

JAD ABUHAMED

Computed Tomography and Childhood Central Nervous System Tumors

Incidence, Trends, and Risk

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ACADEMIC DISSERTATION

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*To Petri
for walking beside me
for kindling hope in moments of doubt
for love that is my harbor and my home*

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ABSTRACT

Childhood central nervous system (CNS) tumors are the most common solid tumors and the leading cause of cancer death in children. Despite their burden, the underlying causes of childhood CNS tumors are still largely unknown. Exposure to high doses of ionizing radiation is a well-established risk factor, whereas evidence regarding the carcinogenic potential of low-dose exposures remains limited and less certain. Computed tomography (CT) is a widely used diagnostic imaging technique that utilizes low doses of ionizing radiation (x-rays) to create detailed cross-sectional images of the human body. Its use in children increased considerably during the 1990s and early 2000s, raising concerns about potential long-term health risks, particularly the risk of radiation-induced malignancies. Children are considered more vulnerable to radiation effects due to their greater biological radiosensitivity and longer lifespan, allowing more time for potential effects to manifest. Epidemiological studies have investigated the association between pediatric CT exposure and subsequent cancer risk, but the risk estimates obtained show variation due to differences in study design, follow-up duration, dose estimation methods, and the handling of confounding factors, particularly confounding by indication, where the underlying condition prompting the CT scan also increases cancer risk.

This doctoral dissertation, conducted within the framework of the RiFaTuB (Risk Factors for Tumors of the Brain in children) project in Finland, aimed to characterize utilization patterns and temporal trends of pediatric CT imaging, estimate incidence rates and trends of childhood CNS tumors, and quantify the risk of childhood brain tumors associated with radiation exposure from CT imaging, considering potential biases. The nationwide, population-based study utilized high-quality Finnish national health registers, enabling a methodologically rigorous assessment of pediatric CT exposure and CNS tumor risk. Cases included 1142 primary childhood CNS tumors (malignant and non-malignant) diagnosed between 1990 and 2016, identified via the Finnish Cancer Registry (FCR). Three controls (3425 total) per case were matched by birth month, year, and sex from the Digital and Population Data Services Agency (DVV).

Information on CTs (73,035 scans) was obtained from ten major Finnish hospitals covering the period 1976–2011, estimated to represent up to 87% of all pediatric CT

scans nationwide. Absorbed brain doses from head/neck CTs were estimated using the National Cancer Institute Dosimetry System for Computed Tomography (NCICT), incorporating scanner-specific information and expert-defined parameters. Data on potential confounders, including cancer predisposition syndromes (CPS), previous malignancies, and parental socioeconomic status (SES), were obtained from various registers. Trends in CT use (1996–2010) and CNS tumor incidence (1990–2017) were analyzed using Joinpoint and Poisson regressions. Conditional logistic regression was used to estimate odds ratios (ORs) and excess odds ratios (EORs) for brain tumor risk per 100 mGy of cumulative brain dose from head/neck CTs, applying a 5-year lag period and adjusting for parental SES. Analyses were performed with and without participants with CPS or previous malignancies to assess confounding by indication.

Pediatric CT utilization in Finland increased between 1996 and 2002 (annual percent change (APC)=4.9%, 95% CI 3.5%, 6.3%), then declined significantly across both academic and central hospitals from 2002 to 2006 (APC=-6.9%, 95% CI -10.4%, -3.2%), after which it stabilized. Head/neck CTs were the most common type (63.5%) but showed the largest decline. The average annual age-standardized incidence rate (ASR) for childhood CNS tumors (1990–2017) was 4.30 (95% CI 4.26, 4.34) per 100,000 child-years, higher in boys and children aged 0–4 years. Pilocytic astrocytoma (30%) and medulloblastoma (10%) were the most frequent subtypes. Overall CNS tumor incidence showed a slight but significant increase (APC=0.8%, 95% CI 0.2%, 1.4%), primarily driven by low-grade (grade 1) tumors (APC=1.0%, 95% CI 0.1%, 2.0%).

After excluding participants with CPS or previous malignancies and applying a 5-year lag, children with ≥ 1 head/neck CT scan had a significantly higher risk of brain tumors compared to non-exposed children (OR=2.84, 95% CI 1.12, 7.19). A dose-response relationship was evident, with an EOR of 5.50 (95% CI 0.31, 10.95) per 100 mGy of cumulative brain dose. Including participants with CPS substantially increased the risk estimates (OR=5.15, EOR=7.80), indicating confounding by indication.

This nationwide Finnish study confirms a significant association between radiation exposure from pediatric CT scans and an increased risk of brain tumors. While CT use in children has declined in Finland since 2002, the observed risk underscores the continued importance of adhering to justification and optimization principles in radiological protection, particularly using pediatric-specific protocols and considering non-ionizing alternatives like magnetic resonance imaging (MRI) and ultrasound when appropriate. The slight increase in overall childhood CNS tumor incidence,

mainly due to low-grade tumors, may be attributable to ongoing improvements in diagnostics and registration, although a genuine modest increase cannot be excluded. The findings highlight the necessity of comprehensive, high-quality national registries for monitoring long-term trends and assessing risks associated with medical exposures. Further research with extended follow-up, refined dosimetry, and investigation of genetic susceptibility is warranted.

TIIVISTELMÄ

Lasten keskushermoston kasvaimet ovat lasten yleisimpiä kiinteitä kasvaimia ja merkittävin syöpäkuolemien syy. Vaikka näiden kasvainten ilmaantuvuus on suurentunut viime vuosikymmeninä, lapsuuden keskushermoston kasvainten syyt ovat suurelta osin tuntemattomia. Altistuminen suurille ionisoivan säteilyn annoksille on tunnistettu riskitekijä, mutta pienten säteilyannosten merkityksestä on niukasti näyttöä ja se on epävarmempaa. Tietokonetomografia (TT) on yleisesti käytetty diagnostinen kuvantamismenetelmä, joka hyödyntää matala-annoksista ionisoivaa säteilyä (röntgensäteitä) luodakseen tarkkoja poikkileikkauksuvia. Sen käyttö lapsilla lisääntyi merkittävästi 1990-luvulla ja 2000-luvun alussa, mikä herätti huolta mahdollisista pitkäaikaisista terveysriskeistä, erityisesti säteilyn aiheuttamista syöivistä. Lapset ovat alttiimpia säteilyn terveysriskeille kehittyvien elinten ja pidemmän elinajan vuoksi, jolloin haittavaikutuksilla on enemmän aikaa ilmetä. Epidemiologisissa tutkimuksissa on selvitetty lasten TT-altistuksen yhteyttä myöhempään syöpäriskiin, mutta tulokset ovat vaihdelleet tutkimusasetelman, seuranta-ajan, annosarviointimenetelmien ja sekoittavien tekijöiden käsittelyn vuoksi. Yksi epävarmuuden lähde on aiheseikoittuneisuus, joka syntyy, mikäli TT-kuvauksen indikaationa oleva sairaus itsessään lisää syöpäriskiä.

Tämä väitöskirja, joka toteutettiin osana RiFaTuB-projektia (Risk Factors for Tumors of the Brain in children), pyrki kuvaamaan lasten TT-kuvausten käyttötapoja ja trendejä, arvioimaan lapsuuden keskushermoston kasvainten ilmaantuvuutta ja sen muutoksia sekä määrittämään TT-kuvantamiseen liittyvän säteilyaltistukseen aiheuttaman aivokasvainriskin suuruuden. Väestöpohjainen valtakunnallinen tutkimus hyödynsi kansallisia terveysrekistereitä. Aineisto koostui 1142 lapsuuden keskushermoston kasvaimesta (pahanlaatuiset ja hyvänlaatuiset), jotka diagnosoitiin vuosina 1990–2016 ja tunnistettiin Suomen syöpärekisteristä (SyRe). Jokaista tapausta kohden valittiin kolme verrokkia (yhteensä 3425), jotka kaltaistettiin syntymäkuukauden, -vuoden ja sukupuolen mukaan Digi- ja väestötietovirastosta (DVV).

TT-kuvausten tiedot (73,035 kuvausta) kerättiin kymmenestä suuresta sairaalasta vuosilta 1976–2011. Aineiston kattavuudeksi jakson lopussa arvioitiin 87 % kaikista lasten TT-kuvauksista. Aivoihin kohdistuvat annokset pään/kaulan TT-kuvauksista

arvioitiin käyttämällä Yhdysvaltain kansallisessa syöpäinstituutissa kehitettyä annoslaskentajärjestelmää (NCICT), joka perustuu laitekohtaisiin tietoihin ja asiantuntijoiden määrittämiin kuvausparametreihin. Tiedot mahdollisista sekoittavista tekijöistä, kuten perinnöllisestä alttiudesta, aiemmista syövästä ja vanhempien sosioekonomisesta asemasta (SES), kerättiin useista rekistereistä. TT-kuvausten (1996–2010) ja keskushermoston kasvainten ilmaantuvuuden (1990–2017) trendit analysoitiin Poisson- ja Joinpoint-regressiolla. Ehdollisella logistisella regressiolla arvioitiin pään/kaulan TT-altistukseen liittyviä aivokasvainriskin vetosuhteita (OR) ja ylimääräisiä vetosuhteita (EOR) per 100 mGy, käyttäen 5 vuoden viivettä ja vakioiden vanhempien SES:n vaikutusta. Analyysit toteutettiin sekä sisällyttäen että sulkien pois tutkimushenkilöt, joilla oli perinnöllinen alttius tai aiempi syöpä aihe-sekoittuneisuuden arvioimiseksi.

Lasten TT-kuvantaminen Suomessa lisääntyi vuosina 1996–2002 (vuotuinen muutos (APC)=4.9%, 95% LV 3.5%, 6.3%), mutta väheni merkittävästi sekä yliopistotettä keskussairaaloissa vuoteen 2006 asti (APC=-6.9%, 95% LV -10.4%, -3.2%), minkä jälkeen taso vakiintui. Pään/kaulan TT-kuvaukset olivat yleisimpiä (63.5%), mutta niiden käyttö väheni eniten. Keskimääräinen ikävakiointu ilmaantuvuus lapsuuden keskushermoston kasvaimille (1990–2017) oli 4.30 (95% LV 4.26, 4.34) tapausta 100 000 lapsivuotta kohden, ollen korkeampi pojilla ja 0–4-vuotiailla lapsilla. Yleisimmät kasvaintyyppit olivat pilosyyttinen astrozytooma (30%) ja medulloblastooma (10%). Kokonaisilmaantuvuudessa havaittiin lievä mutta merkitsevä kasvu (APC=0.8%, 95% LV 0.2%, 1.4%), joka johtui pääosin matalasteisista (gradus 1) kasvaimista (APC=1.0%, 95% LV 0.1%, 2.0%).

Kun perinnöllinen alttius tai aiemmat syöväet poissuljettiin ja sovellettiin 5 vuoden viivettä, vähintään kerran pään/kaulan TT-kuvatuilla lapsilla oli merkitsevästi kohonnut aivokasvainriski verrattuna altistumattomiin (OR=2.84, 95 % LV 1.12, 7.19). Annos-vaste oli merkitsevä, EOR 5.50 (95% LV 0.31, 10.95) 100 mGy kohti. Perinnöllisen alttiuden tutkimushenkilöiden sisällyttäminen analyysiin suurensi riskiarvioita (OR=5.15, EOR=7.80), mikä viittaa aihe-sekoittuneisuuteen.

Tutkimus vahvistaa lasten TT-kuvauksien aiheuttaman säteilyannoksen yhteyden aivokasvainriskeihin. Tulokset korostavat säteilysuojelun merkitystä. Lasten kuvantamisessa on tarpeen käyttää erityisprotokollaa ja harkita vaihtoehtoisia kuvantamismenetelmiä kuten MRI:tä ja ultraääntä. Lasten aivokasvainten ilmaantuvuuden pieni suureneminen liittyyneen diagnostiikan ja rekisteröinnin paranemiseen, vaikka vähäistä todellista yleistymistä ei voi sulkea pois.

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ABBREVIATIONS

APC	Annual Percent Change
ASR	Age-Standardized Rate
CNS	Central Nervous System
CPS	Cancer Predisposition Syndromes
CT	Computed Tomography
CTDI	Computed Tomography Dose Index
DICOM	Digital Imaging and Communications in Medicine
DLP	Dose-Length Product
DRL	Diagnostic Reference Level
DVV	Digital and Population Data Services Agency (Finland)
ED	Emergency Department
EOR	Excess Odds Ratio
ERR	Excess Relative Risk
FCR	Finnish Cancer Registry
Gy	Gray (unit of radiation dose)
IAEA	International Atomic Energy Agency
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
ICRP	International Commission on Radiological Protection
IQR	Interquartile Range
IRR	Incidence Rate Ratio
kVp	Kilovolt Peak (tube potential)
LET	Linear Energy Transfer
mAs	Milliamperere-Seconds (tube current-time product)
mGy	Milligray (unit of radiation dose)
MRI	Magnetic Resonance Imaging
mSv	Millisievert (unit of radiation dose)
NA	Not Available, Not Applicable
NCICT	National Cancer Institute's Dosimetry System for Computed Tomography
NF	Neurofibromatosis
NOS	Not Otherwise Specified
OR	Odds Ratio

PACS	Picture Archiving and Communication Systems
PCD	Photon-Counting Detector
PECARN	Pediatric Emergency Care Applied Research Network
RiFaTuB	Risk Factors for Tumors of the Brain in children (project)
RIS	Radiology Information Systems
SD	Standard Deviation
STUK	Radiation and Nuclear Safety Authority (Finland)
Sv	Sievert (unit of radiation dose)
THL	National Institute for Health and Welfare (Finland)
TSC	Tuberous Sclerosis Complex
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
WHO	World Health Organization

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1 INTRODUCTION

This doctoral dissertation in epidemiology estimates incidence trends of childhood central nervous system (CNS) tumors, characterizes patterns of computed tomography (CT) use in children, and quantifies the associated risk of developing CNS tumors following exposure to radiation from pediatric CT. The research was conducted within the framework of the RiFaTuB project (Risk Factors for Tumors of the Brain in children), a nationwide population-based study designed to assess risk factors contributing to the development of CNS tumors in the pediatric population.

1.1 Childhood central nervous system (CNS) tumors

1.1.1 Definition

The central nervous system (CNS) is the command center of the human body, orchestrating everything from basic survival functions to complex cognitive processes. The CNS has fascinated scientists and philosophers for centuries, with early understandings rooted in ancient civilizations like Egypt and Greece, where the brain was often seen as the seat of intelligence and emotion (Finger, 2005). The human CNS consists of two primary components: the brain and the spinal cord. The brain is divided into several major regions, including the cerebrum, diencephalon, brainstem, and cerebellum (Gould et al., 2016). Within the protective casing of the skull, these structures are often classified as supratentorial, including the cerebrum, or infratentorial, including the brainstem and cerebellum, based on their position relative to the tentorium cerebelli. On the cellular level, the CNS is primarily made up of neurons and glial cells. Neurons are the principal functional units responsible for transmitting information throughout the nervous system. These cells include a cell body, dendrites for receiving signals, and axons for sending signals (Hall & Hall, 2021). Glial cells provide crucial support functions such as maintaining homeostasis,

forming myelin, and providing support and protection for neurons. Glial cells include astrocytes, oligodendrocytes, and microglia.

CNS tumors encompass a complex heterogeneous group of pathologic entities that occur in the tissues of the brain and spinal cord. They are classified by the WHO into grades 1 through 4 based on various factors that reflect tumor aggressiveness (Louis et al., 2016). Grades 1 and 2 are considered low-grade, characterized by slower growth, whereas grades 3 and 4 are high-grade, associated with rapid proliferation and a less favorable prognosis. In parallel, the International Classification of Diseases for Oncology (ICD-O) categorizes CNS tumors by biological behavior: benign (behavior code 0), malignant (code 3), or uncertain/borderline behavior (code 1), reflecting differences in growth potential, invasiveness, and metastatic capacity (WHO, 2013). For epidemiological and surveillance purposes, CNS tumors are often broadly grouped as non-malignant (codes 0 and 1) or malignant (code 3). Non-malignant CNS tumors tend to grow slowly, have well-defined boundaries, and generally do not invade surrounding tissues (Kumar et al., 2021). However, their location can make them life-threatening if they press on vital brain structures. Conversely, malignant CNS tumors exhibit fast growth, irregular boundaries, and invasive behavior, often spreading into adjacent brain tissues. Despite their aggressive nature, malignant brain tumors rarely metastasize outside the CNS.

