rather than in summary indices of social class. Some of these studies reviewed by Poole will be discussed further in the discussion section.
In the present study, we cover a study period of more than 40 years, therefore it is relevant to examine possible period effects. During this period several social and economical factors in Norway have changed including a higher level of education and a higher presentation of mothers in the labour force. This might have lead to changes in risk factor for childhood leukemia and cancer in the CNS such as exposure to infections and carcinogens, changes in diet and improved health care. Since the review by Poole et al. (2006) demonstrated variability in the association of childhood leukemia and SES over time it is necessary to take into account possible period effects in our study.
2. Material and methods

2.1 The study population

All children born alive in the period 1967-2009 in the counties of Oslo, Akershus, Vestfold and Østfold, together with the municipalities of Gran, Jevnaker, Lunner, Lillehammer, Gjøvik, Vestre Toten, Østre Toten, Søndre Land, Ringerike, Hole, Lier, Nedre Eiker, Røyken, Drammen and Hurum, which are situated in the geologic Oslo area (Figure 1) were followed up in connection with radon exposure and socioeconomic status from birth to date of diagnosis, death, end of the study in 2009, or moving out of the area covered by the study.

Figure 1. The study region

Cases were children 0-15 years of age who were diagnosed with leukaemia or cancer in the CNS (paper II and III) between 1 January 1967 and 31 December 2009 in the Cancer Register, classified according to the International Classification of Childhood Cancer, third edition (ICCC-3; Steliarova-Foucher et al, 2005). In Paper II we used the following ICD-10 codes: leukemia (C91-C95), cancer in the CNS (C70-72), acute lymphoblastic leukemia (C91) and brain cancer (C71). In Paper III we used several cancer subtypes and respective morphologic codes as shown in table 1.
Table 1. Subgroups of leukemia and cancer in the central nervous system and ICD-O-3 codes

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid leukemia</td>
<td>983539, 983536, 983639, 983735, 983739, 983636,</td>
</tr>
<tr>
<td></td>
<td>982039, 982636</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>986139, 987439, 984039, 986639, 986739, 987339,</td>
</tr>
<tr>
<td></td>
<td>989139, 989639, 991039</td>
</tr>
<tr>
<td>Ependymomas and choroid plexus tumor</td>
<td>939139, 939009, 939039, 939239, 938319, 939134</td>
</tr>
<tr>
<td>Astrocytomas</td>
<td>940039, 942119, 938039, 944039, 938419, 938031,</td>
</tr>
<tr>
<td></td>
<td>942111, 940029, 940031, 940033, 942031, 944031</td>
</tr>
<tr>
<td>Intracranial and intraspinal embryonal tumors</td>
<td>947039, 947339, 947139, 908009, 947034, 947334</td>
</tr>
<tr>
<td>Other specified intracranial and intraspinal neoplasms</td>
<td>935019, 945039, 950519, 941309, 938239, 943039,</td>
</tr>
<tr>
<td></td>
<td>950509, 950539, 950619, 827109, 935039, 936239,</td>
</tr>
<tr>
<td></td>
<td>945139, 953009</td>
</tr>
</tbody>
</table>

2.2 Demographic data
From The Medical Birth Register of Norway, we obtained date of birth, sex, birth weight, gestational age, congenital malformations and date of death. For the mother, we obtained year of birth, parity and complications during pregnancy, including haemorrhage and hypertensive conditions. Parent’s highest educational level, marital status and annual income were obtained from Statistics Norway, as well data on moving history between municipalities.

2.3 Estimating radon exposure
In paper I, we included all dwellings in the Oslo region to assess radon exposure to each child. We used data on radon measurements collected by The Norwegian Radiation Protection Authority as a result of several radon measurement campaigns in the Oslo region during the period 1998–2010. The programs were based on measurements of indoor radon concentrations in dwellings selected at random from the housing stock. The measurements were performed according to the recommendations from The Norwegian Radiation Protection Authority and The Working Group of the effort against radon in Norway. Radon concentrations in a home can vary over seasons, and it is recommended that measurements are carried out by film tracks for at least two months during the period from October to April. In this study 97.5% of the radon measurements were carried out between October and April; 82.6% were carried out during two months or more.

Data on airborne gamma ray spectrometry measurements, bedrock geology and drift geology used in this study was obtained from The Geological Survey of Norway.
Norwegian Mapping Authority we obtained numerical address for all homes in the municipalities covered by the study. The coordinates were obtained from maps at scale of 1:5000. The accuracy of the coordinates used in this study is within five meters of the buildings center point.

Data from registries used in this study was linked by using the 11-digit Norwegian personal identification number. Statistics Norway identified all women who had given birth in the period 1967-2009 and stayed at one of the addresses in the study area at Statistic Norway’s population censuses in 1970, 1980 or in the period 1986-2009. Through this code, the mother and child were also linked to the place of residence.

All homes in the municipalities were mapped using the Geographic Information Systems (GIS). For each numeric address we estimated the radon concentration. A file containing radon information on all addresses in the geographic area of the study was sent to Statistics Norway. It was linked to The Medical Birth Register of Norway, The Cancer Registry of Norway and Statistics Norway’s population censuses and residential history. We got a de-identified file from Statistics Norway with all data for our analysis.

Residential history. We had accurate information on numerical addresses at 1th of January 1970, 1980 and each year from 1987 to 2009. Moving history between municipalities was available from 1 January 1981. Between 1984 and 1986, all children in the cohort were regarded as living in the same place as in January 1987, and between 1975 and 1983 at the same address as in January 1980. For children in the cohort between 1967 and 1974 residential areas from the census in 1970 were used. Children born before 1987 had at least information on two addresses in the follow-up period. For children with missing information on radon exposure in some of the years of the follow up period, and in the absence of information regarding moving to another municipality, the time-weighted average concentration for the part of the childhood period with known radon concentration was used as a best estimate. If the child moved out of the study area, it was given the known radon concentration of the years the child lived in the study area.