A primary tumor is a neoplasm that originates in the tissue or organ where it is initially detected, in contrast to a metastatic (secondary) tumor, which spreads from another location. The majority of CNS tumors are primary tumors. Based on histologic, biologic, and molecular features, primary CNS tumors are grouped into classes within various classification systems. The World Health Organization (WHO) classification of tumors of the nervous system is a standardized framework for diagnosing and classifying brain and spinal cord tumors. This system has evolved over several decades, reflecting advancements in understanding tumor biology and genetics, with the first edition published in 1979 (Zülch, 1979) and the latest in 2021 (Louis et al., 2021).

A simplistic overview of this classification includes gliomas, neuronal and glioneuronal tumors, embryonal tumors, and several less common groups. Among pediatric populations, the most frequently diagnosed CNS tumors are medulloblastomas, pilocytic astrocytomas, and ependymomas. Medulloblastomas are highly malignant embryonal tumors found in the cerebellum (Dang & Phillips, 2017). Pilocytic astrocytomas are typically benign, slow-growing tumors that most often occur in the cerebellum and are characterized by their well-defined, cystic

nature. Ependymomas, arising from ependymal cells lining the ventricular system, frequently occur in the posterior fossa and can cause obstructive hydrocephalus due to their location.

1.1.2 Occurrence

Childhood CNS tumors differ substantially from adult CNS tumors in terms of incidence, location, histology, genetic alterations, clinical course, and response to therapies (Dang & Phillips, 2017). Therefore, it is essential to collect and analyze cancer data specifically for children. CNS tumors are the most common solid tumors and the leading cause of cancer-related death in children (Steliarova-Foucher et al., 2017). Their global incidence is estimated at 2.8 per 100,000 child-years in children aged 0–14 years. However, this estimate is based on incomplete global data as many countries lack cancer registries to accurately quantify childhood cancer incidence. Furthermore, differences in case ascertainment methods, registration practices, data completeness, and the choice of standard populations for age-adjustment complicate comparisons of incidence rates across cancer registries (Johnson et al., 2014). Additionally, the inclusion of benign brain tumors in reporting varies by registry. For instance, in the US, the registration of non-malignant tumors was not mandated by law until 2004, resulting in limited data before then (United States, 2002). In contrast, the Finnish Cancer Registry (FCR) has recorded both benign and malignant CNS tumors since its establishment in 1953 (Leinonen et al., 2017). Therefore, any interpretation of statistics should take these considerations into account.

From 1973 to 1994, the incidence of malignant CNS tumors among children in the United States rose by 35% (Smith et al., 1998). Similarly, in Europe, between 1978 and 1997, the incidence increased by 1.7% per year, with the highest rates observed in Northern Europe (Peris-Bonet et al., 2006). Advances in diagnostic techniques, particularly enhanced magnetic resonance imaging (MRI) capabilities, have likely contributed to the observed increases in both regions. However, the potential role of environmental and other risk factors cannot be ruled out. The incidence rates of childhood CNS tumors in the Nordic countries are among the highest in the world, partially due to the comprehensive cancer registration systems in place (Schmidt et al., 2011). In Finland, the FCR is recognized for its high accuracy, international comparability, and comprehensive data collection (Leinonen et al., 2017). For childhood tumors, the completeness of the FCR data was estimated to be 94% for the period from 2009 to 2013 (Jokela et al., 2019).

Recent studies from Canada and France have reported stable incidence rates of CNS tumors among children, whereas a study from the US indicated a slight but significant increase (Desandes et al., 2014; Larouche et al., 2020; Ostrom et al., 2018). Since the etiology of CNS tumors remains largely unknown, tracking changes in cancer incidence is crucial both for initiating hypothesis-driven research on potential environmental risk factors and for assessing the associated public health burden (Johnson et al., 2014).

The two primary groups of CNS tumors in children are gliomas and embryonal tumors. The incidence and survival rates of gliomas, which originate from glial cells, differ substantially based on their location and histologic type (Johnson et al., 2014). Pilocytic astrocytoma is the most common CNS tumor in children, accounting for approximately 18% of all childhood CNS tumors and 33% of all gliomas (Dang & Phillips, 2017). These tumors are low-grade, slow-growing, commonly located in the infratentorial region, and rarely undergo malignant transformation (Collins & Pollack, 2020). The most common genetic alterations in pilocytic astrocytomas are those involving the mitogen-activated protein kinase (MAPK) pathway. In contrast, high-grade gliomas, including glioblastoma and diffuse midline glioma, are malignant and usually fatal CNS grade 4 tumors.

Embryonal tumors in children arise from precursor brain cells and tend to become metastatic early in their development. Medulloblastoma is the most common CNS embryonal tumor, accounting for approximately 10% of all childhood CNS tumors and ranking second in incidence after pilocytic astrocytoma (Dang & Phillips, 2017). This tumor originates in the cerebellum or dorsal brainstem and often extends into the fourth ventricle, causing mass effect and obstructing cerebrospinal fluid (CSF) flow. Due to their highly proliferative nature, medulloblastomas are classified as grade 4 tumors.

1.1.3 Etiology and risk factors

The underlying causes of most childhood CNS tumors remain elusive, with only a few established risk factors and numerous suspected ones. Table 1 presents a summary of the most researched risk and protective factors for CNS tumors, categorized based on the strength of scientific evidence (Johnson et al., 2014; Patil et al., 2022). CPS increase the risk of CNS tumors in children through genetic mutations that disrupt normal cellular functions, ultimately leading to tumorigenesis (Foss-Skiftesvik & Stoltze, 2022). Approximately 10% of childhood CNS tumors can be linked to rare

pathogenic variants in genes associated with known CPS. However, the inclusion of these syndromes in studies investigating the risk factors for CNS tumors, such as computed tomography (CT) imaging, has been inconsistent, potentially leading to confounding by indication. This occurs when a CT scan is performed for a condition that itself increases the risk of brain tumors.

Advanced parental age, male sex, and white and Asian race have been shown to be associated with an increased risk of developing CNS tumors in children (Hoang et al., 2022). While there is some evidence suggesting that a family history of cancer may elevate the risk of these tumors, the data remains limited (Dearlove et al., 2008). Two meta-analysis studies have concluded that higher birth weight is associated with increased childhood CNS cancer risk, particularly for astrocytoma and embryonal tumors, but not for ependymoma (Dahlhaus et al., 2017; Georgakis et al., 2017). The increased risk might be due to higher cell counts in the brains of larger infants, resulting in increased mitotic events and somatic mutations. Additionally, alterations in maternal hormones and growth factors that stimulate rapid fetal growth could potentially facilitate carcinogenesis.

Maternal folate intake has been shown to decrease the risk of CNS tumors by regulating DNA synthesis and repair and thus preventing DNA damage that can lead to tumor formation (Chiavarini et al., 2018). Allergic and atopic conditions in childhood, such as asthma and eczema, may also have protective effects against CNS tumors as the heightened immune activity could help interrupt carcinogenic processes before tumor development (Johnson et al., 2014). However, there is inconsistency in the literature and further research is needed.

Ionizing radiation has the capacity to induce carcinogenesis by depositing energy that removes electrons from atoms within biological tissues, initiating molecular changes that can lead to cellular damage and genetic mutations (Martin et al., 2019). Among environmental exposures, moderate to high doses of ionizing radiation represent the most established risk factor for CNS tumors in children. This is supported by evidence from the Life Span Study of atomic bomb survivors and radiotherapy treatment cohorts (Bowers et al., 2013; A. V. Brenner et al., 2020). In contrast, the association between low levels of ionizing radiation, such as the exposure to natural background radiation, and childhood CNS tumor risk remains less conclusive. While some studies suggest an association, findings have been heterogeneous, and several methodological limitations complicate interpretation (Kendall et al., 2021). Current evidence regarding cancer risk associated with exposure to low doses of radiation from CT imaging will be explored further in the literature review chapter. Lastly, for non-ionizing radiation such as that emitted by

microwaves and mobile phones, current evidence does not support a causal association with an increased risk of CNS tumors in children (Hoang et al., 2022).

1.1.4 Clinical presentation and treatment

Childhood CNS tumors often present with symptoms related to increased intracranial pressure, such as headaches, nausea, vomiting, irritability, lethargy, and changes in behavior (Dang & Phillips, 2017). These symptoms are often caused by obstructive hydrocephalus due to the tumor's location and growth. Additionally, other symptoms can be related to the tumor's specific location within the CNS, including vision loss, seizures, gait and balance disorders, and focal neurological deficits. Treatment options for brain and spinal cord tumors are influenced by several factors, including the tumor's type and location, the extent of its growth or spread, the presence of specific gene or chromosome changes in the tumor cells, and the patient's age and overall health (Damodharan & Puccetti, 2023). The treatment often involves a multidisciplinary approach, incorporating surgery, chemotherapy, radiation therapy, and emerging targeted therapies. Surgery remains a cornerstone, aiming for maximal tumor resection to alleviate symptoms and provide tissue for histopathological and molecular diagnosis. In cases where complete resection isn't feasible, biopsy and subsequent adjuvant therapies are employed.

Advances in molecular genetics have shifted treatment paradigms, enabling more personalized approaches. For instance, tumors with specific genetic alterations, such as BRAF V600E mutations in low-grade gliomas, are now treated with targeted therapies like BRAF inhibitors (Damodharan & Puccetti, 2023). New techniques in neuroimaging and intraoperative monitoring have also improved surgical outcomes and reduced morbidity. Moreover, novel therapies like Tumor Treating Fields (TTFs) and immunotherapy are being explored, with some showing promising results in clinical trials (Kumaria, 2022).

The prognosis for childhood CNS tumors varies significantly based on tumor type, location, molecular characteristics, and patient age. In the United States, the five-year survival rate for all malignant and non-malignant childhood CNS tumors was 84% (Ostrom et al., 2022). Low-grade gliomas generally have a more favorable prognosis, especially when complete resection is achieved with a 97% five-year survival rate for pilocytic astrocytoma. However, high-grade gliomas and certain embryonal tumors like medulloblastomas present a more challenging outlook. The integration of molecular profiling into diagnostic criteria has refined prognostic

assessments, allowing for improved risk stratification and more tailored therapies (Louis et al., 2016). For instance, patients with WNT-activated (Wingless) medulloblastomas have a notably favorable prognosis, whereas those with SHH-activated (Sonic Hedgehog) TP53-mutant medulloblastomas face a poorer outcome.

Advances in molecular diagnostics and targeted therapies hold promise for improving survival rates and quality of life. However, long-term follow-up remains essential to detect and manage late-onset morbidities resulting not only from the tumor itself but also from its treatment (Roddy & Mueller, 2016). These late effects include neurocognitive disorders, neuromuscular deficits, and secondary malignancies and can emerge months or years after completing cancer therapy. Younger children, those treated with cranial radiation, and those with tumors in critical CNS regions are at the highest risk.

Table 1. Risk and protective factors for childhood CNS tumors.

More established risk factors are highlighted in bold		
	<i>Reduced risk</i>	<i>Increased risk</i>
Demographics		Race/Ethnicity
		Male sex
		Parental age
Growth/Development		Intrauterine growth rate
		High birthweight
		Head circumference
		Congenital anomalies
Germline susceptibility	Common SNPs	Cancer syndromes
	Epimutations	Common SNPs
	Maternal genetic effects	Maternal genetic effects
Immune system	Allergic conditions	
	Early-life infection exposure	
Environmental factors	In utero folic acid	Ionizing radiation
		Air pollution
		Pesticides
Somatic alterations		Dietary nitroso compounds
		Somatic mutations
		Epigenetic alterations
		Tumor microenvironment

Note: Adapted from Cancer Epidemiology, Biomarkers & Prevention, 2014, 23(12), 2716–2736, Johnson KJ, Cullen J, Barnholtz-Sloan JS, et al., Childhood Brain Tumor Epidemiology: A Brain Tumor Epidemiology Consortium Review, with permission from the American Association for Cancer Research (AACR). Abbreviations: SNP=single nucleotide polymorphism.

1.2 Exposure to radiation

Radiation is a natural phenomenon that exists all around us and has been present since the formation of the Earth (UNEP, 2016). All matter is made up of atoms, which consist of various components. The nucleus of an atom contains tiny particles called protons and neutrons, while the atom's outer shell holds particles known as electrons (Bogard et al., 2023). The nucleus has a positive electrical charge, whereas the electrons carry a negative electrical charge. These internal forces strive to maintain a strong, stable balance by eliminating excess atomic energy, a process known as radioactivity. During this process, unstable nuclei may release a certain amount of energy, and this spontaneous release is referred to as radiation. In addition to terrestrial radioactivity, other natural sources of ionizing radiation exist, most notably cosmic radiation, which arises from high-energy particles traveling through space and originating in the sun and other celestial phenomena (UNSCEAR, 2000a). Radiation can also be generated artificially by machines, such as x-ray machines and particle accelerators, which produce radiation through controlled physical processes. Radiation travels from its source as energy waves or energized particles.

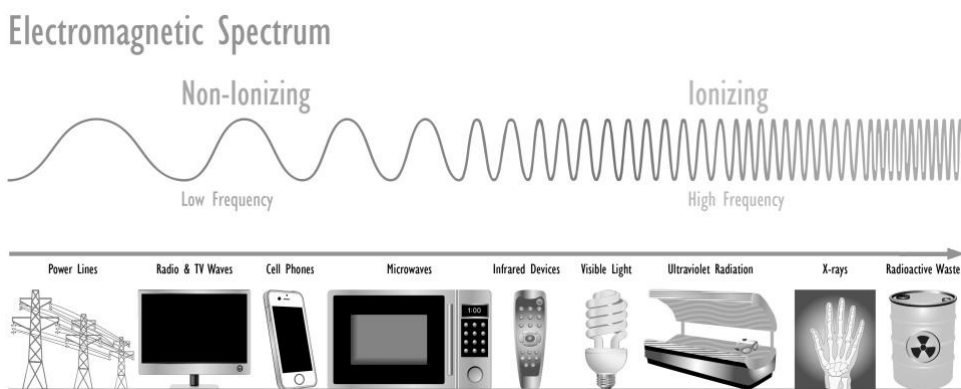
1.2.1 Types of radiation

Radiation can be classified in different ways depending on the context and focus. One widely used categorization is ionizing and non-ionizing radiation, each differing in characteristics and potential health effects (Martin et al., 2019). Ionizing radiation, which includes x-rays, gamma rays, and alpha and beta particles, carries enough energy to detach electrons from atoms as they pass through matter, a process known as ionization. This process can pose health risks by damaging tissues and DNA in genes (UNSCEAR, 2000b). Non-ionizing radiation, on the other hand, includes electromagnetic fields (EMFs) from power lines, radiofrequency radiation from mobile phones, ultraviolet (UV) radiation from the sun, and visible light. This type of radiation possesses sufficient energy to cause atoms in a molecule to move or vibrate, but it lacks the energy required to remove electrons from atoms.

In terms of physical forms of radiation, matter emits energy (radiation) in two fundamental ways. One type of radiation is pure energy without mass, known as electromagnetic radiation (UNEP, 2016). This form consists of vibrating or pulsating rays or waves of electrical and magnetic energy. Examples include sunlight, x-rays, radar, and radio waves. All electromagnetic waves travel at the speed of light in a

vacuum but have a wide range of frequencies, wavelengths, and photon energies. The electromagnetic spectrum encompasses all electromagnetic radiation and is divided into subranges that are named based on their emission, transmission, and absorption behaviors, as well as their practical applications (Figure 1). The boundaries between these subranges are not precisely defined and often overlap. The other type, known as particle radiation, involves tiny, fast-moving particles that possess both energy and mass (Martin et al., 2019). This less familiar form of radiation includes alpha particles, beta particles, and neutrons.

Figure 1. The electromagnetic spectrum.



Source: U.S. Environmental Protection Agency (EPA), Radiation Basics. <https://www.epa.gov/radiation/radiation-basics>. Public domain.

1.2.2 Computed Tomography (CT)

Computed Tomography (CT) is a sophisticated imaging technique that utilizes x-rays to create detailed cross-sectional images of the body (Rubin, 2014). Unlike traditional x-ray imaging, which provides only two-dimensional views, CT scans produce comprehensive three-dimensional images, allowing for the examination of internal organs, bones, soft tissues, and blood vessels with high clarity. This is achieved by rotating the x-ray source and detectors around the patient, capturing multiple images from different angles, which are then processed by a computer to generate an extensive representation of the area being studied. CT scans are invaluable in diagnosing a variety of conditions, including cancers, cardiovascular diseases,

infectious diseases, trauma, and musculoskeletal disorders, making them a crucial tool in modern medical diagnostics and treatment planning (STUK, 2012).

The history of clinical CT scanning began with the EMI (Electric and Musical Industries) scanner, invented by Nobel laureate Godfrey N. Hounsfield in the early 1970s (New et al., 1974). Early CT images were produced using a translate-rotate geometry, with the patient's head inserted into a water-filled box to minimize air interference (Rubin, 2014). By the 1980s, third generation rotate-rotate geometry became the standard. Initial scanners operated in a step-and-shoot mode, causing delays and artifacts. Soon after, the development of continuous gantry rotation with a slip ring and continuous table translation enabled helical scanning, allowing for faster and more detailed imaging.

Subsequent advancements included the introduction of four-detector row CT in 1998, which greatly enhanced spatial resolution and CT angiography capabilities (Hu et al., 2000). This was followed by 16-detector row CT in 2002 and 64-detector row CT in 2004, making three-dimensional visualization routine and improving cardiac imaging (Boone, 2006). Further advancements came in 2006 with dual-source dual-detector CT and in 2010 with a 320-row detector system capable of single-heartbeat imaging (Hsiao et al., 2010). Photon-counting detectors (PCDs) are a significant advancement in CT imaging, approved for clinical use in 2021. Unlike traditional scintillating detectors, PCDs convert x-ray energy directly into electrical signals, preserving information about individual photons and enabling the counting of x-rays in different energy ranges (McCollough et al., 2023). This results in the elimination of electronic noise, improved dose efficiency, and better spatial resolution, which is needed in imaging of the inner ear, bones, small blood vessels, heart, and lungs.

CT scan parameters play a pivotal role in balancing image quality with patient radiation exposure. Among the key settings, tube potential (kVp) determines the energy of the x-ray beam and directly influences image contrast (Raman et al., 2013). The tube current-time product (mAs) controls the number of x-ray photons produced and thus influences how much detail can be captured in the final image. Image noise, characterized by random pixel value fluctuations that appear as graininess or speckling, can obscure subtle anatomical details and compromise diagnostic clarity. Lowering kVp or mAs reduces the radiation dose, but each parameter influences image quality differently (Zhao et al., 2022). Reductions in mAs tend to produce a linear and relatively predictable increase in noise. In contrast, lowering kVp can lead to nonlinear, exponential increases in noise, often requiring a compensatory increase in mAs to maintain diagnostic image quality.

Another important parameter in helical scanning is pitch, defined as the table travel per rotation divided by beam width (Raman et al., 2013). A pitch of 1 indicates contiguous slices (no gaps or overlaps), <1 means overlapping slices (higher dose, better image quality), and >1 means gaps between slices (lower dose, but risk of artifacts). Increasing pitch reduces radiation dose linearly if all else is constant. Low-pitch scans offer better image quality with less noise and fewer artifacts, while higher pitches may lead to unacceptable image degradation. For routine body CT, a pitch of 1 is generally sufficient. Furthermore, scan length, which defines the total anatomical coverage, is directly proportional to radiation exposure and should be minimized to cover only the clinically necessary region.

Radiation dose in CT imaging is commonly quantified using the CT dose index volume (CTDIvol), which characterizes the average radiation output per slice delivered by the scanner, standardized using a phantom and accounting for pitch in helical scans (Zhao et al., 2022). A related metric, the dose-length product (DLP), calculated as CTDIvol multiplied by the scan length, provides an estimate of the total scanner output for the entire scan. However, neither CTDIvol nor DLP directly measures the dose absorbed by individual patients, and estimating the effective dose or organ-specific dose requires additional modeling and patient-specific information, as described later in this section.

CT offers undeniable benefits in pediatric medicine, yet its use in children has raised significant concerns. During the 1990s and early 2000s, the frequency of pediatric CT scans increased globally with several studies showing that children undergoing CT scans face a higher risk of developing malignancies, which will be discussed in detail in the literature review chapter.

1.2.3 Other sources of radiation

The units and concepts used to quantify radiation dose are discussed in detail in the following subsection. Finns receive an average annual effective radiation dose of 5.9 millisieverts (mSv) according to 2018 data (STUK, 2018). The largest contributor to this dose is background radiation, including 4 mSv from indoor radon and 1.1 mSv from other naturally occurring sources. Less than one millisievert is caused by the medical use of radiation such as conventional radiography, CT imaging, and nuclear medicine. The effective dose contribution from artificial radioactive substances present in the environment is negligible. Radon is a naturally occurring radioactive gas that is produced by the decay of uranium found in soil and rock (WHO, 2009). In

Finland, high levels of radon are common, largely due to the country's geological composition, construction methods, and climate (STUK, 2021). Radon typically enters buildings through cracks in foundations, accumulating indoors, especially in poorly ventilated spaces like basements. In adults, long-term exposure to elevated radon levels is the second leading cause of lung cancer after smoking (WHO, 2009). A pooled analysis showed that the relative risk of lung cancer per 100 Bq/m³ of radon exposure was similar across smoking groups, indicating a multiplicative interaction. However, because smokers have a much higher baseline risk of lung cancer, the absolute risk increase attributable to radon is substantially greater among smokers (Darby et al., 2005). The specific effects of radon exposure in children are less well-characterized (Kendall et al., 2021).

1.2.4 Dosimetric concepts

Dosimetry is the science of measuring and assessing radiation doses absorbed by matter, particularly human tissue. It plays a crucial role in fields such as medical imaging, radiation therapy, nuclear safety, environmental monitoring, and radiation biology and epidemiology. The three primary dosimetric quantities are absorbed dose, equivalent dose, and effective dose, each serving a specific function in assessing radiation's impact on biological tissues (UNEP, 2016). These concepts are fundamental to understanding how radiation interacts with the body and informs protective measures and risk assessments.

The absorbed dose represents the amount of radiation energy deposited per unit mass of tissue and is measured in gray (Gy) (ICRP, 2007). It quantifies the energy imparted during procedures like CT imaging or radiation therapy. However, it does not account for how the type of radiation influences biological damage. This is determined in part by the radiation's linear energy transfer (LET), a measure of how much energy is deposited per unit path length in tissue. Radiation with high LET, such as alpha particles, creates densely ionizing tracks that cause more severe biological damage than low-LET radiation like x-rays.

The equivalent dose addresses these differences by applying a radiation weighting factor to the absorbed dose, reflecting variations in radiological effectiveness (Bogard et al., 2023). In CT imaging, where low-LET x-rays are used, the weighting factor is 1, making the equivalent dose numerically equal to the absorbed dose. However, it is expressed in sieverts (Sv), which allows for comparisons across radiation types.

The effective dose takes this a step further by incorporating tissue-specific sensitivity using tissue weighting factors. For example, the lungs and red bone marrow carry higher weights due to their greater vulnerability to radiation-induced damage, particularly cancer, compared to less sensitive tissues like the skin (Bogard et al., 2023). Also measured in sieverts, the effective dose provides an estimate of overall long-term health risks from radiation exposure and is crucial for setting occupational exposure limits and public health radiation safety standards. The effective dose is primarily intended for population-level risk assessments rather than predicting individual outcomes, as it is a calculated approximation rather than a direct physical measurement (ICRP, 2007).

These dosimetric concepts are applied to both external and internal radiation exposure scenarios. Internal radiation exposure involves radioactive materials being ingested, inhaled, or entering the body through wounds (Martin et al., 2019). In these cases, specialized dosimetric methods, including internal dosimetry, are needed to calculate the absorbed doses in specific organs. Internal dosimetry is especially crucial in the context of nuclear accidents or contamination events, where radioactive substances such as iodine-131 or cesium-137 may enter the body (Bogard et al., 2023). Following such incidents, internal dosimetric assessments help evaluate health risks and guide long-term monitoring and interventions to reduce potential harm.

In addition to these core dosimetric quantities, several other concepts are crucial to understanding radiation exposure in clinical and environmental settings. The dose rate (measured in Gy/s, Sv/s, or similar units) refers to how quickly radiation is delivered, which influences biological effects (Martin et al., 2019). Higher dose rates can cause more immediate tissue damage, while lower dose rates spread out over time may allow for some cellular repair. Additionally, the cumulative dose is important for understanding the total radiation exposure a person has received over a prolonged period, which is especially relevant for patients undergoing repeated diagnostic imaging or cancer treatments, or workers in nuclear power or healthcare settings (UNEP, 2016).

1.3 Epidemiological concepts

1.3.1 Epidemiological study designs

Epidemiology is the study of the distribution and determinants of health and disease conditions in specified populations (Szklo & Nieto, 2019). This field seeks to understand patterns, causes, and effects of health-related events and apply this knowledge to control health problems. Epidemiology is categorized into descriptive and analytical branches. Descriptive epidemiology uses available data to analyze how health outcome rates, such as mortality and incidence, vary according to demographic characteristics, geographical regions, and seasonal or long-term trends. It identifies high-risk groups for prevention and generates causal hypotheses based on disparities observed in person, place, and time (Celentano et al., 2019). Analytical epidemiology, on the other hand, focuses on study designs that test hypotheses about associations between risk factors and health outcomes. These studies are either observational or experimental (randomized clinical trials). Cohort, case-control, cross-sectional, and ecological designs are the basic types of observational studies.

In a cohort study, a group of individuals (a cohort) who are free of the outcome of interest at the beginning is identified and followed over a specific period to determine the occurrence of health-related events (Rothman et al., 2021). The primary goal of a cohort study is to examine whether the incidence of these events is associated with a defined exposure. In a case-control study, two groups of individuals, one with the outcome (cases) and one without (controls), are compared by collecting information on their past exposures to a certain risk factor to identify potential associations with the outcome.

Case-control studies are efficient for studying rare diseases, as they start with individuals who already have the disease, making them relatively quick and inexpensive (Szklo & Nieto, 2019). However, they may be prone to recall bias depending on how information is collected and can approximate risk under certain conditions but do not provide a direct measure of incidence. In contrast, cohort studies allow for the direct measurement of incidence and the establishment of the temporal sequence between exposure and outcome (Rothman et al., 2021). Cohort studies are less prone to certain biases than case-control studies but typically require more resources, take longer to conduct, and necessitate larger sample sizes, which can make them less feasible for studying rare diseases.

1.3.2 Measures of disease frequency and association

Incidence is best understood within the context of prospective (cohort) studies, which can include either static or dynamic populations, depending on whether individuals enter or exit the cohort during the study period (Celentano et al., 2019). The fundamental structure of any incidence metric is expressed as the number of events occurring in a specific population during a given time period (numerator), divided by either the population at risk for that event or the sum of follow-up times (person-time) over that period (denominator) (Szklo & Nieto, 2019). Accordingly, there are two main types of incidence measures, distinguished by the type of denominator used: incidence based on the number of individuals at risk (cumulative incidence or incidence proportion), and incidence based on person-time units at risk (incidence rate).

The ratio of the incidence of the outcome in the exposed group to the incidence of the outcome in the unexposed group is called the risk ratio (relative risk) when cumulative incidences are compared, or the rate ratio when incidence rates are compared (Rothman et al., 2021). Both measures are used to assess the association between an exposure and an outcome, depending on the study design and type of population. On the other hand, odds compare the probability of an event happening to the probability of it not happening (Szklo & Nieto, 2019). They are a key concept in case-control studies, where the odds of exposure among cases are compared to the odds of exposure among controls, leading to the calculation of the odds ratio. The odds ratio is a good approximation of the relative risk when the outcome or disease being studied is rare (the event occurs in less than 10% of the population).

1.3.3 Biases, confounding, and validity

Validity in epidemiology is crucial for ensuring that the associations identified between exposures and outcomes reflect the true relationship. Internal validity refers to the degree to which the study accurately measures the association between exposure and outcome within the study population (Szklo & Nieto, 2019). It is compromised when biases or confounding are present. Bias occurs when systematic errors in study design or conduct lead to a flawed estimate of the association, often due to systematic differences between the comparison groups (e.g., cases and controls). Two common types of bias are selection and information bias.

Selection bias arises when procedures used to select or retain study participants, either at entry or during follow-up, result in a study population in which the association

between exposure and outcome differs from that in the source (target) population (Rothman et al., 2021). This systematic error distorts effect estimates and may lead to invalid inferences about causality. For example, in a study investigating if tuberculosis protects against cancer, researchers selected controls from a hospital autopsy pool where tuberculosis was a major reason for admission (Celentano et al., 2019). This flawed method created a control group with an artificially high prevalence of tuberculosis, leading to the false conclusion that the disease was protective against cancer when the observed association was merely an artifact of this biased selection.

Information bias stems from imperfect definitions of study variables or flawed data collection procedures, leading to systematic errors in the classification of exposure status and/or outcome status (Szklo & Nieto, 2019). These errors can result in misclassification for a substantial proportion of study participants, thereby distorting effect estimates. A classic example is recall bias: in case-control studies of lung cancer, cases may report past smoking behavior more thoroughly than controls, resulting in differential exposure ascertainment. Misclassification can be broadly categorized as either differential or non-differential, depending on whether the measurement error varies by outcome or exposure status. Non-differential misclassification of a binary exposure typically biases effect estimates toward the null and reduces statistical precision. In contrast, differential misclassification can bias associations in either direction, potentially generating spurious findings or masking true effects (Rothman et al., 2021).

It is important to distinguish systematic error (bias) from random error, where inaccuracies occur unpredictably and affect all study groups without a consistent pattern (Rothman et al., 2021). While bias affects the validity of an estimate (whether it reflects the true value), random error affects its precision (the degree of variability due to chance). Both forms of error influence the interpretation of epidemiologic results and must be considered when evaluating study quality.

Another major threat to internal validity is confounding, which occurs when the association between exposure and outcome is distorted by a third variable that is related to both but not on the causal pathway (Greenland & Morgenstern, 2001). For instance, if a study on coffee consumption and heart disease does not account for smoking, a known risk factor for heart disease that is often associated with coffee drinking, the study may incorrectly attribute heart disease risk to coffee instead of smoking.

In addition to internal validity, external validity (generalizability) is critical for determining whether the findings of the study can be applied to broader populations beyond the study sample (Szklo & Nieto, 2019). A study with strong internal validity

may still lack external validity if the study population is too specific or not representative of the general population. For instance, a study conducted solely on male participants may not accurately reflect the effects of the exposure in females.

The consequences of a lack of validity in epidemiological studies are significant. Incorrect or biased conclusions can lead to misguided public health recommendations, ineffective interventions, and wasted resources (Soumerai et al., 2015). Moreover, the credibility of epidemiological findings can be undermined if issues of validity are not properly addressed. To ensure the highest possible validity, researchers must design studies carefully to minimize biases, use appropriate analytical techniques to adjust for confounding, and consider how representative their sample is of the population to which they hope to generalize their findings. By improving both internal and external validity, epidemiological studies can provide more reliable and actionable insights into public health.

2 LITERATURE REVIEW

This chapter is based on a narrative literature review aiming to synthesize key epidemiological studies on pediatric CT use and childhood CNS tumor incidence and risk. While not a formal systematic review, relevant peer-reviewed publications were identified through searches in PubMed and Semantic Scholar, using combinations of keywords such as “CT imaging”, “pediatric”, “childhood brain tumors”, “radiation exposure”, “incidence trends”, and “cancer risk”. Preference was given to high-quality observational studies, including large cohort and case-control studies, as well as systematic reviews and consensus reports from authoritative bodies such as the International Commission on Radiological Protection (ICRP) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). No formal inclusion or exclusion criteria were applied. However, emphasis was placed on studies published after 1990, corresponding to the widespread adoption of pediatric CT imaging. Articles not in English or not focused on pediatric populations were generally excluded unless they provided essential background information. The review aimed to reflect geographic diversity and methodological variation, including differences in study design, exposure timing and lag assumptions, dose estimation methods, tumor classification schemes, cancer outcome ascertainment, and approaches to confounding adjustment, in order to contextualize the findings of the current study.

2.1 Patterns and trends in pediatric CT use

The history of CT use has evolved significantly since its invention in the 1970s. The global average annual number of CT examinations, including those performed on children, grew from 6.1 per 1000 population in the 1970s to 48 per 1000 population in the 1990s (UNSCEAR, 2000a). The development of helical CT in 1989 facilitated this increase as it led to shorter scanning times, improved image quality, and further scanning techniques such as CT endoscopy and CT fluoroscopy (Rubin, 2014). In children, CT scans are commonly used to assess head, abdomen, and thorax injuries following trauma, identify the causes of abdominal pain, diagnose and stage cancers,

track the response to cancer treatment, and detect or monitor infectious and inflammatory diseases (STUK, 2012).

With the increasing use of medical imaging in pediatric populations, concerns have grown about the potential adverse effects from exposure to ionizing radiation, especially since CT parameters historically weren't adjusted for age or exam type (Paterson et al., 2001). This lack of adjustment has consequently resulted in pediatric patients receiving unnecessarily high radiation doses from CT imaging. In response, ICRP issued guidelines in publication 73 aimed at enhancing radiation safety in medical settings, emphasizing the principle of justification of medical exposures and optimization of radiological protection (ICRP, 1996). These guidelines highlight the importance of balancing diagnostic or therapeutic benefits against radiation risks, advocating that radiation doses be kept as low as reasonably achievable (ALARA), while still ensuring image quality adequate for the intended clinical purpose.