Radon exposure assessment. Radon exposures were assigned to each residential address in the Oslo region using GIS. We had on-site indoor radon measurements only for 6% of the residences in the study region. Therefore, we used a buffer model with different radius size to
estimate radon exposure to the rest of the dwellings (Figure 2). The model was based on 41,515 indoor radon measurements. For dwellings without indoor radon measurements, the geometric mean of indoor radon measurements from at least five dwellings found in a buffer of 300 meters around the non-measured unit were used to estimate a radon value. If less than five measurements were encountered inside the buffer the radius was increased to 500, 1000 or 2000 meters until the buffer included at least five measured dwellings. If we could not find five measured dwellings within a radius of 2,000 meters, the house got the same value as the nearest measured dwelling. In addition, we had information on detailed maps of radon potential areas in the Oslo region. The radon potential corresponds to the probability that a home that has not had a radon measurement would have a long-term average radon concentration above the action level. The radon potential categories were based on indoor radon measurements, distribution of uranium-rich rock types, uranium concentrations in the ground and permeable drift deposits found at each coordinate point. Houses occupied by children born after 1986 got a radon potential category (low, medium or high).

Radon values from buffers were compared to indoor radon values of measured houses and radon values from a regression model constructed with radiometric data, equivalent concentrations of thorium, uranium and bedrock geology.

Intraclass correlation coefficients (ICCs) were used to study the agreement between these measurements. The ICC originally introduced by Fleiss (1986) is generally used to assess agreement between two variables and can be interpreted as a measurement of reproducibility or reliability. The agreement becomes important when one wants to know whether one method or instrument compared with another obtain equivalent results. ICC can be useful either from the point of view of how well it classifies the house according to their radon value, the reliability of the method or the reproducibility of the results. Regarding ICC values 1.00 represents perfect agreement and 0.00 no consistency, values below 0.4 indicate low agreement, values between 0.4 and 0.75 indicates fair to good agreement, and values above 0.75 indicate very good agreement.

The population census in 1970 included only residential area and lacked information on numerical addresses. Residential areas identified from this census were assigned radon mean concentrations found on measured dwellings in their actual residential area.
2.4 Income

To take into account the changes of family income over time for each year family income was categorized into quartiles and grouped into three categories. First quartile represented family income below the official Norwegian poverty line defined by The Organization for Economic Co-operation and Development (OECD-50 limit).\textsuperscript{68} Second and third quartiles were classified as medium income, and the fourth quartile was families with high income.

2.5 Outcomes

In paper II and III, the outcomes under study were diagnosis of leukemia and cancer in the CNS.

2.6 Covariates included in the study

Based on the introduction, we considered several factors that may affect the association between leukemia, cancer in the CNS and radon exposure. They include socioeconomic status and factors related to the birth. In Paper II we adjusted for parental education, annual family income, the child's sex, birth weight, congenital malformations and parity.

In paper III, in addition to the covariates used in paper II, we also used parity as proxy for family size. In the calculations of poverty lines equivalence scales are usually used to the number of adults and children in the household.\textsuperscript{69} We also adjusted for marital status. Marital status was classified according to The Norwegian standard classification of families. We had accurate information on marital status in 1970, 1980, and each year from 1987 to 2009. Between 1984 and 1986, all children were assigned the parent’s marital status from 1987, and
between 1975 and 1983 the marital status from 1980. For children born between 1967 and 1974 information on marital status from 1970 was used. We used information on marital status from the first live born child born after 1987 or from the year there was data available for the rest of children.

2.7 Statistical analyses of the radon study
To study the association between indoor radon exposures and the risk of childhood leukemia and cancer in the CNS we used logistic regression and Cox regression. Radon exposure was assessed for each child at different points in times, during the first year of life, between birth and four years and in the whole study period (0-15 years).

Radon exposure was divided into tertiles (1–56.8, 56.9–93.2 and 93.3–6315 Bq/m$^3$), which were rounded to <50, 50–100 and >100 Bq/m$^3$. We also grouped exposure into <100, 100–199 and >200 Bq/m$^3$, according to national and international recommendations. To explore a possible trend, we analyzed radon exposure as a continuous variable grouped into five groups by increments of 100 Bq/m$^3$. Exposure was estimated for each year from birth to whatever came first: the age of 15 years, the date of diagnosis of leukemia or cancer in the CNS, emigration, death or the end of the follow-up period. We adjusted for the available variables that could confound the association (parental education, annual family income, the child's sex, birth weight, congenital malformations and parity).

2.8 Statistical analyses of the socioeconomic status study
To study the association between family income and the risk of childhood leukemia and cancer in the CNS, every child was followed from birth to whatever came first, the age of 15, the date of cancer diagnosis, emigration, death or the end of the follow-up period. We analyzed family income in the first two years of life for children who got cancer later than two years of age to explore possible exposure windows as described in the introduction. Odds ratios (OR) and 95 percent confidence intervals (CIs) were computed by logistic regression models. We also made a second analysis where we took into account each year from 0 to 15 years every child contributed in the study using Cox regression with time-dependent variables. Age was used as time scale. Finally, in the age group 0-2 years we made a trend analysis of income, treating the four quartiles of income as a continuous variable.
OR and hazard ratios (HR) for family income were calculated as crude and adjusted. The adjusted model included family size measured as the number of previous children born by the mother, marital status, mother’s age, mother and father’s level of education, sex, birth weight and congenital malformations. Crude and adjusted ORs were also calculated for parents’ educational level. Parents’ educational level was categorized in three subgroups according to the International Standard Classification of Education (ISCED), low: less than 10 years, medium: 10-12 years and high with 13 or more years. SPSS version 20 was used in the analyses.

2.8.1 Subanalyses
Regarding radon exposure, we had more detailed residential information for the time period 1987-2009 including type of dwelling and level of radon potential (low, medium or high) referred on page 16. Thus, we performed separate subanalyses for children born in 1987 or later to gain further insight into the relation between radon exposure and cancer risk. First, we included only dwellings with information of numeric address and excluding children living in high apartment buildings. Second, we analyzed children living in detached and semidetached dwellings. Third, we only included children living in houses with on-site indoor radon measurements. Finally, we performed an analysis of radon exposure adjusted by the level of radon potential (low, medium or high).

Since the review by Poole et al (2006) demonstrated variability in the association of childhood leukemia and SES over time, we made a subanalysis by stratifying across time periods, 1967-1979, 1980-1989, 1990-1999 and 2000-2009. In order to get enough cases in each stratum, we only analyzed total leukemia and total cancer in the CNS. To explore possible critical exposures windows, we analyzed both family income in the first two years of life excluding children diagnosed with cancer before the age of three and all years each child contributed in the study. OR and hazard ratios (HR) was used to analyze the association in each time period.
3. Results

3.1 Radon values and exposure validation (Paper I)

Radon values were estimated for 1,055,495 dwellings in the Oslo region. 53.7% of the dwellings were assigned a radon value from five or more measured dwellings within a radius of 300 meters. For 17.9% the radius had to be increased to 500 m to find at least five measured dwellings, for 15.5% radius were of 1000 meters, and 13% a radius of 2000 meters.

When using intraclass correlation coefficients (ICCs) studying the agreement between radon values from the buffer method, indoor radon measurements and the regression model constructed with radiometric data and bedrock geology, the level of agreement between buffers and the regression model varied between 0.54 and 0.67, while ICC values comparing the buffer method and indoor radon values from measured houses were between 0.63 and 0.68. These correlations are relatively high.

3.2 Radon exposure and risk of leukemia and cancer in the CNS (Paper II)

In all, 712,674 children were followed from 1967 to 2009 from birth to diagnosis of cancer diagnosis, death, emigration or 15 years of age. A total of 864 cancer cases were identified, 437 children got leukemia and 427 got cancer in the central nervous system.

Table 2 in Paper II shows crude and adjusted odds and hazard ratios for leukemia and cancer in the CNS in the different radon exposure categories. Mean radon concentration was analyzed in three exposure periods, at birth, in the first four years of life and in the whole follow up period. We found no association between leukemia and cancer in the CNS in relation to radon exposure in the adjusted model. There were only a few marginal changes in the effect estimates across the various models. When only taking into account the exposure during the first 0-4 years of life, we observed a trend of 17% increase for CNS cancers for each 100 Bq/m$^3$ increase in exposure. It was only borderline significant after adjustments. No association was observed when radon exposure was classified in just three categories <100, 100–199 and >200 Bq/m$^3$.

Subanalyses showed the same results as the main results for leukemia. For CNS cancer we observed a non significant 36% increased risk for every 100 Bq/m$^3$ increase in exposure.
among children living in houses in which radon measurements were performed (27,186 children (cases=28)), and a non-significant increased risk of HR=2.33, 95% (CI: 0.70–7.69) in houses with radon concentrations above 100 Bq/m³. Subanalysis taking into account the level of radon hazard of the houses occupied by the children in the first year of life showed no association.

We checked the proportional hazard assumption by plotting the cumulative survival function and statistical tests based on Schoenfeld residuals and by examining the variation in incidence of leukemia and cancer in the CNS over time. The proportional hazards assumption was satisfied.

3.3 Socioeconomic status and the risk of leukemia and cancer in the CNS (Paper III)

We observed no association between leukemia or cancer in the CNS and family income when taking into account all years the children contributed in the study. We found a positive association between low family income and lymphoid leukemia when taking into account the mean family income only during the first two years of the child’s life (OR = 1.72, 95% CI 1.11-2.64). Trend analysis with continuous income categories for lymphoid leukemia in the adjusted model showed a 21% increased risk (95% CI 1.05-1.39) for each quartile with decreased family income. For acute myeloid leukemia we observed a reduced risk in both of the two lowest income categories, only significant in the medium income group in the adjusted model covering 0-15 years (HR=0.55, 95% CI: 0.31-0.98).

For cancer in the CNS we found no difference in the risk related to family income. Analyzes of subgroups gave the impression of random variation and no consistent pattern with elevated risk estimates for astrocytomas in the middle income category in the adjusted model (OR=1.73, 95% CI=1.06-2.85) and a reduced risk of intracranial and intraspinal embryonal tumors in the middle-income category (OR= 0.54, 95% CI=0.19-1.48).

Result of the analysis across time periods showed a non-significant increased risk of leukemia at the five percent level among children in the lowest income category, most pronounced in relation to the income during the first two years of life. The increase was highest for children born between 1980 and 1989. For cancer in the CNS the results were less clear with the
highest risk found in middle category except for the periods 1967-1979 and 1990-1999 taking into account whole follow up period. The highest increased risk for cancer in the CNS was observed in the intermediate income category for children born in the period between 1967 and 1979 (OR=1.96, 95% CI=1.03-2.73).

We also conducted an analysis where we excluded children with congenital malformations, but this had no impact on the results. The increase of risk for acute myeloid leukemia was no longer significant after removing children with congenital malformations (data not shown).

The parents’ educational level did not seem to have any impact in the risks of leukemia and cancer in the CNS.