Publication 73 also recommended the use of diagnostic reference levels (DRLs), which serve as dose benchmarks for common radiological exams such as CT scans and conventional radiography (ICRP, 1996). These reference values enable medical facilities to compare their dose levels to established standards. If radiation doses consistently exceed the DRLs, it indicates a need for review of imaging protocols and potential dose reduction, provided that diagnostic image quality remains adequate. Building upon these principles, the European Commission's Radiation Protection 109 report from 1999 reinforced the value of DRLs and recommended their application in pediatric imaging, highlighting the need for specific reference levels tailored to children (EC, 1999).

D. J. Brenner et al. (2001) reported that by extrapolating risk models from higher radiation doses received by atomic bomb survivors to lower doses, pediatric patients, particularly very young children, had a significantly higher lifetime cancer risk from radiation exposure from CT scans than adults. In a subsequent influential article, D. J. Brenner and Hall (2007) further highlighted the increasing use of CT scans in both adults and children, drawing widespread attention to the associated risks. They argued that the risks of CT imaging are not merely theoretical but based on observed increases in cancer rates among individuals exposed to organ doses comparable to those used in CT procedures. These articles paved the way for epidemiological studies on CT-related cancer risks and pediatric-focused radiation safety campaigns such as Image Gently (Goske et al., 2008).

By the early 2000s, national survey studies began focusing on CT use in children and suggesting DRLs for national use. The pediatric fraction of CT imaging varied between countries from 1% in Germany and Switzerland, 2.7% in Japan, to 6.5% in

the USA (CRCPD, 2007; Galanski et al., 2005; Nishizawa et al., 2004; Verdun et al., 2008). Head CT was by far the most common CT type ranging between 52% and 80% of all CTs. CT use, particularly head CT, was more common in younger age groups. These studies reported large dose variations across countries and institutions especially when automatic dose control was not used. Multi-slice CT (MSCT), concentrated in large hospitals, generally resulted in higher doses compared to single-slice CT (SSCT). In a British survey, effective doses from head and chest CTs in very young children were higher than for adults (Shrimpton et al., 2005). A subsequent prospective multinational survey coordinated by the International Atomic Energy Agency (IAEA) further highlighted geographic disparities in pediatric CT usage (Muhogora et al., 2010). The proportion of pediatric CT examinations was highest in Africa (20%), followed by Asia (16%) and Eastern Europe (5%). Notably, in several centers, adult CT scan protocols were applied to pediatric patients, substantially increasing radiation exposure. For instance, radiation doses for chest CT were reduced by approximately 38–53% in Sudan and Thailand after parameter adjustments.

Subsequent studies examined the trends of CT use in children over longer time periods (Table 2), showing a marked increase from the 1990s through the early 2000s. The use of pediatric CT doubled in Great Britain between 1993 and 2002 and in Australia between 1985 and 2000 with rates stabilizing thereafter (Brady et al., 2016; Pearce et al., 2012a). In the US, the rates doubled for children younger than 5 years of age and tripled for children 5 to 14 years of age between 1996 and 2005 (Miglioretti et al., 2013). Similarly, CT use in children younger than 5 years of age in France increased by 15% between 2000 and 2006 (Bernier et al., 2012). In the Netherlands, pediatric CT use tripled between 1990 and 2012 (Meulepas et al., 2016). These studies reported hospital-based differences in CT equipment, protocol standardization, and regulatory oversight, which contributed to substantial variability in both dose levels and pediatric CT usage across various settings. The mean number of CT examinations per child ranged from 1.3 to 1.9 across the studies, with two studies showing an upward trend in this average over time (Bosch de Basea et al., 2016; Brady et al., 2016). In the French study, younger children, especially infants, were more likely to undergo multiple scans (Bernier et al., 2012).

Several studies conducted in the US, summarized in Table 3, focused on pediatric populations treated at the emergency department especially for head injuries and abdominal pain as diagnostic imaging is often part of the management plan. Overall, the utilization of pediatric CT during emergency department visits increased markedly from the mid-1990s until the late 2000s, followed by a plateau, although one study

showed a slight decrease in the 2010s (Marin et al., 2020). For children presenting with head trauma, the use of CT doubled from 12.8% in 1995 to 22.4% in 2003 (Blackwell et al., 2007). After 2008, the use of head CT stabilized overall but continued to increase at nonteaching hospitals (Ukwuoma et al., 2021). Similarly, the use of CT to manage children presenting with a fall doubled between 2001 and 2009 (Shahi et al., 2015). For patients presenting to the emergency department with abdominal pain, 16.6% underwent a CT scan in 2010 compared to 1.2% in 1997 (R. C. Wang et al., 2021). A diagnosis of appendicitis was coupled with a CT scan in 70% of the cases in 2016, up from 5.2% in 1997.

Collectively, the use of CT tended to increase with patient age, with the highest utilization rates observed in older pediatric groups, particularly in cases involving traumatic injuries. Non-pediatric and non-teaching emergency departments reported higher CT utilization rates compared to pediatric-focused and teaching emergency departments. Pediatric-focused emergency departments frequently opted for non-radiating alternative imaging methods like ultrasonography. Head CT utilization for specific complaints like seizures and head injuries decreased, while ultrasound became more frequently utilized for abdominal assessments (ultrasound-first approach) and MRI for ventricular shunt procedures and head trauma.

Table 2. Summary of studies on the trends of CT use in children.

Reference	Time period	Number of CTs	Age (yrs)	CT use trends by CT numbers	CT use trends per 1000 child-years	CT use trends by APC (95% CI)
Bernier et al. 2012 France	2000–2006	44,417	0–4	Increased by 14.8%	NA	NA
Pearce et al. 2012a Great Britain	1993–2002	361,559	0–21	Increased by 93.8%	NA	NA
Miglioretti et al. 2013 USA	1996–2010	NA	0–4	NA	11 (1996) to 20 (2005–2007) 20 (2005–2007) to 15.8 (2010)	NA
Miglioretti et al. 2013 USA	1996–2010	NA	5–14	NA	10.5 (1996) to 27 (2005–2007) 27 (2005–2007) to 23.9 (2010)	NA
Bosch de Basea et al. 2016 Spain	1991–2013	131,655	0–20	NA	15.2 (2005) to 18 (2013)	4.5% (2.0, 7.2) (1991–2013)
Brady et al. 2016 Australia	1985–2005	896,306	0–19	NA	4 (1985) to 11 (2005)	NA
Meulepas et al. 2016 Netherlands	1990–2012	236,066	0–17	Increased by 236.6%	2 (1990) to 3.4 (2000) 3.4 (2000) to 6.7 (2012)	10.9%* (1990–1993) 3.9%* (1993–2003) 11.3%* (2003–2007) 2.4% (2007–2012)
Smith-Bindman et al. 2019 USA	2000–2016	5,439,874	0–17	NA	18 (2000) to 22 (2016)	10.1% (7.8, 12.5) (2000–2005) –3.4% (–5.7, –1.0) (2006–2011) –1.8% (–4.5, 1.1) (2012–2016)
Kim et al. 2022 S. Korea	2012–2017	576,376	0–17	Increased by 7.7%	9 (2012) to 11 (2017)	4.6% (2012–2017)

Abbreviations: APC=annual percentage change, *=APC is significantly different from 0 (P<0.05).

Table 3. Summary of studies on pediatric CT use in the emergency department.

Reference	Time period	ED visit Focus	Number of ED visits	Number of ED visits with CT	Age (yrs)	CT use trends by the percentage of ED visits with CT
Blackwell et al. 2007 USA	1995–2003	Head trauma	2747	NA	0–18	12.8% (1995) to 22.4% (2003), Peak of 28.6% (2000)
Larson et al. 2011 USA	1995–2008	All	104,243	3402	0–17	1.2% (1995) to 5.9% (2008)
Menoch et al. 2012 USA	2003–2010	All	987,932	54,797	NA	No change during 2003–2010 (5%)
Shahi et al. 2015 USA	2001–2010	Falls	9763	NA	0–17	5.3% (2001) to 11.3% (2010) Peak of 16.6% (2009)
Marin et al. 2020 USA	2009–2018	All	26,082,062	NA	0–17	3.9% (2009) to 2.9% (2018) Plateau 2014–2018
Ukwuoma et al. 2021 USA	2008–2013	Closed head injury	4,552,071	1,181,659	0–17	No change during 2008–2012 (26%)
R. C. Wang et al. 2021 USA	1997–2016	Abdominal pain	54,815	NA	0–18	1.2% (1997) to 14.7% (2016) Peak of 16.6% (2010)
R. C. Wang et al. 2021 USA	1997–2016	Appendicitis	1401	NA	0–18	5.2% (1997) to 71.0% (2016)

Abbreviations: CT=computed tomography, ED=emergency department.

2.2 Trends in childhood CNS tumor incidence

Analyzing incidence trends of childhood CNS tumors across different studies, regions, and countries involves several methodological challenges. A major issue concerns variability in the quality and completeness of cancer registry data, as well as differences in cancer reporting and registration practices (Steliarova-Foucher et al., 2017). For example, non-malignant CNS tumors were not systematically recorded in U.S. cancer registries until 2004, whereas several European registries began including these tumors much earlier, in some cases as far back as the 1950s (United States, 2002). Another complexity arises from the use of different classification systems, such as the International Classification of Childhood Cancer (ICCC) and the WHO CNS tumor classification system, each adopting distinct approaches to categorizing tumors, making direct comparisons of tumor histology groups challenging (Louis et al., 2016; Steliarova-Foucher et al., 2005). Additionally, temporal changes in classification systems, including reclassification of tumor types and the incorporation of molecular parameters in newer editions, introduce further inconsistencies in incidence data (Horbinski et al., 2024). Disparities in healthcare infrastructure and access, and differences in population demographics, such as age distribution, also influence trend analyses. These factors must be taken into account when interpreting the literature review presented in this section.

Comparing incidence rates across time periods or regions is more reliable when adjusted for age structure differences, given the strong age dependence of cancer risk (Sung et al., 2021). Age-standardized rates (ASRs) achieve this by weighting age-specific incidence rates against a standard population, with results typically expressed per 100,000 person-years (Szklo & Nieto, 2019). However, variability arises when different standard populations are used, as they assign different weights to age groups. For instance, the world standard population 2000–2025 gives greater weight to younger ages than the European standard population 2013, which can influence overall ASRs and affect cross-population comparisons (Ahmad et al., 2001; EC, 2013). This effect is minimized when analysis is restricted to a narrower age band, such as children aged 0–14 years, since only the relative weights within that specific age range are applied, rather than those across the full age spectrum. Another key metric is the annual percent change (APC), which quantifies the yearly rate of change in a trend, typically calculated using log-linear regression models.

In the United States, the reported incidence of childhood malignant brain tumors increased from 2.76 per 100,000 child-years in 1977–1981 to 3.34 per 100,000 child-years in 1990–1994, reflecting a 21% increase (Smith et al., 1998). This study

explained the observed increase in incidence by a jump model, indicating a step increase occurring around the mid-1980s, rather than a continuous linear increase over time. The timing aligns with the widespread adoption of MRI technology to manage CNS conditions in children, considerably improving tumor detection. Notably, low-grade gliomas in the cerebrum and brain stem accounted for much of the observed increase, but without a parallel rise in mortality. The authors thus concluded that the trend likely reflected diagnostic improvements and classification changes rather than a true increase in tumor occurrence.

Three Nordic studies covering similar periods reported increasing incidence rates of childhood CNS tumors: Sweden (1973–1992), Norway (1970–1999), and Denmark (1980–1996) (Hjalmarsson et al., 1999; Johannesen et al., 2004; Raaschou-Nielsen et al., 2006). The APC in incidence was 3.2% (95% CI 2.2%, 4.2%) in Sweden, 2.0% (95% CI 1.2%, 2.8%) in Norway, and 2.9% (95% CI 1.3%, 4.5%) in Denmark. Markedly, the Danish study described a steady linear increase rather than a jump model. A pooled study of 19 European countries reported a statistically significant APC of 1.7% ($p < 0.0001$) for malignant and non-malignant CNS tumors between 1978 and 1997 (Peris-Bonet et al., 2006). The overall ASR of childhood CNS tumors in Europe was 2.99 per 100,000 child-years, compared to 4.38 in Northern Europe, 3.18 in Eastern Europe, and 2.93 in Southern Europe. The stepwise increase identified in U.S. data could not be replicated, likely due to the heterogeneous diagnostic and healthcare practices across Europe.

Between the mid-1980s and early 2000s, CNS tumor incidence rates were reported to be stable or only slightly increasing (Lannering et al., 2009; McKean-Cowdin et al., 2013; Schmidt et al., 2011; Spix et al., 2008). In the past two decades, national studies from France (2000–2008, ASR=3.90 per 100,000 child-years), Canada (2001–2015, ASR=3.80), and Germany (2010–2019, ASR=4.33) have shown stable incidence rates of childhood CNS tumors (Desandes et al., 2014; Larouche et al., 2020; Wellbrock et al., 2024). However, examining a longer period in Germany revealed a marked rise from 2.86 in 1990–1999 to 4.33 in 2010–2019, subsequent to the introduction of the German Childhood Cancer Registry in the 1980s. In the United States, between 2000 and 2015, the incidence of malignant CNS tumors increased by an APC of 0.6% (95% CI 0.3%, 0.9%) (Ostrom et al., 2018). For non-malignant CNS tumors, the increase was more pronounced, with an APC of 2.3% (95% CI 1.6%, 2.9%).

The data summarized in this paragraph reflect the range of estimates reported in the previously cited studies, focusing on children aged 0–14 years. Astrocytomas represented the most common group of CNS tumors, with ASRs between 1.18 and

1.87 per 100,000 child-years, followed by embryonal tumors, which ranged from 0.71 to 0.77 per 100,000 child-years. In total, 55–87% of childhood CNS tumors were classified as malignant. Incidence rates for all CNS tumors were generally higher in boys than in girls and tended to decline with age, with the highest incidence observed in children under five years old. Specific tumor histology groups also demonstrated age- and sex-based differences in incidence. Boys had higher rates of ependymal tumors and medulloblastoma, whereas girls had a higher incidence of astrocytomas. For pilocytic astrocytoma, incidence rates showed a bimodal peak, occurring around ages 4 and 12 years. Ependymomas were most frequently diagnosed within the first two years of life. While the incidence of ependymomas and embryonal tumors declined with age, the incidence of germ cell tumors and craniopharyngiomas increased in older children. Malignant tumors had the highest incidence in the youngest group of patients (0–5 years).

Temporal trends in childhood CNS tumors varied considerably among tumor histology groups. In Sweden, the incidence of astrocytomas increased by an APC of 3.0% (95% CI 1.6%, 4.4%) between 1973 and 1992 (Hjalmars et al., 1999). The increase was more pronounced in girls, particularly those aged 6–15 years. Pilocytic astrocytomas, particularly, exhibited marked increases, with Denmark reporting an APC of 11.9% (95% CI 6.2%, 17.9%) between 1980 and 1996 (Raaschou-Nielsen et al., 2006). In contrast, rates of astrocytomas not otherwise specified (NOS) had decreased, likely reflecting improved diagnostic specificity (McKean-Cowdin et al., 2013). Ependymomas showed stable incidence rates in Europe and Sweden between the 1970s and 1990s (Hjalmars et al., 1999; Peris-Bonet et al., 2006). Similarly, there was no change in ependymoma incidence rates in the US between 2004 and 2018 (Ostrom et al., 2022). Embryonal tumors increased in Germany during the 1980s (APC=5.9%, 95% CI 1.7%, 10.2%), with a smaller but statistically significant increase in the Nordic countries between 1985 and 2006 (APC=0.97%, 95% CI 0.02%, 1.94%). However, between the 1990s and 2010s, embryonal tumor incidence decreased in the United States (APC=-0.88%, 95% CI -1.33%, -0.43%) and Germany (APC=-1.1%, 95% CI -1.8%, -0.3%) (Tulla et al., 2015; Withrow et al., 2018).

Overall, these trends likely reflect the combined influence of technological advancements in imaging, changes in classification and registration practices, and potentially genuine biological changes. However, the extent to which rising incidence rates represent true epidemiological shifts versus enhanced detection capabilities remains debated. This uncertainty persists even decades after the widespread adoption of MRI, as no consensus has emerged on whether incidence rates have

stabilized at a new level. These issues, along with other potential contributing factors, will be revisited in the discussion chapter.