We checked the proportional hazard assumption by plotting the cumulative survival function and statistical tests based on Schoenfeld residuals and by examining the variation in incidence of leukemia and cancer in the CNS over time. The proportional hazards assumption was satisfied.
4. Discussion

We observed no association between childhood leukemia and radon exposure in this study. An elevated risk for cancer in the central nervous system was observed. This association must be interpreted with caution, however, because of few cancer cases, the crude assessment of radon exposure and possibilities of confounding.

Being born into a household of low family income during the first two years of life was observed to be a risk factor for development of lymphoid leukemia before the age of 15. The associations found between parents’ educational level and the risk of childhood leukemia and cancer in the CNS was not significant in our study.

4.1 Validity, reliability and bias

Validity refers to whether or not a study is well designed and provides results that are appropriate to generalize to the population of interest. Validity is used in three different ways, internal validity, external validity and measurement validity. Reliability is the degree to which an assessment tool produces stable and consistent results.

Internal validity is an estimate of the degree to which conclusions about causal relationships can be made (e.g. cause and effect), based on the measures used, the research setting, and the whole research design. Most violation of internal validity can be classified into tree general categories: confounding, selection bias, and information bias.

Confounders are factors (exposures, interventions, treatments, etc.) that explain or produce all or part of the difference between the measure of association and the measure of effect that would be obtained with a counterfactual ideal. Selection bias are distortions that result from procedures used to select subjects and from factors that influence the study participation. One example of selection bias is Berkson’s bias. Information bias occurs during data collection. Bias in estimating an effect can be caused by measurement errors in the need of information. For discrete variables (variables with only a countable number of possible values), measurements error is usually called misclassification. It can be differential and nondifferential misclassification.
Differential misclassification occurs when the error rate or probability of being misclassified differs across groups of study subjects. The bias caused by differential misclassification can either exaggerate or underestimate an effect. Differential misclassification ordinarily exaggerates the effects under study. Nondifferential misclassification is when all groups or categories of a variable (whether exposure, outcome, or covariate) have the same error rate or probability of being misclassified for all study subjects. Bias introduced by nondifferential misclassification of a binary exposure or disease is predictable in direction toward the null value.

Sensitivity and specificity are measures of validity and inform about the accuracy of a study. Sensitivity refers to the test's ability to correctly detect patients who do have the condition/exposure. It measures the proportion of positives test results that are correctly identified. Specificity relates to the test's ability to correctly detect patients without a condition/exposure.

4.2 Validity and reliability in our study
A major strength of this study is the prospective cohort approach and the quality of data on cancer diagnoses and multiple risk factors, which allowed us to adjust for several conditions that may confound an association between childhood cancer, radon exposure and socioeconomic position. To our knowledge, this study is the second cohort study following radon exposure published so far.

4.2.1 Validity and buffer model
Residential radon exposure was calculated within small geographical areas and the approaches we used to validate the precision of radon exposure showed good agreement with the buffer method. Several approaches we used to validate the precision of radon exposure showed good agreement with the buffer method (Paper I). Radon values from the buffers were compared with indoor radon measurements carried out in dwellings, and with radon values estimated from a regression model based on important predictors as radiometric data, equivalent concentrations of thorium, uranium and bedrock geology. It was possible to assess individual radon exposure based on measurements from dwellings with measured radon values within small geographical areas. We used GIS models which also can be used in other geographical areas in other parts of the world to calculate radon exposures.
We conducted sensitivity and specificity analyses with data from radon measures against radon values from the buffer model. First, radon exposure was divided into two categories $<100 \text{ Bq/m}^3$ and $\geq 100 \text{ Bq/m}^3$ and in a second analysis radon was divided into $\leq 200$ and $>200 \text{ Bq/m}^3$. In addition, sensitivity and specificity were analyzed taking into account number of radon measurements within the buffers ($<5$, $\geq 5$, $\geq 10$, $\geq 20$ measurements).

The sensitivity and specificity in the first analysis of radon exposure ($<100 \text{ Bq/m}^3$ and $\geq 100 \text{ Bq/m}^3$) were 79% and 56% respectively for identifying the high exposure dwellings. The accuracy was 66%, which means that 66% of the houses were correctly identified. The sensitivity and specificity in the second analysis of radon exposure ($\leq 200$ and $>200 \text{ Bq/m}^3$) were 52% and 88% respectively, with an accuracy of 80%. Sensitivity and specificity were constant when taking into account number of measurements into the buffers. Thus our results using the buffer model must be considered as robust.

The wide range of radon exposures on region area was an advantage in this study, with large numbers of persons having relatively high exposures as well as persons with low exposures (Paper I). Our mean radon concentration is the highest reported in analytical childhood cancer studies so far. The mean radon concentration for all cohort members in our study was 91 Bq/m$^3$. It is important to note that if exposures tend to be homogeneous or have low variability their effects might be underestimated or even completely obscured. The high heterogeneity of radon exposure will improve the statistical power of the present study.

We used a model to estimate radon exposure in as short distances as possible around each unmeasured building. Only two other studies used such radon density measurements to characterize individual radon exposure within small geographical areas. Results of these studies are in accordance with our results for leukemia and cancer in the CNS. When estimating radon concentrations with radon measurements taken in the same area as the unmeasured buildings, it is more likely that the dwellings share important factors associated with radon concentration, such as geology and ground permeability. It is also likely that radon estimates from this method might express similarities in other factors influencing indoor radon concentrations such as type of building, number of floors, building materials, as well living habits such as ventilation.
Reliability is considered to be relative good. In this study we used data from the Norwegian Radiation Protection Authority, the Geological Survey of Norway and the Norwegian Mapping Authority. Radon measurements were selected from the housing stock which gives the possibility to detect radon hazard areas and generalizability, applying results from a sample of measurements larger areas from which the sample was selected. We used GIS to construct the buffers model. Data and method are standard which make it possible to repeat the procedure or method again.

4.2.2 Validity and residential history
In the present study, residential history was available for more than half the years of follow-up, most detailed after 1987. This allows us to have a relatively accurate estimate of lifetime exposure of the children. Exposure during pregnancy is important because fetuses may be more sensitive to radiation owing to immature biologic response, fast growth and a high level of cellular divisions.\textsuperscript{74} Residential address at birth is the best proxy available for the place of residence during pregnancy. In this way, we may get a good surrogate estimate of radon exposure for mothers during pregnancy.

We had accurate information on numerical addresses at 1th of January 1980 and each year from 1987 to 2009. For children with missing information on radon exposure in some of the years of the follow up period, and in the absence of information regarding moving to another municipality, the time-weighted average concentration for the part of the childhood period with known radon concentration was used as a best estimate. If the child moved out of the study area, it was given the known radon concentration of the years the child lived in the study area. Table 2 below, show the distribution of the children’s residential history throughout the follow up period (0-15 years). Nearly three quarter of the children had complete residential history and radon exposure.
Table 2. Percent children with complete and incomplete residential history

<table>
<thead>
<tr>
<th>Number of year with missing residential history</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with complete residential history</td>
<td>306551</td>
<td>73.9</td>
</tr>
<tr>
<td>1</td>
<td>11112</td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td>14564</td>
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<td>13</td>
<td>3945</td>
<td>1.0</td>
</tr>
<tr>
<td>14</td>
<td>3856</td>
<td>0.9</td>
</tr>
<tr>
<td>15</td>
<td>5252</td>
<td>1.3</td>
</tr>
<tr>
<td>16</td>
<td>3363</td>
<td>0.8</td>
</tr>
<tr>
<td>Total</td>
<td>414.796</td>
<td>100</td>
</tr>
</tbody>
</table>

For children born in 1987 or later we made an analysis of residential history to evaluate how often the children changed residence during two age groups, the first four years and through whole study period (0-15 years). For the youngest children (0-4 years), around 50% was living in the same residence as at birth the next four years. 30.9% moved once, 11.7% moved twice and 7.1% moved more than three times. During the whole study period (0-15 years) 33.3% were living in the same house from birth and throughout the study period. 23.7% moved once before the age of 15, 15.3% moved twice and 27.8% moved more than two times. In the period before 1987 we did not have residential history for all years of follow up but at least each child had information on radon exposure in two of the residences where they lived.

The results presented in this section will be discussed further in the next section.

4.3 Possible bias in our study

The main limitation of our study is the risk of exposure misclassification which may lead to a reduction of the estimated estimates. The uncertainty of the radon values increases with increasing radius, but only for 15% of the dwellings. Radon values from the buffers were validated by comparing them with indoor radon measurements and radon values from a regression model constructed with important radon predictors as radiometric data, equivalent concentrations of thorium, uranium and bedrock geology. The agreement was found to be good using both methods (Paper I). Another limitation was that for 4.4% of the dwellings in
the study area we could not find any measured dwelling inside a buffer of 2000 meter radius. These dwellings were given the same radon value as the nearest house.

Some factors related to the buildings that might influence the radon concentration such as floor level and ventilation. This information was not available in our data set. The concentration of radon gas decreases with the elevation above ground level. Only 15.5% of the buildings in the Oslo region are apartment blocks. Subanalyses excluding blocks were, however, in accordance with the main results.

In our study the same approximate radon value in the buffer was used for all dwellings within the buffer. It may lead to Berkson error, ie. when exposures are estimated from observed determinants of exposure with an exposure prediction model. Berkson error may occur also if exposure has to be approximated due to missing values in the measurements, for example when we used the time-weighted average concentration for the part of the childhood period with known radon concentration when there was missing residential history for some of the children. However, Berkson error causes little or no bias in the measurements in our study since all study subjects have the same probability of being misclassified.

Radon mean concentrations was used to analyses the radon exposure for each child at different times during the follow up period (0-15 years). We used mean radon concentrations during the first year of life, between birth and four years and in the whole study period (0-15 years). Taking into account that around 27% of families with children moved more than two times in the follow up period, this might lead to exposure misclassification. We therefore performed subanalyses of radon exposure in the first years of the child’s life. For children born in 1987 or later more than 50% of children aged 0-4 years were living in the same residence during the first 4 years of age. Risk of misclassification in this period may be less likely since more than 60% of the cases of leukemia were younger than age 5. For cancer in the CNS 45% of the cases were before age 5 years. As previous mentioned in the introduction based in risk models, radiation doses in early life are much more important than doses later in childhood, and for this reason it may be more important to have radon exposure at the place of residence at the time of birth. We did not have information on how many hours the children spend at home. Children in school age are often away from home large part of the day and that may lead also to misclassification of radon exposure.
In our study as in other mentioned studies the association observed between radon concentrations and the risk of leukemia or cancer in the CNS could be biased by the existence of confounding factors of which we did not have information and could not adjust for. There are not many known substantial risk factors for childhood cancer apart from ionizing radiation, although confounding by unknown major risk factors must remain a possibility.

We did not have information on other sources of background radiation such as radiation of radon daughters, radiation in water, cosmic radiation, radiation coming from food intake and medical radiation. Other factors linked with childhood cancer are chemical exposures (solvents, benzene and other hydrocarbons, pesticides) parental smoking, parental alcohol consumption, diet and vitamin supplementation, iron or folate supplementation, medications, infections, breast feeding and allergies.