2.3 Radiation-related CNS tumor risk in children

The association between radiation exposure from CT imaging and the risk of childhood CNS tumors has been the focus of several epidemiological studies in recent years. This section critically examines risk estimates, methodological considerations, and advancements in dosimetry, aiming to provide a nuanced understanding of the complexities in assessing radiation-related CNS tumor risks in children. The studies span multiple countries, with foundational work conducted in Great Britain (Berrington de Gonzalez et al., 2016; Pearce et al., 2012b), followed by investigations in Australia (Mathews et al., 2013; Smoll et al., 2023), France (Foucault et al., 2022; Journy et al., 2015, 2016), Germany (Krille et al., 2015), South Korea (Hong et al., 2019), the Netherlands (Meulepas et al., 2019), Taiwan (Huang et al., 2014; Li et al., 2020; W.-H. Wang et al., 2023), and the Europe-wide EPI-CT study (Hauptmann et al., 2023). Most of the studies were retrospective cohorts, either population-based or exposure-based, and utilized varying cohort sizes, methodologies, and risk assessment models (Table 4).

2.3.1 Variability in risk estimates

The excess relative risk (ERR) is a key measure in radiation epidemiology, used to quantify the proportional increase in the risk of an outcome per unit of radiation dose (conventionally per 100 mGy) relative to the baseline risk (UNSCEAR, 2013). ERR is particularly useful for assessing low-dose ionizing radiation exposures, as it provides a standardized method for comparing risks while accounting for baseline differences. Pearce et al. (2012b), one of the earliest large-scale retrospective cohort studies involving 176,587 exposed individuals in Great Britain, reported an ERR of 2.3 per 100 mGy (95% CI 1.0, 4.9) for childhood CNS tumors following exposure to radiation from CT, establishing a benchmark for risk estimation in subsequent research. Prior to this study, CT-related risk estimates were primarily based on projection models derived from atomic bomb survivor data and other high-dose exposure studies (D. J. Brenner & Hall, 2007; Chodick et al., 2007; Stein et al., 2008). Mathews et al. (2013), in an Australian cohort of 680,211 exposed individuals, found a slightly higher ERR of 2.9 per 100 mGy (95% CI 2.3, 3.7), while Smoll et al. (2023) refined this estimate

to 0.80 per 100 mGy (95% CI 0.54, 1.06) by incorporating an extended follow-up and new organ dose estimates. The original British cohort, as well as the original and updated Australian cohorts, did not consider predisposing factors associated with CNS tumors, such as cancer predisposing syndromes (CPS) and previous malignancies. These factors could potentially confound the observed association or modify the radiation-related risk following exposure to radiation from CT (confounding by indication).

More recent investigations have sought to address this issue by adjusting for or excluding participants with cancer predisposing factors from the analysis, leading to arguably more accurate estimates. In France, utilizing a cohort of 58,620 exposed individuals, Journy et al. (2015) reported an elevated but non-significant ERR of 1.2 per 100 mGy (95% CI -1.3, 3.7). Building on this work, Foucault et al. (2022) analyzed an expanded cohort of 103,015 exposed individuals, incorporating data from CT scans performed outside the primary study hospitals, and reported a statistically significant ERR of 0.5 per 100 mGy (95% CI 0.1, 0.9). Similarly, studies conducted in Germany (2015) and the Netherlands (2019) reported ERRs of 0.8 per 100 mGy (95% CI 0.4, 1.3) and 0.79 per 100 mGy (95% CI 0.16, 2.10), respectively. Adding to this body of evidence, the multinational EPI-CT study (2023), one of the largest and most recent cohorts to date, reported an ERR of 1.27 per 100 mGy (95% CI 0.51, 2.69). This study, which harmonized data across multiple European countries, strengthens the generalizability of risk estimates through its expansive sample size and standardized dosimetry. Nevertheless, unlike several recent cohorts, it did not adjust for cancer predisposing factors.

The variability in risk estimates across studies can be attributed to multiple factors, including how confounding by indication is addressed. Advances in dose estimation methods, from survey-based models to standardized, metadata-driven approaches, have enhanced exposure assessment. Other key factors include cohort size, length of follow-up (latency capture), exclusion and lag periods (addressing reverse causation), dose-response modeling strategies (e.g., linear no-threshold vs. categorical exposure analysis), and inclusion criteria for CNS tumors. These interconnected dimensions highlight the complexity of this research field, several of which will be explored in greater detail in the following subsections.

2.3.2 Temporal patterns in risk

Reverse causation occurs when the disease process itself influences exposure status or its measurement, leading to a biased interpretation of the association if the reversal of temporal order is not recognized (Rothman et al., 2021). In radiation epidemiology, researchers frequently apply exclusion and lag periods to mitigate this bias. An exclusion period refers to a predefined interval following radiation exposure during which cancer cases are excluded from the analysis. In contrast, a lag period designates a time window prior to cancer diagnosis during which radiation exposures are ignored in cumulative dose calculations. Both strategies are intended to account for cancer latency, the interval between exposure and clinical disease manifestation, and to minimize the misclassification of exposures that are not etiologically relevant to tumor development.

The diagnostic pathway for childhood CNS tumors can be prolonged and complex. Children may undergo multiple healthcare visits and imaging procedures before a definitive cancer diagnosis is established (Coven et al., 2018). The median time from symptom onset to diagnosis for childhood CNS tumors typically ranges from several weeks to months and may be even longer particularly for lower-grade tumors (Kehoe et al., 2023; Weile et al., 2024). This extended symptom-to-diagnosis interval increases the risk of reverse causation in epidemiological studies, as exposures may be misinterpreted as causal when they are, in fact, part of the diagnostic process prompted by early tumor symptoms.

Several retrospective cohort studies have implemented both an exclusion period following the first CT exposure and a lag period for subsequent exposures prior to cancer diagnosis. Others have applied only an exclusion period after each CT scan. In contrast, case-control studies more commonly apply a lag period before the cancer diagnosis, rather than an exclusion period. Although terminology may vary between studies, the underlying objective is similar: to mitigate reverse causation and account for the latency period of radiation-induced malignancies. In this dissertation, we will refer to both exclusion and lag periods collectively as the “lag period” for consistency.

A five-year lag period is commonly used in studies of pediatric radiation exposure, grounded in long-term evidence from the Life Span Study showing that solid tumors typically emerge at least five years post-exposure (Preston et al., 2007). This approach was adopted by Pearce et al. (2012b) for childhood CNS tumors and has since become a reference standard in subsequent research. However, several studies have opted for shorter lag periods, often supported by sensitivity analyses showing minimal variation in risk estimates across different lags (Journy et al., 2015;

Mathews et al., 2013; Smoll et al., 2023). These studies argued that shorter lag periods may sufficiently exclude preclinical cases while preserving statistical power and often cited alignment with prior literature using similar time frames.

Temporal patterns in risk estimates reveal important insights into the biological and epidemiological dynamics of radiation-related CNS tumors. A recurrent observation in the literature is the heightened radiosensitivity of younger children, particularly those exposed before the age of five. Several studies, including Mathews et al. (2013), Huang et al. (2014), and W.-H.Wang et al. (2023), reported the highest risk in the youngest age group, with risk decreasing as age at exposure increased. However, Pearce et al. (2012b) reported a significant increase in ERR with increasing age at exposure. A similar, though non-significant, trend was observed in the EPI-CT study. In contrast to age-related discrepancies, time since exposure demonstrates more consistent associations, with risk attenuating over time. This is potentially explained by biological recovery or the influence of competing risk factors as cohort members age. Applying different lag periods, the British, Australian, Dutch, and EPI-CT studies reported decreasing trends in risk with increasing years since exposure, although these trends were not statistically significant in some of the studies.

2.3.3 Impact of predisposing factors

A critical challenge in epidemiological studies examining the association between pediatric CT scans and cancer risk is accounting for predisposing factors, such as cancer predisposition syndromes (e.g., neurofibromatosis, tuberous sclerosis) and previous malignancies. Confounding by indication occurs when the underlying medical condition necessitating the CT scan, rather than the radiation exposure itself, is associated with increased cancer risk, thereby distorting risk estimates (Rothman et al., 2021). Early studies, such as those by Pearce et al. (2012b) and Mathews et al. (2013), did not explicitly exclude individuals with CPS or previous malignancies, potentially leading to inflated risk estimates due to confounding by indication. Subsequent research sought to address this limitation. For instance, Berrington de González et al. (2016) updated the risk estimates from the UK cohort study, finding that the exclusion of individuals with CPS reduced the ERR per mGy from 0.023 to 0.019, and the exclusion of individuals with previous malignancies lowered the ERR to 0.016. In the Dutch study (Meulepas et al., 2019), the authors observed a slight decrease in ERR after excluding children with tuberous sclerosis, from 0.86 to 0.79 per 100 mGy.

Different studies have included different sets of CPS in their analyses, reflecting variability in study designs and data availability. Since different CPS confer varying levels of risk for CNS tumors, the extent to which predisposing factors influence risk estimates may depend on the specific CPS considered in each study (Patil et al., 2022). These predisposing factors were identified using sources such as hospital discharge records, radiologists' comments, and pathology reports. However, differences in documentation, potential misclassification, and limited genetic data may have led to suboptimal ascertainment and low classification accuracy.

Three French studies have analyzed the influence of predisposing factors using the same cohort. Journy et al. (2015) reported that adjusting for predisposing factors led to an almost 50% reduction in the ERR, from 2.2 to 1.2 per 100 mGy. However, subsequent analyses found that risk estimates remained largely unchanged before and after excluding children with predisposing factors (Journy et al., 2016; Foucault et al., 2022). Additionally, the radiation-related risk of CNS tumors among children with predisposing factors was lower than in both the overall cohort and in children without predisposing factors (Cardis & Bosch de Basea, 2015). These discrepancies have sparked debate regarding whether predisposing factors act primarily as confounders, effect modifiers, or both. Additionally, other methodological concerns, such as competing risks and selection bias, may contribute to the observed differences.

Another key consideration is the frequency of CT scans among children with predisposing conditions. Several studies have reported that children with CPS undergo CT imaging more frequently than the general population. Journy et al. (2015) found that children with predisposing factors received more scans on average (1.8 vs. 1.4) and had a higher cumulative brain dose (33 mGy vs. 23 mGy) compared to those without such conditions. Similarly, Meulepas et al. (2019) reported that children with tuberous sclerosis had significantly more CT scans during follow-up compared to other cohort members (24 vs. 1.5 scans), more head CTs (1.8 vs. 1.0), and a higher cumulative brain dose (86.9 mGy vs. 38.4 mGy). However, there remains no consensus on the association between CPS and CT imaging. Differences in study design, cohort selection, and healthcare practices may contribute to the variability in findings.

2.3.4 Inclusion criteria for CNS tumors

As mentioned in the introduction chapter, CNS tumors are classified based on their biological behavior using standardized ICD-O-3 numeric codes: 0 for benign tumors, 1 for tumors of uncertain or borderline behavior, and 3 for malignant tumors (WHO, 2013). Broadly, CNS tumors are categorized as non-malignant (behavior codes 0 and 1) or malignant (behavior code 3). This classification aligns with the WHO grading system, which stratifies tumors into low-grade (1 and 2) and high-grade (3 and 4) based on histopathological features and clinical aggressiveness (Louis et al., 2016). Tumor classification and grading have evolved over time. For instance, pilocytic astrocytoma (ICD-O-3 code 9421) was reclassified from behavior code 3 (malignant) to behavior code 1 (borderline/uncertain) in the third edition of the ICD-O (WHO, 2000).

Although classified as non-malignant, some benign and borderline CNS tumors can still pose significant clinical risks due to their intracranial location, growth patterns, or surgical inaccessibility. Differences in inclusion criteria across epidemiological studies may influence risk assessments. While the EPI-CT and original Australian studies included only malignant CNS tumors, most other studies encompassed both malignant and non-malignant cases. Excluding non-malignant tumors may underestimate the true burden of radiation-related CNS tumors and limit the ability to detect differences in risk estimates across subgroups, which could provide insights into biological differences in tumor development following radiation exposure.

2.3.5 Advances and limitations in dosimetry

Accurate estimation of radiation doses from CT scans is critical for evaluating cancer risk in epidemiological studies, particularly in pediatric populations. In an ideal scenario, dosimetric parameters essential for precise dose calculations, including CT machine manufacturer and model, tube potential (kVp), tube current (mA), pitch, collimation, scan length, CT dose index volume (CTDI_{vol}), and dose-length product (DLP), would be routinely documented alongside patient-specific factors such as age and sex. These parameters enable reliable estimation of effective and organ-specific doses through computational human phantoms and detailed scanner modeling embedded in validated software tools, such as the National Cancer Institute's Dosimetry System for Computed Tomography (NCICT) (Lee et al., 2015). However, the availability of such detailed information varies depending on the time period

covered by the study, institutional practices, scanner manufacturers, and adherence to standardized reporting protocols.

Radiology information systems (RIS), picture archiving and communication systems (PACS), and the digital imaging and communications in medicine standard (DICOM) play essential roles in managing radiological data and facilitating access to dosimetric parameters crucial for estimating radiation doses from CT exposures (Shah et al., 2022). RIS is primarily used for scheduling, tracking, and managing patient imaging records, while PACS serves as a centralized system for storing and retrieving medical images. DICOM, the standard format for medical imaging data, includes metadata containing key CT dosimetric parameters.

Older CT scan data often lack comprehensive individual dosimetric records, requiring supplementation through national surveys, published literature, and expert consensus to reconstruct plausible exposure scenarios. More recent data benefit from improved standardization and the integration of dose management systems (e.g., radiation dose structured reports), facilitating more accurate dose reconstruction (Loose et al., 2021). Advances in computational dosimetry have further enhanced dose estimation by incorporating anatomically variable phantoms that account for age-dependent anatomical differences in organ size, tissue composition, and radiation sensitivity, as well as scanner-specific beam characteristics, x-ray spectra, bowtie filter designs, and collimation profiles, improving the realism of dose simulations to better reflect real-world scanner performance (ICRP, 2020; Lee et al., 2015).

Early approaches, such as those by Pearce et al. (2012b) and Journy et al. (2015), relied on Monte Carlo simulations paired with computational phantoms to model organ-specific doses (e.g., red bone marrow, brain). Pearce utilized UK-wide machine setting surveys, revealing 2–3 times higher pre-2001 doses due to non-optimized pediatric protocols, while Journy incorporated departmental scan protocols and published literature. By contrast, post-2015 studies increasingly adopted the NCICT software (Smoll et al., 2023; Meulepas et al., 2019; Hauptmann et al., 2023; Foucault et al., 2022), leveraging DICOM metadata, national diagnostic reference levels, and predictive models to estimate doses. Studies without direct access to machine parameters, such as Mathews et al. (2013) and Krille et al. (2015), derived effective doses from literature or extrapolated organ dose catalogs. Collectively, methodological approaches have evolved from survey-dependent models to standardized, metadata-driven tools. However, challenges persist in managing protocol heterogeneity across institutions and time periods, as well as in accurately quantifying uncertainties.

The EPI-CT study has advanced pediatric CT dose estimation by analyzing 437,249 CT scans from 948,174 patients across nine European countries (Thierry-Chef et al., 2021). The study combined DICOM metadata, national surveys, and institutional questionnaires to reconstruct thousands of age- and protocol-specific dose models spanning decades. It introduced a two-dimensional Monte Carlo (2DMC) method to propagate uncertainties in shared (e.g., hospital protocols) and individual (e.g., scan length) parameters, generating 200 probabilistic dose realizations per individual for robust error analysis. Probability density functions (PDFs) derived from empirical datasets were applied to probabilistically impute missing parameters, enhancing retrospective reliability. The study also accounted for historical shifts in CT practices, including the transition to pediatric protocols and the adoption of automatic exposure control, as well as scanner advancements like the adoption of multislice CT, addressing dose variability across different eras.

2.3.6 Summary

A growing body of epidemiological evidence links CT scans to an increased risk of CNS tumors in children. Several studies indicated a dose-dependent increase in cancer incidence, reinforcing concerns about the long-term effects of ionizing radiation from medical imaging. Recent methodological advances, including large-scale cohort studies and refined dose estimation techniques, have contributed to more precise risk estimates. Nevertheless, considerable heterogeneity in reported risk magnitudes persists across studies. Limitations in the literature include residual confounding, particularly confounding by indication, incomplete or inconsistent CT exposure histories, differences in case ascertainment methods, variability in tumor inclusion criteria, and institutional differences in imaging protocols.

Table 4. Summary of studies on childhood CNS tumor risk following exposure to CT imaging.