4.4 Discussion of results of radon and childhood cancer

4.4.1 Buffer model and other predictions models
Several models have been developed to predict indoor radon concentrations. Hauri et al, 2012 based their prediction model on 44,632 indoor radon measurements. In addition to radon measurements several other radon predictors related to geology (soil texture and tectonic units) and to building characteristics (house type, floor and year of construction) have been used. They included also degree of urbanization. The sensitivity analysis demonstrated that the prediction model was robust with a sensitivity of 31% and specificity of 92% when dichotomizing radon exposure at the 90th percentile (218 Bq/m$^3$). In Denmark, Adersen et al, 2007 developed a model to estimate indoor radon in 21,000 houses. The model used several radon predictors such as house type, floor number where radon measurement were taken, fraction of the house with basement, geology, geographical region, floor number, row house, and building materials. The study found a sensitivity of 80% for low radon concentration ($\leq 50$ Bq/m$^3$) and 60% for high radon concentration ($>100$ Bq/m$^3$).

Comparable methods to our buffer method have been described by Miles and Appleton, (2005). They identify homes with high radon levels by inspecting geological combinations and indoor radon measurements within squares of 1 x 1 and 5 x 5 km. They used a kind of buffer method with no predefined limit to get at least 30 indoor radon measurements as basis for calculations of radon values that would be given to the whole square. The integrated
mapping method allowed identified significant variations in radon potential within bedrock geological units.

It is difficult to directly compare our method with the two last mentioned models since our radon prediction was based on only radon measurements within circles. As Miles and Appleton, (2005) point out, radon measurements together with geology and permeability are important factors in detecting radon expose areas. Unfortunately we did not have complete information on geology and permeability for each building in the study area. However, even when lacking geology and permeability data, the sensitivity in our buffer model was as high as 79% for detecting high radon exposure (>100 Bq/m$^3$) with a specificity of 56%. 52% of the houses above the radon action level where correctly identified by the buffer model when dichotomizing radon exposure under and above the radon action level (200 Bq/m$^3$), the sensitivity and specificity was 52 and 88% respectively, with an accuracy of 80%.

4.4.2 Comparison between the Danish study, the Cairo study, and the present one
Two case control studies found an association between acute lymphoblastic leukemia and radon exposure (Raasschou-Nielsen et al, 2008 and Maged et al, 2000), but no association with cancer in the CNS or other cancers (Raasschou-Nielsen et al, 2008).

The study of Raasschou-Nielsen et al, 2008 have several strengths, such as a larger number of cancers than our study with 1,153 cases of leukemia and 922 cases of cancer in the CNS. It is a register-based study which makes the possibility of selection bias less likely. They had residential history and could adjust for several risk factors, such as birth order, mother’s age, traffic density and electromagnetic fields. The study did not have information on SES.

The Danish study used predicted residential radon concentration calculated from a model based on a previous measurement program and a number of explanatory variables such as house type and geology. These model predictions of radon concentrations in homes avoid the bias potentially associated with limited participation in a measurement program, which has been a major problem in some of the previous mentioned studies, but given the variation in domestic radon concentrations, the model estimates may inevitably introduce uncertainties in the risk estimates. The errors associated with the radon concentration predictions were thought to be largely Berkson’s error, so that appreciable bias in the trend estimate would not be expected, but taking into account the radon variation as Miles and Appleton (2005) point
out, the use of estimated parameters in the Danish study can introduce classical error, which can induce bias in the regression.

In epidemiological studies there may be differences between exposed and unexposed groups in some unmeasured factor(s) that affect the risk of childhood leukemia and that may be correlated with exposure, i.e. confounding. Raaschou-Nielsen et al, 2004,\cite{78} in a previous study found an association between area-based SES and leukemia. The municipalities they observed with low-income were located in rural areas and on small islands. Municipalities on the coast were over-represented among the low-income municipalities. Some explanations of the association observed was that community behavior and factors acting early in life might be important. Moreover, at the geographic area where the low-income municipalities were located was according with Greaves “delayed infection” hypothesis. It suggests that exposure to common infections agents can trigger B-precursor lymphoid leukemia in predisposed children, and that the predisposition is more likely to occur in children who were relatively sheltered from infection at infancy.\cite{79} Not taking into account SES of the children when matching with controls or not adjusting for SES may cause an overestimate of the true association (positive confounding). Other birth risk factors such as birth weight and congenital malformations were not included in the Danish study. Children with congenital malformations have a higher risk of developing cancer, especially leukemia. Down syndrome is a common congenital anomaly, and children with Down syndrome have a substantially higher risk of leukemia.\cite{80} Birth weight is another risk factor associated with the risk of childhood cancer. A register based study from the Nordics countries, including Denmark, showed an increased risk of 26% for acute lymphoblastic leukemia per 1-kg increase in birth weight.\cite{81} Including these birth factors in our study could therefore give a more direct effect of radon exposure on the risk of childhood leukemia.

Another consideration is the possibility that the Danish study was underpowered, implying that the significant association found is likely to be due to chance. It also could affect our study. However, Kendal et al, 2013 in a large population-based study included 7,267 cases of lymphoid leukemia, found no association between the risk of leukemia and radon exposure. The study used a model similar to which we used in our study. Homes were grouped by grid squares and including factors regarding geology. About 400,000 radon measures were included.
The other case-control study reporting a positive association is Maged et al, 2000. They included 50 cases and 110 controls in Cairo. Only 10% of the children who met criteria for inclusion could be included in the study. The cases were selected from hospital registers in Cairo. The study did not report use of residential history or adjusting for possible individual confounders. Radon measurements were taken at home of the children.

Low participation rates imply a risk for selection bias, in particular if the participation rates of cases and control differ, which can affect the risk estimates in a case-control study in either direction. Another possible bias reported in the study was the difference in mean radon concentrations between cases and controls. The mean radon concentration was markedly higher for cancer case subjects than for controls. The mean indoor radon concentration in houses of patients was 75 Bq/m$^3$ while it was 55 Bq/m$^3$ in houses of controls. Cases not diagnosed in the Cairo hospital may be also underreported in the hospital registers.

Since only one other study since 1987 (Maged et al, 2000), with only a participation rate among cases of 10%, has observed and increased risk of leukemia this might be due to chance. Raaschou-Nielsen et al, 2008 had access to more cases than our study. However Kendall et al, 2013 with a larger number cases than Raaschou-Nielsen et al, 2008 found no association between childhood leukemia or cancer in the CNS and indoor radon exposure.

Considering all strengths and limitations of previous epidemiological studies we try to answer the question on radon exposure is a risk factor for leukemia and cancer in the CNS in children. Most of the studies published in the last decades indicate a negative association, but as showed above, methodological limitations in all previous studies including ours makes it impossible to be conclusive in to answer this question.

### 4.5 Discussion of results for socioeconomic status and childhood cancer

We observed no association between total leukemia or cancer in the CNS and family income when taking into account all years the children contributed in the study (0-15 years). When analyzing cancer subgroups we found a positive association between low family income and lymphoid leukemia when taking into account only the first two years of age.
For cancer in the CNS we found no difference in the risk related to family income. Analyses of subgroups gives the impression of a random variation and no consistent pattern with elevated risk estimates for astrocytomas in the middle income category in the adjusted model and a reduced risk of intracranial and intraspinal embryonal tumors also in middle-income category. The lack of consistence in these associations indicates that the observations might be due to chance.

We did not find any significant association with the parents’ educational level.

Our findings for leukemia and SES are consistent with studies of childhood cancer from the USA (Pant et al, 2010) and Denmark (Raaschou-Nielsen et al, 2004). Contrary to our results, studies from the UK (Kroll et al, 2011) and Canada (Bourugian et al, 2005) reported higher incidence rates in relatively affluent communities. Other studies in the UK report no significant associations (Smith et al, 2006; Dockerty et al, 2001).

Few studies on the association between childhood cancer in the CNS and socioeconomic status are reported in the literature (Keegan et al, 2013; Pant et al, 2010). Keegan et al, reported higher risk of cancer in the CNS with parent’s high social class, and contrary Pant et al, 2010 observed higher risk in high poverty areas compared with affluent areas.

Previous studies have used different measurements of SES. Pant et al, 2010; Raaschou-Nielsen et al, 2004; Kroll et al, 2011; Bourugian et al, 2005 and Smith et al, 2006 used area-based measures. Few studies have used individual measurements of SES (Dockerty et al, 2001; Carozza et al, 2010; Keegan et al, 2013; Raaschou-Nielsen et al, 2004). Two area-based studies observed a positive association between leukemia and low SES (Pant et al, 2010; Raaschou-Nielsen et al, 2004) and two studies found low risk of leukemia in low SES (Kroll et al, 2011 and Bourugian et al, 2005).

Area-based measures are most commonly aggregated from individual level or small area data. They can be used to characterize areas from deprived to affluent, as well as a proxy for the SES of the people living in these areas when these are not available. The link between area-based SES and the risk of childhood cancer is based on some exposure related to the neighborhood, such as early contact with infections agents, with might be more prevalent in neighborhoods with lower income and poorer living conditions (Kroll et al, 2011 and
Bourugian et al, 2005; Dockerty et al, 2001; Keegan et al, 2013; Raaschou-Nielsen et al, 2004). Greaves, 2006 have proposed the infection-based hypothesis. He suggests that many childhood leukemias arise as a consequence of an abnormal immune response to common infection, but the biological mechanisms remains unknown.

Other explanations regarding use of area-based SES measurements in the risk of childhood cancer are that SES may influence the environment or exposure to risk factor linked with childhood cancers, social support, health care accessibility, and community culture (Pant et al, 2010; Carozza et al, 2010; Raaschou-Nielsen et al, 2004).

Pan et al, 2010 examined area socioeconomic variations in childhood cancer incidence rates among children aged 0-19 in the United States. SES measure was based on percentage of persons in the county living below the national poverty thresholds at the age of the diagnosis. They found higher incidence rates in poor counties than affluent counties. Similar results for leukemia showed Raaschou-Nielsen et al, 2004. They found an association with area-based SES measurement (the annual average income in the municipality of residence at the time of birth), but not with family-based measures of SES (job titles of parents) or associations with SES at the age of the diagnosis. They concluded that community behavior rather than individual lifestyle might be important and that factors acting early in life might be important.

Kroll et al, 2011 and Bourugian et al, 2005 reported higher incidence of childhood leukemia in affluent areas compared with areas with low SES. Area-based measure at the time of the diagnosis from the Kroll et al, 2011 study was derived from the Carstairs deprivation index widely used in the UK. Studies in the UK appear to be contradictory. Several studies in the same country and using the same index have shown no association (Smith et al, 2006; Dockerty et al, 2001). Bourugian et al, 2005 used neighbourhood income quintiles at the time of the diagnosis.

Carozza et al, 2010 used parental education as measure of SES. They found no association between SES and childhood cancers as we found.

We found two studies including analysis of the risk of childhood cancer in the CNS and SES. Keegan and colleagues investigated possible associations between paternal occupational exposure and childhood CNS tumours in the UK, taking into account occupational social class.
They found an increased risk of CNS tumours with parental exposure to solvents, animals and parental jobs with high social contact. They found increased risk for astrocytomas for children with parents in high social class. Pan et al, 2010 included percentage of persons in the county living below the national poverty thresholds at the age of the diagnosis. They found higher incidence rates of CNS cancers in poor counties than affluent counties.