Reference	Study design	Sample size	Age (yrs)	Follow up period	Lag (yrs)	Adj for PFs	ERR per 100 mGy (95% CI)	Risk/odds ratio (95% CI)
Pearce et al. 2012b Great Britain	Retro-Cohort	176,587 exposed	0–21	1985–2008	5	No	2.3 (1.0, 4.9)	2.82 (1.33, 6.03) <5 vs 50–74 mGy
Mathews et al. 2013 Australia	Retro-Cohort	680, 211 exposed	0–19	1985–2007	1	No	2.9 (2.3, 3.7)	2.44 (2.12, 2.81) exposed vs unexposed
Huang et al. 2014 Taiwan	Retro-Cohort	24,418 exposed	0–17	1998–2008	2	Yes	NA	2.56 (1.44, 4.54) exposed vs unexposed
Krille et al. 2015 Germany	Retro-Cohort	44,584 exposed	0–14	1980–2010	2	Yes	0.8 (0.4, 1.3)	1.35 (0.54, 2.78) external comparison
Jourmy et al. 2015 France	Retro-Cohort	58,620 exposed	0–9	2000–2011	2	No	2.2 (–1.6, 6.1)	NA
						Yes	1.2 (–1.3, 3.7)	NA
Berrington de Gonzalez et al. 2016 Great Britain	Retro-Cohort	176,587 exposed	0–21	1985–2008	5	Yes	1.6 (0.6, 3.7)	NA
Jourmy et al. 2016 France	Retro-Cohort	58,620 exposed	0–9	2000–2011	2	No	0.5 (–0.5, 0.9)	NA
						Yes	0.7 (–0.1, 1.0)	NA
Meulepas et al. 2019 Netherlands	Retro-cohort	106,530 exposed	0–17	1979–2014	5	No	0.86 (0.20, 2.22)	0.91 (0.43, 1.93) <5 vs 51–64 mGy
						Yes	0.79 (0.16, 2.10)	0.91 (0.43, 1.93) <5 vs 51–64 mGy
Hong et al. 2019 S. Korea	Retro-Cohort	1,179,021 exposed	0–19	2006–2015	2	No	NA	1.65 (1.35, 2.01)
Li et al. 2020 Taiwan	Case-control	838 cases	0–15	1997–2013	2	Yes	NA	1.56 (1.04, 2.33)
Foucault et al. 2022 France	Retro-Cohort	103,015 Exposed	0–9	2000–2016	5	No	0.6 (0.2, 0.9)	NA
						Yes	0.5 (0.1, 0.9)	NA
Hauptmann et al. 2023 Europe	Retro-Cohort	658,752 exposed	0–21	1977–2014	5	No	1.27 (0.51, 2.69)	2.2 (1.2, 4.1) <5 vs 56–64 mGy
Smoll et al. 2023 Australia	Retro-Cohort	611, 544 exposed	0–19	1985–2012	2	No	0.80 (0.54, 1.06)	1.67 (1.40, 2.98) exposed vs unexposed
Wang et al. 2023 Taiwan	Nested case-control	2245 cases	0–24	2000–2013	3	Yes	NA	0.69 (0.40, 1.20) one CT vs unexposed

Abbreviations: Adj for PFs=adjusted for predisposing factors, ERR=excess relative risk (proportional increase in risk per unit of radiation dose relative to the baseline risk in the unexposed group).

3 AIMS OF THE STUDY

The overarching aim of this dissertation was to evaluate the use of computed tomography (CT) imaging in children in Finland and estimate its association with the risk of childhood central nervous system (CNS) tumors. The specific objectives were:

1. To characterize utilization patterns and temporal trends in pediatric CT imaging in Finland between 1996 and 2010 (I).
2. To estimate incidence rates and long-term trends of childhood CNS tumors in Finland from 1990 to 2017 (II).
3. To quantify the association between exposure to CT imaging and the risk of childhood brain tumors (III).

4 MATERIALS AND METHODS

This dissertation is based on three interrelated peer-reviewed publications (I–III), each addressing a distinct aspect of pediatric CT imaging and childhood CNS tumor epidemiology in Finland, leveraging nationally integrated data sources and registry linkages. Publication I analyzed temporal trends in pediatric CT use (1996–2010) using radiological datasets from university and central hospitals. Joinpoint regression was applied to estimate changes in imaging rates over time. Publication II assessed incidence trends of childhood CNS tumors (1990–2017) using data from the Finnish Cancer Registry. Annual percent changes were estimated using Poisson regression models. Publication III employed a case-control design to investigate radiation-related CNS tumor risk. Cases and controls were individually matched on age and birth year. Exposure assessment was based on reconstructed organ doses from CT imaging histories, and conditional logistic regression was used to estimate odds ratios. Extensive efforts were undertaken to address potential sources of bias, including confounding by indication and reverse causation.

4.1 Study design and population selection

4.1.1 Overview of methodological approach

The study populations and analytical methods were tailored to the specific aims of each of the three original publications. For the descriptive components, the objective was to provide a comprehensive overview of population-level trends. Accordingly, the CT utilization analysis (I) encompassed all types of CT scans, while the incidence analysis (II) included all primary CNS tumors. To ensure these estimates reflected the entire study population, individuals with cancer predisposition syndromes (CPS) or a history of previous malignancy were retained in the analyses. In contrast, the case-control analysis (III) was designed to test a specific etiological hypothesis and therefore required a more targeted approach. To strengthen causal inference, the exposure and outcome definitions were restricted to head/neck CT scans and brain

tumors, respectively. Additional measures were taken to reduce bias: individuals with CPS or previous malignancies were excluded from the primary case-control analysis to minimize confounding by indication, and a five-year lag period was applied to the exposure window to mitigate the risk of reverse causation.

4.1.2 Case ascertainment

Finland has a well-established and comprehensive system of social and health registers that is notable for its high quality and integration (Keskimaki et al., 2019). These registers are unique compared to many other countries due to their extensive coverage, the cross-linking of multiple data sources, and the long history of data collection. The use of a personal identity code system, assigned to all residents, since 1967 has enabled seamless individual-level linkage of data across different registers, enhancing the reliability, comprehensiveness, and completeness of social and health information (DVV, 2024). This system supports scientific research and health monitoring capabilities that are exemplary on an international scale.

The Finnish Cancer Registry (FCR) has been collecting cancer data on the national level since 1953 (Leinonen et al., 2017). Institutions and healthcare professionals are required by law to report all cancer cases to the FCR through clinical and pathological notifications. This mandatory reporting is supplemented by multiple independent sources, including data on causes of death from Statistics Finland and information on treatment periods, visits, and further examinations related to cancer diagnoses from the Care Register of Health Care (HILMO) (Pitkäniemi et al., 2020). For the period 2009–2013, the FCR reported a completeness rate of 96% for solid tumors and 86% for non-solid tumors (Leinonen et al., 2017). Pathological verification was achieved in 93% of cases, further validating the accuracy of the data. Specific to pediatric cancers, the FCR's completeness was estimated at 94% for the same period (Jokela et al., 2019). These rigorous data validation processes, along with continuous communication with clinicians and hospitals to ensure uninterrupted data flow, contribute to the registry's high standards.

This nationwide population-based study is part of the RiFaTuB project. Cases included primary childhood CNS tumors (malignant and non-malignant) diagnosed in Finland between 1990 and 2017 and identified through the FCR using the following topographical categories: brain, meninges, and central nervous system (ICD-10 codes C70–72, D32–33, and D42–43). We excluded second primary tumors and CNS lymphomas. Of all cases, 91% were verified by pathology. One case was

excluded due to data usage opt-out, leaving 1142 cases (Figure 2). A subset of the cases was restricted to brain tumors, excluding tumors of the spinal cord and the spinal meninges. Individual case data included the child's date of birth, sex, diagnosis date, tumor topography, morphology, behavior (ICD-O-3 codes), basis of diagnosis, and cancer type and stage. The FCR also provided data on other primary malignancies diagnosed in cases prior to CNS tumor diagnosis. For the analysis of CNS tumor incidence trends, all CNS tumors diagnosed in children aged 0–14 years between 1990 and 2017 were included (II). However, for analyzing risks associated with head/neck CT exposures, only brain tumors diagnosed in children aged 0–15 years between 1990 and 2016 were considered (III).

4.1.3 Control selection

The Digital and Population Data Services Agency (DVV) sampled the pediatric population in Finland for three controls for each case, individually matched by the month and year of birth and sex. Controls were required to have no prior cancer diagnoses up to the index date, which corresponds to the date of cancer diagnosis for the case. The DVV also provided a list of biological and adoptive parents for each of the study participants for linkage with other registers. Place of birth and mother tongue were also obtained. After excluding one control due to data usage opt-out, 3425 controls remained (Figure 2).

4.1.4 Classification of CNS tumors

CNS tumors were coded using the ICD-O-3 (first and second revision) and grouped according to the 2016 WHO classification of CNS tumors (Louis et al., 2016). As shown in Table 5, tumors were divided into six histology groups: 1) diffuse astrocytic and oligodendroglial tumors, 2) other astrocytic tumors (low-grade gliomas), 3) ependymal tumors, 4) neuronal and mixed neuronal-glia tumors, 5) embryonal tumors, and 6) other tumors which included other gliomas, malignant glioma not otherwise specified (NOS), choroid plexus tumors, tumors of the cranial and paraspinal nerves, meningiomas, mesenchymal tumors, melanocytic tumors, germ cell tumors, and unclassified tumors. Additional morphology codes integrated into the 2016 WHO classification included 9381 for gliomatosis cerebri (growth pattern), 9423 for polar spongioblastoma, 9380 for malignant glioma NOS, 8800, 8963, and 8990 for other sarcomas, and 9081 for teratocarcinoma.

Tumors were classified as gliomas if they fell under diffuse astrocytic and oligodendroglial tumors, other astrocytic tumors, ependymal tumors, malignant glioma NOS, or other gliomas (angiocentric glioma, astroblastoma, and polar spongioblastoma). Tumor location groups (Table 6) included supratentorial tumors, infratentorial tumors, spinal cord tumors, meningiomas, unspecified and overlapping lesions. The WHO grading system for CNS tumors was employed to classify tumors into four grades (1, 2, 3, 4), representing the potential aggressiveness of each tumor type (Table 7) (Louis et al., 2016). Classification was conducted with the assistance of a neuropathologist to ensure accuracy. Tumor behavior codes, based on the ICD-O-3 system and supplemented by the FCR, were assigned as follows: 0 for benign, 1 for uncertain/borderline, and 3 for malignant (WHO, 2013).

Figure 2. Flowchart of the selection of participants in the study. CPS: Cancer predisposition syndromes.

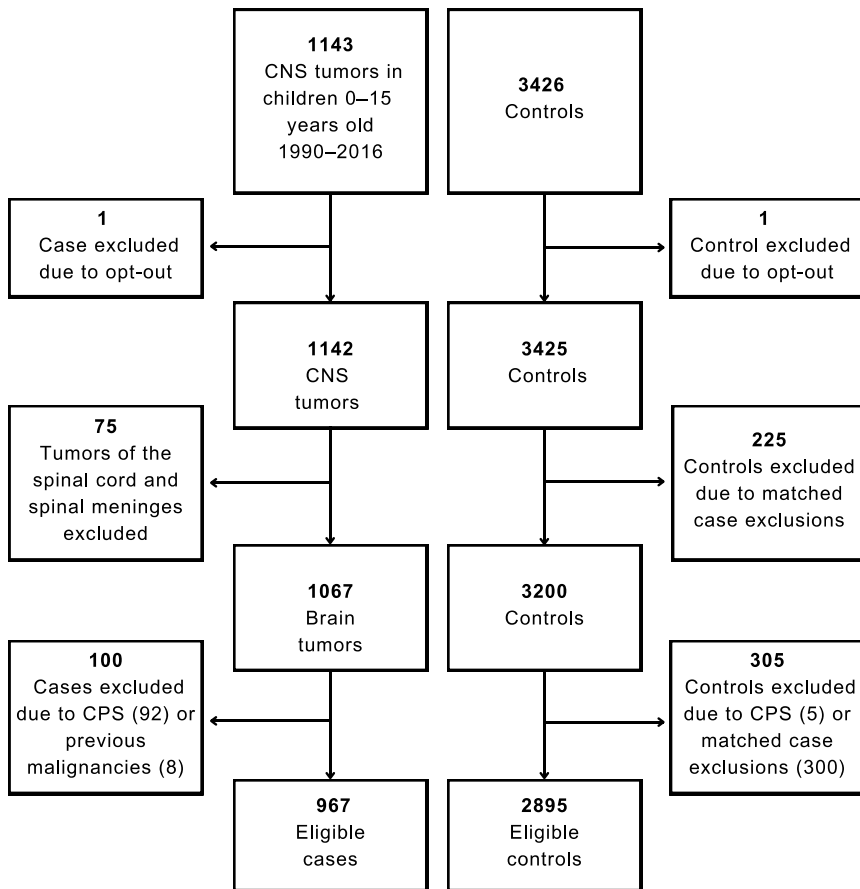


Table 5. Classification of CNS tumors into tumor histology groups.

Tumor subtype	Tumor name	Morphology code/ behavior code
Group 1		
Diffuse astrocytic and oligodendroglial tumors	Diffuse astrocytoma	9400/3, 9401/3
	Oligodendroglioma	9450/3, 9451/3
	Oligoastrocytoma NOS	9382/3
	Glioblastoma	9440/3, 9441/3
	Gliomatosis cerebri (growth pattern)	9381/3
Group 2		
Other astrocytic tumors (Low-grade gliomas)	Pilocytic astrocytoma	9421/1
	Pilomyxoid astrocytoma	9425/3
	Subependymal giant-cell astrocytoma	9384/1
	Pleomorphic xanthoastrocytoma	9424/3
Group 3		
Ependymal tumors	Subependymoma	9383/1
	Myxopapillary ependymoma	9394/1
	Ependymoma	9391/3, 9392/3
	Ependymoma, RELA fusion-positive	9396/3
Group 4		
Neuronal and mixed neuronal- glial tumors	Dysembryoblastic neuroepithelial tumor	9413/0
	Gangliocytoma	9492/0
	Ganglioglioma	9505/1
	Dysplastic gangliocytoma of cerebellum	9493/0
	Desmoplastic infantile ganglioglioma	9412/1
	Central neurocytoma	9506/1
	Papillary glioneuronal tumor	9509/1
Group 5		
Embryonal tumors	Medulloblastoma	9470/3, 9471/3, 9474/3
	CNS neuroblastoma	9500/3
	Ganglioneuroblastoma	9490/3
	CNS embryonal tumor NOS	9473/3
	Atypical teratoid/rhabdoid tumor	9508/3
Group 6		
Other gliomas	Angiocentric glioma	9431/1
	Astroblastoma	9430/3
	Polar spongioblastoma	9423/3
Unspecified malignant gliomas	Malignant glioma NOS	9380/3
Choroid plexus tumors	Choroid plexus tumor	9390/0, 9390/1, 9390/3
Tumors of the cranial and paraspinal nerves	Schwannoma	9560/0
	Neurofibroma	9540/0
	Plexiform neurofibroma	9550/0

Table continues on next page

Tumor subtype	Tumor name	Morphology code/ behavior code
Meningiomas	Meningioma	9530/0, 9530/3, 9531/0, 9537/0, 9538/3
	Atypical meningioma	9539/1
Mesenchymal, non- meningothelial tumors	Hemangioma	9120/3
	Ewing sarcoma	9364/3
	Hemangiopericytoma	9150/3
	Other sarcomas	8800/3, 8963/3, 8990/3
Melanocytic tumors	Melanocytic tumor	8728/3
Germ cell tumors	Germinoma	9064/3
	Teratoma	9080/0, 9080/1, 9080/3, 9081/3, 9084/0
	Mixed germ cell tumor	9085/3
Unclassified tumors	Unclassified tumor	8000/0, 8000/1, 8000/3, 8982/3

Abbreviations: NOS=not otherwise specified.

Table 6. Classification of CNS tumors into tumor location groups.

Tumor location group	Tumor location	Topography code
Supratentorial	Cerebrum, except lobes and ventricles	710
	Frontal lobe	711
	Temporal lobe	712
	Parietal lobe	713
	Occipital lobe	714
	Cerebral ventricle	715
	Optic nerve	723
Infratentorial	Cerebellum	716
	Brain stem	717
	Acoustic nerve	724
	Other and unspecified cranial nerves	725
Spinal cord	Spinal cord	720
Meninges	Cerebral meninges	700
	Spinal meninges	701
	Meninges, unspecified	709
Unspecified and overlapping lesions	Overlapping lesion of brain	718
	Brain, unspecified	719
	CNS, unspecified	729

Table 7. Classification of CNS tumors into tumor grade groups.

Tumor grade	Morphology code
Grade 1	9084, 9383, 9384, 9394, 9412, 9413, 9421, 9423, 9431, 9492, 9493, 9505, 9509, 9530, 9531, 9537, 9538, 9540, 9550, 9560
Grade 2	9150, 9382, 9391, 9396, 9400, 9424, 9425, 9430, 9450, 9506, 9539
Grade 3	9390, 9392, 9401, 9451
Grade 4	8800, 8990, 9064, 9081, 9120, 9364, 9381, 9385, 9440, 9441, 9470, 9471, 9473, 9474, 9490, 9500, 9508
Not available	8000, 8728, 8982, 9080, 9085, 9380

4.2 Assessment of exposure and covariates

4.2.1 Maternal and birth characteristics

To account for potential confounders, data on various health and social determinants was obtained from the national registers. The Medical Birth Register, established in 1987, had undergone reforms in 1990, 1996, 2004, and 2017 to enhance its reliability (THL, 2023a). It contains data on live births and stillbirths for fetuses with a birth weight of at least 500 grams or a gestational age of at least 22 weeks, along with information about the mothers. We collected data on maternal smoking during pregnancy and birth characteristics such as birth weight. Birth weight was classified as large for gestational age (LGA), defined as a birth weight exceeding two standard deviations (SD) above the reference mean birth weight in Finland, adjusted for the newborn's sex, gestational age, parity, and birth plurality (Sankilampi et al., 2013). Maternal smoking during pregnancy was categorized as smoking or non-smoking, with missing values accounting for 22% of the data overall. The proportion of missing values was higher in the early study period but improved notably after 1990.

4.2.2 Socioeconomic indicators

Statistics Finland, the national statistical authority of Finland, is responsible for collecting, analyzing, and disseminating comprehensive data on various aspects of Finnish society (Statistics Finland, 2024). We utilized longitudinal data on parental

education levels, recorded at five-year intervals from 1975 to 1985 and annually thereafter. Education levels were categorized into early childhood education (e.g., daycare centers), primary education, lower secondary education, upper secondary education, post-secondary vocational education, bachelor's degree, and master's or doctoral degrees (Statistics Finland, 2021a). Similarly, data on parental socioeconomic status (SES) was collected at five-year intervals from 1975 to 2005 and annually thereafter. SES was classified into self-employed, upper-level employee, lower-level employee, manual worker, and other. Data points closest to the index date were selected for analysis. Missing values accounted for 0.2% of maternal SES data, 2% of paternal SES data, 12% of maternal education data, and 20% of paternal education data.

4.2.3 Cancer predisposition syndromes

The Care Register for Health Care (Hilmo), established in 1994, replaced the Hospital Discharge Register (1969–1993) to provide broader data on inpatient care, outpatient care, day surgeries, and end-of-year patient counts, supporting statistics, research, and planning (THL, 2023b). The Register of Congenital Malformations, established in 1962, contains national-level data on congenital chromosomal and structural anomalies, as well as other anomalies like congenital hypothyroidism and teratomas, detected or suspected in stillborn and live-born infants and fetuses (THL, 2023c). We reviewed these three registers to identify cases of cancer predisposition syndromes known to increase susceptibility to CNS tumors (Johnson et al., 2014; Patil et al., 2022). These syndromes included neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), tuberous sclerosis complex (TSC), Li-Fraumeni syndrome, nevoid basal cell carcinoma syndrome (NBCCS), Turcot syndrome, Cowden syndrome, hereditary retinoblastoma, and Rubinstein-Taybi syndrome.

4.2.4 CT dataset

In Finland, before 2023, primary healthcare was delivered through health centers managed by municipalities. Secondary and tertiary medical care were organized into twenty hospital districts, each featuring a central hospital (Keskimäki et al., 2019). These districts were further grouped into five catchment areas, each served by a university hospital for highly specialized medical treatment. CT scan data was collected from ten individual hospital radiological databases across Finland, with

explicit permission obtained separately from each hospital. Dedicated IT staff at each hospital were responsible for securely extracting and transmitting the data, ensuring compliance with privacy and data protection standards. The data was subsequently merged and harmonized by our research team into a comprehensive, unified CT dataset. This dataset included all CT scans performed on children aged 0–15 years in Finland's five university hospitals and the five largest central hospitals. The time periods covered by CT data varied between hospitals, as radiological databases were introduced at the hospitals at different times (Table 8).

While coverage was lower in the earlier years of the period 1976–2011, we estimated that by the later years, the dataset encompassed up to 87% of all pediatric CT scans conducted nationwide (Nikkilä et al., 2018). This estimate was based on actual annual pediatric CT scan numbers from Helsinki University Hospital, the largest in Finland, between 1990 and 2011. Helsinki University Hospital was the second facility from which CT scan data was collected, enabling the strategy to be established at an early stage. A linear decrease to zero CT scans by 1975 was assumed, the year when CT scanner use began to increase in Finland. Annual CT scan numbers for Helsinki (1975–2011) were extrapolated to the nine other hospitals using proportional adjustments based on the average distribution of CT scans across hospitals in 2008 and 2011, as reported by the Radiation and Nuclear Safety Authority (STUK) (Helasvuo, 2013; Tenkanen-Rautakoski, 2010). The estimated total number of pediatric CT scans from the ten largest hospitals in the dataset was then compared with the expected nationwide total derived from the 2008 and 2011 surveys.

Each CT scan record included a personal identity code, scan date, scan code, the child's date of birth, and sex. The scan types were categorized based on a national coding system for medical procedures, ensuring standardization and comparability across all hospital systems (THL, 2021). Individuals who opted out of data usage were excluded. This resulted in the removal of nine scans from five individuals, leaving a final dataset comprising 73,035 CT scans, which was employed in the case-control analysis to assess the risk of brain tumors associated with radiation exposure from CT imaging (III) (Figure 3).

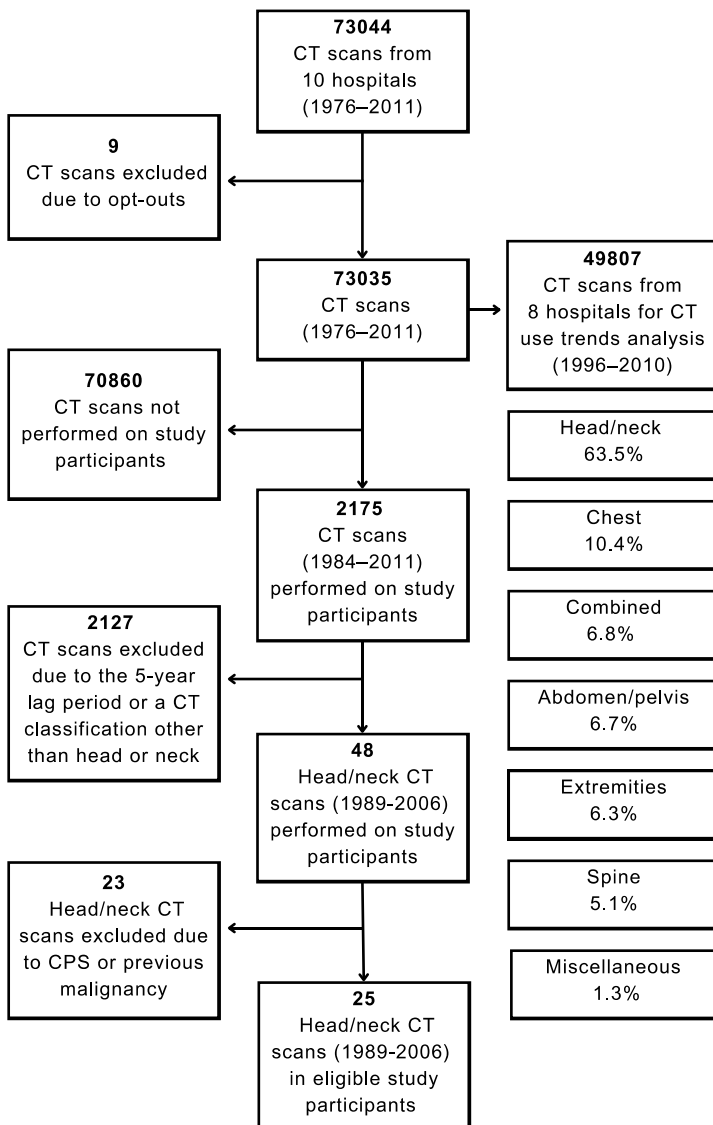
A subset of the final CT dataset, comprising 49,807 scans performed between 1996 and 2010 at the five university hospitals and three central hospitals (North Karelia, Satakunta, and Seinäjoki), was utilized to analyze trends in CT use among children (I). For this subset, three university hospitals (Tampere, Oulu, and Kuopio) provided ICD-10 clinical diagnosis codes recorded for children up to seven days prior to the CT examination. These diagnostic codes were analyzed to gain insights into

the clinical pathways that may have led to the decision to perform the CT scan. CT examinations were categorized based on sex, hospital type, CT examination type, age group, and repeat imaging status. For analyses involving sex and repeated examinations, 818 CT scans (1.6% of all subset examinations) were excluded due to missing or incomplete personal identity codes or unknown sex. CT examinations were classified into seven categories: head/neck, chest, abdomen/pelvis, spine, extremities, combined, and miscellaneous/unknown. The “combined” category encompassed scans covering more than one anatomical region, such as chest/abdomen/pelvis or abdomen/pelvis/lower extremity. The miscellaneous/unknown group included CT examinations labeled “others”, and unknown CT examinations (0.3 % of all subset examinations).

Table 8. Number of CT scans and periods covered by participating hospitals.

Hospital	Period	Number of CT scans (%)
Helsinki University Hospital	1990–2011	28454 (39.0)
Tampere University Hospital	1976–2011	17448 (23.9)
Oulu University Hospital	1993–2011	8720 (11.9)
Turku University Hospital	1996–2011	5806 (8.0)
Kuopio University Hospital	1996–2011	4115 (5.6)
North Karelia Central Hospital	1993–2011	3033 (4.2)
Satakunta Central Hospital	1995–2011	2031 (2.8)
Central Finland Central Hospital	2002–2011	1635 (2.2)
Seinäjäki Central Hospital	1999–2011	1346 (1.8)
Päijät Häme Central Hospital	2000–2011	447 (0.6)

Figure 3. Flowchart of the selection of pediatric CT scans in the study. CPS: Cancer predisposition syndromes.



4.2.5 Dose estimation

The National Cancer Institute Dosimetry System for Computed Tomography (NCICT) was employed in two distinct approaches to estimate effective and organ doses resulting from radiation exposure during CT scans (Lee et al., 2015). NCICT uses five computational pediatric phantoms representing ages 0, 1, 5, 10, and 15 years for both sexes, with dosimetric adjustments based on the scan region (16 cm head phantom or 32 cm body phantom).

The first approach, employed in publication I, estimated the average effective and organ doses received during head, chest, and abdomen CT scans. For each age-group phantom and scan type, CTDIvol, DLP, and tube potential were entered into NCICT. These values were based on averages derived from a Finnish survey conducted between 2011 and 2013, which included 1,049 CT examinations from four university hospitals (Helsinki, Tampere, Kuopio, Oulu) (Järvinen et al., 2015). The annual collective dose was estimated by multiplying the average effective dose per CT scan by the number of scans performed for each type (head/neck, chest, and abdomen) over the study period, summing the total, converting the result from millisieverts to person-sieverts through division by 1,000, and averaging over 15 years. This annual collective dose was divided by the total population to calculate the average effective dose per person per year.

The second approach, employed in publication III, focused on estimating brain doses from head/neck CT scans in cases and controls. This method incorporated CT machine manufacturer and model, scan protocol, tube potential, current, pitch, and collimation. STUK provided details on the CT machines used in the hospitals. Where information was missing, the latest available CT machine at each hospital was assumed. For two hospitals, Satakunta (2.8% of all CT scans) and Central Finland (2.2%), the most commonly used CT machine in Finnish hospitals was presumed. Based on the scan year and the child's age, an experienced hospital physicist estimated values for tube potential (kVp), current (mA), pitch, and collimation, with older scans (dating back to 1984) relying on parameters estimated for the year 2002. If a contrast medium was used during the scan, the dose was multiplied by a factor of 1.5 based on the literature (Amato et al., 2013; Sahbaee et al., 2017). The cumulative brain dose was calculated as the sum of brain doses from all CT exposures up to the index date, accounting for the lag period.

4.3 Statistical analysis

4.3.1 Trends analyses

The Joinpoint Regression Program, developed by the National Cancer Institute (NCI), is a statistical tool designed to analyze temporal trends in data by identifying points where significant changes occur (Kim et al., 2000). It is widely used in epidemiological and public health research to assess trends in cancer rates, mortality, and other health outcomes. Joinpoint regression fits multiple linear segments connected at “joinpoints”, in order to determine whether a single trend exists or whether the trend changes at specific points. The program calculates annual percent changes (APCs) and average annual percent changes (AAPCs) to quantify the magnitude and direction of trends over specified periods, along with statistical significance testing. We applied Joinpoint regression to evaluate trends in CT scan utilization (I) (Joinpoint Regression Program, Version 4.7.0.0. February 2019; Statistical Research and Applications Branch, National Cancer Institute). For CNS tumor incidence trends (II), we used Poisson regression, a method that models the number of cases relative to the population at risk and is well-suited for estimating cancer incidence trends. It accounts for stratification by covariates such as age and sex and enables the calculation of incidence rate ratios (IRR) and APCs (Kirkwood et al., 2003).

Population data, stratified by single-year age and sex, were obtained from Statistics Finland for each year within the study period (Statistics Finland, 2021b). For the analysis of CNS tumor incidence trends (II) (1990–2017), the mean annual population for all children in Finland aged 0–14 years was 924,605. Incidence rates were age-standardized to the 2013 European standard population and expressed per 100,000 child-years (EC, 2013). For the analysis of CT utilization trends (I) (1996–2010), the mean annual child population corresponding to the eight participating hospital districts was 687,108. CT utilization rates were reported as the number of examinations per 10,000 children.

4.3.2 Conditional logistic regression

Logistic regression is a statistical method for modeling the relationship between independent variables and a binary outcome, estimating probabilities and odds ratios to assess associations (Kirkwood et al., 2003). It assumes independence among observations and is widely used in fields like medicine and epidemiology. Conditional

logistic regression extends this approach to matched or stratified data, focusing on within-stratum variation by conditioning on matched sets, making it particularly useful in case-control studies and situations where confounding variables are controlled through matching. The unit of analysis in this study was the case-control set, which comprised one case and three matched controls, except for one set that included two controls due to participant opt-out. We implemented a 5-year lag period, excluding head/neck CT scans conducted within 5 years before the index date to reduce reverse causation. The selection of this lag period was based on empirical data and conventions in radiation epidemiology, where at least 5 years are generally considered necessary to observe radiation-induced brain tumors (Preston et al., 2007).

Analyses were performed both with and without participants diagnosed with CPS or previous malignancies, and separate analyses were conducted for gliomas and malignant tumors. Radiation exposure was categorized based on CT usage (head/neck CT: any versus none) and dose levels divided into tertiles (with zero dose as the reference) or analyzed as a continuous variable in milligray (mGy). A log-linear conditional logistic regression model estimated odds ratios (ORs) and 95% confidence intervals (CIs) using the formula $OR = \exp(\beta \times \text{dose})$, where β represents the regression coefficient per mGy of cumulative brain dose. Excess odds ratios (EOR), defined as $EOR = OR - 1$, were calculated per 100 mGy of cumulative brain dose. The likelihood ratio test was used to assess the differences between subgroups.

Parental socioeconomic status (SES) was identified as a potential confounder using Directed Acyclic Graphs (DAGs). The relationship between SES and childhood CNS tumor risk is multifaceted, influenced by various potential causal pathways and case ascertainment linked to healthcare access. Several studies showed a higher risk for childhood CNS tumors among higher-SES groups, possibly due to greater diagnostic surveillance, while other findings suggested an increased risk is associated with lower socioeconomic status, potentially through environmental or nutritional factors (Del Risco Kollerud et al., 2015; Erdmann et al., 2020; Francis et al., 2021). The link between SES and CT exposure is also documented, with research showing socioeconomic variations in imaging utilization (Lodwick et al., 2019; Marin et al., 2021; Pearce et al., 2012c). It is plausible that this association exists for the likelihood of undergoing a CT scan, influenced by factors related to healthcare utilization, awareness of radiation risks, and disease burden, rather than for the specific radiation dose administered once a scan is decided upon.

SES was confirmed to be associated with both CT utilization and brain tumor risk in our data. To adjust for this, odds ratios were stratified by maternal and paternal socioeconomic status, categorized into five groups: self-employed, upper-level employee, lower-level employee, manual worker, and other. Maternal smoking during pregnancy, infants born large for gestational age, and parental education levels were excluded as confounders due to the absence of a priori associations with CT exposure. All statistical analyses were conducted using Stata software (StataCorp, 2019, Stata Statistical Software: Release 16, College Station, TX: StataCorp LLC) and RStudio (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>). Statistical significance was defined as p-values <0.05, with all tests being two-tailed.