Overall, studies utilizing area-based socioeconomic measures have demonstrated contradictory results on the risk of childhood leukemia and cancer in the CNS. Most of these studies included SES measurements at the time of the cancer diagnosis. Some studies conducted in the UK (Kroll et al, 2011; Smith et al, 2006; Dockerty et al, 2001), USA (Pan et al, 2010) and Canada (Bourugian et al, 2005) may be affected by bias, as they discuss, specially, because of selective underreporting of cancer in the poorest neighborhoods. Another possible source of bias in these studies is that the effect of high infant childhood mortality rates observed in low socioeconomic areas may reduce the survival of children otherwise at risk for developing cancer. On the other hand, the results of the studies of SES and childhood leukemia using individual level assessment (Carozza et al, 2010) and area-based SES measures (Raaschou-Nielsen et al, 2004) show similar results as we found in our study.

It is well established that parental income is positively associated with nearly every dimension of child well-being that social scientists measure. Poverty and low socioeconomic status have been associated with higher risk of death, exposure to infections, chronic illness, low birth weight and child mental health problems. The contribution of parent’s educational level and the influence on childhood cancer in developed countries may be less pronounced than in less developed countries. Norway has a free and evenly distributed healthcare system. Routines for prenatal care and birth in hospitals have been improving in Norway during the last years, as well as the legislation around working conditions for pregnant women. In addition, Norway has a high education level in general.

We had missing data for marital status for some of the years in the follow up, but we did not observe significant changes of the estimates if excluding this variable. It is likely that during the follow up period some of the parents will change marital status. The number of members in the family can change and also the family income. However, the Norway Act on Children and Parents states that if one parent or both parents do not live with the child, they shall pay
regular cash grants to support and education of the child. This will improve the economy of single parents living with children and reduce the error introduced by periods of missing marital status. The median income related to the poverty line in our study was slightly higher than the median income for the whole of Norway. This is probably due to the fact that we take into account mainly people in productive ages, and they might have a higher income than the average population.

Lack of information on several environmental factors linked to childhood leukemia and cancer in the CNS may account for all or part of an apparent association observed. They include environmental exposures, parental lifestyle factors, such as parental smoking, parental alcohol consumption, diet habits and use of medications during the pregnancy. We lack also information on breast feeding.

The question of SES and its potential association with childhood leukemia and cancer in the CNS remains unclear. Methodological difficulties regarding the quality of the registers in previous studies, type of SES measurements used, and time of measure in the life course of the child may have an important significance, having in mind that these factors may be linked to different exposures. Norway has a well-developed health system, as well as a social security system giving the opportunity of a lift to families with economic difficulties. Consequently, the family income is more homogeneous in Norway than in countries with fewer facilities, making a possible association of SES and childhood cancer more difficult to discover. Inequalities in health in relation to SES are well stablished, and children who are persistently poor are at high risk of many adverse health outcomes. Leukemia seemed to be one of the rare exceptions with studies reporting higher risk among children in high SES compared to low SES groups. It is clear that much additional work will be required to get complete understanding of the association between leukemia and cancer in the CNS.
5. Conclusion

Based on the need for more information on risk factors for childhood leukemia and cancer in the CNS, we took advantage of the high occurrence of radon in Norwegian homes, the high incidence of brain cancer and leukemia in Norway and the distribution of family income in the area. This in combination with good cancer and population registration makes studies of this type suitable in Norway.

Our buffer model for assessing radon exposure can be used for exposure assessment in epidemiologic studies. The model was validated against other methods showing that the correlation between the methods was relatively high. Although the method has certain limitations, we regard it as acceptable for use in epidemiological studies.

We did not find any association between radon exposure at home and the risk for developing leukemia or cancer in the CNS among children under 15 years of age living in the Oslo area.

This study demonstrates that being born into a household of low family income during the first two years of life might be a risk factor for development of lymphoid leukemia before the age of 15. For cancer in the CNS we found no difference in risk related to family income.

The association between parents’ educational level and the risk of childhood leukemia and cancer in the CNS was not significant in our study.

6. Impact of the results and social relevance

At a national and international level there is a need for research helping to clarify possible causes of childhood cancers. Potential prevention of possible causes of the disease is an important intervention that can account for children suffering a chronic illness such as cancer.

Prevention of childhood cancer remains the most promising strategy for reducing the incidence and mortality due to this disease. Identifying risk factors and eliminating exposure to carcinogens may help understanding the mechanisms of the disease and lead to prevention
and active intervention to reduce the risk of cancer in children. From the very start of life the socioeconomic position of parents might influence intrauterine conditions and the types of environments in which the children grow up. We found that children from poor families may have higher risk of getting leukemia compared to families in high income groups. Considering that Oslo is among of the cities with highest childhood poverty in Norway, our results may be important in the identification of high risk groups. If the observed risks for lymphoid leukemia among children below two years of age in relation to income are correct, they will, in the study area, lead to approximately six and five extra cancer cases, respectively, during a four year period.

Radon is a well-established human lung carcinogen.\textsuperscript{96,97,98} International Agency for Research on Cancer (IARC) considered that there is sufficient evidence to classify radon and its decay products as carcinogenic to humans.\textsuperscript{99,100} Ionizing radiation is one of the few established causes of cancer in children, and the fact that the effect of radon exposure can be detected in epidemiological studies generate public interest. We found no association between indoor radon exposure and childhood leukemia and cancer in the CNS in the present study.

Oslo municipality is responsible for health surveillance and monitoring of the environmental factors that affect health including radon. The Health and Welfare Agency is Oslo’s central resource center for health promotion and preventive health care, as well as for district-wide administrative tasks within the Municipal Health Services and Diseases Act. Results of our study can provide increased knowledge when the agency makes decisions regarding preventive policies and be used to get a better overview of radon exposure in the Oslo Region, as well as provide better knowledge of radon health risks and in the general population.
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