4.4 Ethical issues and permissions

This research project complied with Finnish legislation governing register-based research, which does not require ethical approval or informed consent when participants are neither contacted nor subjected to intervention (Lehtonen, 2002). Data permits were obtained from various national registers and transferred to the Finnish Social and Health Data Permit Authority (Findata) (diary number THL/3023/14.02.00/2020). These permits covered data from the following sources: the Finnish Cancer Registry, the Care Register for Health Care (Hilmo), the Hospital Discharge Register, the Medical Birth Register, the Register of Congenital malformations, Statistics Finland, the Digital and Population Data Services Agency (DVV), Helsinki University Hospital, Tampere University Hospital, Oulu University Hospital, Turku University Hospital, Kuopio University Hospital, North Karelia Central Hospital, Satakunta Central Hospital, Central Finland Central Hospital, Seinäjoki Central Hospital, and Päijät-Häme Central Hospital. The data was accessed by the research team exclusively through a secure remote environment (Kapseli) managed by Findata. External access to these data requires separate approval from Findata, in accordance with the Finnish Act on the Secondary Use of Social and Health Data (Act 552/2019).

In addition to complying with Finnish legislation, this study adhered to the principles outlined in the Declaration of Helsinki and international ethical guidelines for research. Measures were implemented to ensure robust data protection and participant confidentiality, including pseudonymization of data and compliance with

the general data protection regulation (GDPR). Data minimization practices were employed, ensuring that only essential data was accessed for the study's objectives. The project protocol was designed with transparency, and a detailed data management plan was followed to ensure accountability throughout the research process. Data retention and disposal procedures were also established in accordance with Finnish and European Union regulations, ensuring secure storage for the duration of the study and proper disposal post-research.

5 RESULTS

5.1 Characteristics of cases and controls

The study population included 1142 cases of childhood CNS tumors and 3425 age- and sex-matched controls (Figure 2). More than half of the participants were boys (54%). The distribution of the study population across the three age groups at index date (0–4, 5–9, and 10–15 years) was balanced, accounting for 36.0%, 30.4%, and 33.6%, respectively. The median age at index date was 7.3 years (interquartile range (IQR) 3.5, 11.5). Cases and controls were comparable with respect to place of birth, mother tongue, birth weight, and parental education (Tables 9 and 10). However, cancer predisposition syndromes (CPS) were significantly more prevalent among cases (8.9%) compared to controls (0.2%). Neurofibromatosis was the most common CPS, followed by tuberous sclerosis complex (Table 11).

Table 9. Demographic and perinatal characteristics with odds ratios (95% CI) from conditional logistic regression analysis for CNS tumor cases and controls before exclusions.

		Cases N (%)	Controls N (%)	Odds ratio (95% CI)
Sex	Boys	620 (54.3)	1860 (54.3)	
	Girls	522 (45.7)	1565 (45.7)	
Age group at index date	0–4	411 (36.0)	1233 (36.0)	
	5–9	347 (30.4)	1041 (30.4)	
	10–15	384 (33.6)	1151 (33.6)	
Place of birth	Finland	1108 (97.0)	3331 (97.3)	Reference
	Outside Finland	34 (3.0)	94 (2.7)	1.09 (0.73, 1.62)
Mother tongue	Finnish	1047 (91.7)	3115 (91.0)	Reference
	Other languages	95 (8.3)	310 (9.1)	0.91 (0.72, 1.16)
Large for gestational age (LGA)	No	874 (76.5)	2636 (77.0)	Reference
	Yes	35 (3.1)	100 (2.9)	1.07 (0.72, 1.57)
	Missing	233 (20.4)	689 (20.1)	
Cancer predisposition syndromes (CPS)	No	1040 (91.1)	3420 (99.9)	
	Yes	102 (8.9)	5 (0.2)	61.20 (24.94, 150.19)

Table 10. Parental socioeconomic and lifestyle characteristics with odds ratios (95% CI) from conditional logistic regression analysis for CNS tumor cases and controls before exclusions.

		Cases N (%)	Controls N (%)	Odds ratio (95% CI)
Mother's education	Upper secondary	509 (44.6)	1528 (44.6)	Reference
	Post-secondary vocational	244 (21.4)	707 (20.6)	1.01 (0.84, 1.21)
	Bachelor's degree	122 (10.7)	372 (10.9)	0.96 (0.75, 1.22)
	Master's or doctoral degree	126 (11.0)	410 (12.0)	0.95 (0.75, 1.20)
	Missing	141 (12.4)	408 (11.9)	
Father's education	Upper secondary	546 (47.8)	1591 (46.5)	Reference
	Post-secondary vocational	150 (13.1)	440 (12.9)	0.99 (0.79, 1.22)
	Bachelor's degree	93 (8.1)	308 (9.0)	0.84 (0.64, 1.09)
	Master's or doctoral degree	138 (12.1)	381 (11.1)	1.01 (0.81, 1.27)
	Missing	215 (18.8)	705 (20.6)	
Mother's socioeconomic status	Self-employed	76 (6.7)	313 (9.1)	Reference
	Upper-level employee	190 (16.6)	592 (17.3)	1.33 (0.98, 1.80)
	Lower-level employee	407 (35.6)	1344 (39.2)	1.25 (0.95, 1.64)
	Manual worker	254 (22.2)	585 (17.1)	1.79 (1.34, 2.40)
	Other	214 (18.7)	582 (17.0)	1.52 (1.13, 2.04)
	Missing	1 (0.1)	9 (0.3)	
Father's socioeconomic status	Self-employed	141 (12.4)	495 (14.5)	Reference
	Upper-level employee	222 (19.4)	663 (19.4)	1.18 (0.93, 1.50)
	Lower-level employee	226 (19.8)	590 (17.2)	1.33 (1.04, 1.69)
	Manual worker	357 (31.3)	1090 (31.8)	1.14 (0.92, 1.42)
	Other	173 (15.2)	518 (15.1)	1.16 (0.90, 1.50)
	Missing	23 (2.0)	69 (2.0)	
Mother's smoking during pregnancy	No	757 (66.3)	2322 (67.8)	Reference
	Yes	135 (11.8)	367 (10.7)	1.13 (0.92, 1.41)
	Missing	250 (21.9)	736 (21.5)	

Table 11. Cancer predisposition syndromes diagnosed in cases and controls.

Syndrome	Number of cases	Number of controls
Neurofibromatosis type 1 and type 2 (NF)	75	3
Tuberous sclerosis complex (TSC)	22	1
Nevoid basal cell carcinoma syndrome (NBCCS)	1	0
Turcot syndrome	2	1
Cowden syndrome	1	0
Rubinstein-Taybi syndrome	1	0
Li-Fraumeni syndrome	0	0
Hereditary retinoblastoma	0	0
Total	102	5

5.2 CT utilization in children

Over a 15-year period from 1996 to 2010, a total of 49,807 CT scans were performed on patients younger than 16 years in eight Finnish hospitals (Figure 3). The overall annual number of CT examinations increased significantly between 1996 and 2002, with an annual percentage change (APC) of 4.9% (95% CI 3.5%, 6.3%) (Table 12). However, this upward trend reversed after 2002, with CT numbers decreasing significantly (APC=-6.9%, 95% CI -10.4%, -3.2%). After 2005, the decline continued but was more gradual and statistically insignificant (APC=-1.0%, 95% CI -3.6%, 1.6%).

By 2010, the annual pediatric CT imaging rate was 43.5 examinations per 10,000 children, slightly above the rate of 42.5 in 1996. The peak occurred in 2002, with 59 examinations per 10,000 children. Declines were observed across both academic and central hospitals. The majority of patients underwent a single CT scan (76% of all patients), while 13% underwent two CT scans during the study period. A small subset (1.2%, 373 children) underwent 10 or more scans, nearly half of which were head/neck CTs (46.2%). The mean number of CT scans was 1.6 scans per person.

More CT examinations were performed on boys (55.5%) than girls (42.8%). Older children underwent more CT scans than younger children, with infants under one year comprising 8.1% (4036 scans) of all examinations. Among CT types, head/neck

CTs were the most common (63.5%, 31,643 scans), followed by chest CTs (10.4%, 5196 scans) and abdomen/pelvis CTs (6.7%, 3311 scans) (Figure 3). CT utilization trends varied by age group. In infants under one year, the number of CT scans showed a slight but non-significant decrease over time (Table 12). In contrast, CT use initially increased among the other age groups before decreasing after 2001–2002, with the steepest decline observed in children aged 1–5 years (APC=–10.2%, 95% CI –17.3%, –2.6%). Among scan types, head/neck CT underwent the largest decline, with an APC of –13.3% (95% CI –24.8%, –0.1%). The use of head/neck CTs either decreased or stabilized across all age groups in recent years. Abdomen CT usage began declining after 1998, marking the earliest decrease among scan types. In contrast, chest, spine, and extremity CTs continued to rise throughout the study period.

Common diagnoses associated with head CT included intracranial injury, headache, convulsions, hearing loss, and migraine, with the frequency of these scans significantly decreasing toward the end of the study period. For abdomen CTs, the most frequent associated diagnoses were intra-abdominal organ injuries and abdominal or pelvic pain. The average brain dose from head CT was 17.7 mGy, and the average red bone marrow dose was 4.4 mGy from head CT and 1.7 mGy from abdomen CT. Among girls, the average breast dose was 1.9 mGy from chest CT and 3.3 mGy from abdomen CT.

The average effective doses were 1 mSv for head CT, 1.1 mSv for chest CT, and 2.8 mSv for abdomen CT. For these three most frequently performed CT types, the cumulative effective dose per patient ranged from 1.4 to 61 mSv, with a median cumulative dose of 6.2 mSv. Together, head, chest, and abdomen CTs accounted for 81% of all examinations and resulted in an annual average collective dose of 3.7 person-Sv. This corresponds to an annual effective dose of 0.004 mSv per child in the population.

Table 12. Trends of CT use in children according to hospital type, child's age, and scan type.

	Period	APC	95% CI
Total	1996–2002	4.9	3.5, 6.3
	2002–2006	-6.9	-10.4, -3.2
	2006–2010	-1.0	-3.6, 1.6
University hospitals	1996–2002	5.6	4.0, 7.2
	2002–2005	-7.0	-14.7, 1.4
	2005–2010	-1.9	-3.9, 0.2
Central hospitals	1996–2001	2.7	-1.3, 6.8
	2001–2006	-12.5	-7.5, 7.3
	2006–2010	-0.4	-7.5, 7.3
<1 year	1996–2010	-1.0	-3.0, 1.2
1–5 years	1996–2001	3.0	-0.5, 6.7
	2001–2005	-10.2	-17.3, -2.6
	2005–2010	-3.7	-7.9, 0.6
6–10 years	1996–2001	6.9	5.5, 8.5
	2001–2006	-8.8	-10.6, -7.0
	2006–2010	-1.1	-3.3, 1.2
11–15 years	1996–2002	8.4	6.0, 10.8
	2002–2010	-1.4	-2.6, -0.1
Head CT	1996–2002	5.2	2.8, 7.7
	2002–2005	-13.3	-24.8, -0.1
	2005–2010	-2.4	-5.8, 1.2
Chest CT	1996–2010	4.4	3.0, 5.9
Combined CT	1996–2003	9.9	3.4, 16.7
	2003–2010	-17.4	-23.1, -11.1
Abdomen/pelvis CT	1996–1998	15.8	-4.9, 41.0
	1998–2010	-8.6	-9.9, -7.3
Extremities CT	1996–2010	10.6	8.4, 12.8
Spine CT	1996–2010	7.5	5.6, 9.4

Abbreviations: APC=annual percentage change.

5.3 Incidence trends of CNS tumors in children

The average annual age-standardized rate (ASR) for all childhood CNS tumors combined during 1990–2017 was 4.30 per 100,000 child-years (95% CI 4.26, 4.34) (Table 13). The ASR was higher in boys compared to girls, with an incidence rate ratio (IRR) of 1.17 (95% CI 1.04, 1.32). Male predominance was most notable in embryonal tumors, where the IRR was 1.76 (95% CI 1.31, 2.34). The incidence rate of CNS tumors declined with age, with the highest rate observed in children aged 5 years or younger (5.08 per 100,000 child-years, 95% CI 4.60, 5.56) and the lowest in children aged 10–14 years (3.70, 95% CI 3.30, 4.10). Overall, 35% of all grade 1 tumors occurred in children aged 10–14 years, while 42% of all grade 4 tumors were found in the youngest age group (0–4 years). Tumors in the spinal cord and meninges were most commonly diagnosed in the age group 10–14 years.

The most common tumor location was the infratentorial region, with an ASR of 1.80 per 100,000 child-years (95% CI 1.77, 1.83), followed by the supratentorial brain (ASR=1.34, 95% CI 1.32, 1.37) and the spinal cord (ASR=0.25, 95% CI 0.24, 0.26) (Table 13). Tumors with an unspecified location made up 19% of all cases. Gliomas constituted half of all tumors, with low-grade gliomas being the largest tumor group in the study. Pilocytic astrocytoma was the most common tumor type, with an ASR of 1.30 (95% CI 1.28, 1.33), followed by medulloblastoma, with an ASR of 0.45 (95% CI 0.43, 0.46), accounting for 30% and 10% of all tumors, respectively. Most embryonal tumors and low-grade gliomas were located in the infratentorial region, at 71% and 52%, respectively. Low-grade tumors (grade 1) made up 48% of all cases (ASR=2.05, 95% CI 2.02, 2.08), while highly malignant tumors (grade 4) accounted for 22% (ASR=0.95, 95% CI 0.93–0.97). In total, 32% of infratentorial tumors and 17% of supratentorial tumors were classified as grade 4. Among the 66 tumors located in the spinal cord, 18% were pilocytic astrocytomas, and 12% were ependymomas.

The overall ASR increased from 4.12 per 100,000 child-years (95% CI 4.03, 4.21) in 1990–1994 to 4.81 (95% CI 4.71, 4.91) in 2013–2017. The APC for all tumors was 0.8% per year (95% CI 0.2%, 1.4%) (Table 13). The ASR increased annually by 0.4% (95% CI –0.8%, 1.5%) for children aged 1–4 years, by 1.0% (95% CI –0.4%, 2.3%) for children aged 5–9 years, and by 1.1% (95% CI –0.3%, 2.4%) for those aged 10–14 years. Incidence rate trends remained stable across tumor histology and location groups. The incidence of low-grade tumors (grade 1) showed a statistically significant annual increase, with an APC of 1.0% (95% CI 0.1%, 2.0%).

Table 13. Incidence trends and age-standardized rates of childhood CNS tumors in Finland (1990–2017).

	ASR (95% CI)	APC (95% CI)
Total	4.30 (4.26, 4.34)	0.8 (0.2, 1.4)
Age group		
0–4 years	5.08 (4.60, 5.56)	0.4 (–0.8, 1.5)
5–9 years	4.20 (3.77, 4.63)	1.0 (–0.4, 2.3)
10–14 years	3.70 (3.30, 4.10)	1.1 (–0.3, 2.4)
Tumor grade		
Grade 1	2.05 (2.02, 2.08)	1.0 (0.1, 2.0)
Grade 2	0.60 (0.58, 0.61)	–0.5 (–2.5, 1.5)
Grade 3	0.38 (0.37, 0.39)	2.6 (0.0, 5.3)
Grade 4	0.95 (0.93, 0.97)	0.7 (–0.4, 1.8)
Tumor location		
Supratentorial	1.34 (1.32, 1.37)	–0.9 (–2.1, 0.4)
Infratentorial	1.80 (1.77, 1.83)	0.4 (–0.8, 1.6)
Cerebellum	1.24 (1.22, 1.27)	0.1 (–1.2, 1.4)
Brain stem	0.53 (0.52, 0.55)	1.6 (–0.4, 3.7)
Spinal cord	0.25 (0.24, 0.26)	1.0 (–1.3, 3.4)
Unspecified	0.80 (0.78, 0.82)	2.5 (–2.5, 7.8)
Tumor histology		
Diffuse astrocytic tumors	0.62 (0.61, 0.64)	–1.7 (–3.5, 0.1)
Other astrocytic tumors	1.44 (1.42, 1.46)	0.6 (–0.6, 1.8)
Pilocytic astrocytoma	1.30 (1.28, 1.33)	0.4 (–0.9, 1.7)
Ependymal tumors	0.33 (0.31, 0.34)	1.9 (–0.5, 4.4)
Neuronal/glial tumors	0.46 (0.44, 0.47)	1.4 (–1.3, 4.2)
Embryonal tumors	0.73 (0.71, 0.74)	1.2 (–0.1, 2.6)
Medulloblastoma	0.45 (0.43, 0.46)	1.6 (–0.4, 3.6)
Other tumors	0.73 (0.71, 0.74)	1.5 (–0.0, 3.1)

Note: Incidence rates were calculated using Finnish population data stratified by single-year age and sex, with a mean annual population of 924,605 individuals. Abbreviations: APC=annual percentage change, ASR=age-standardized rate.

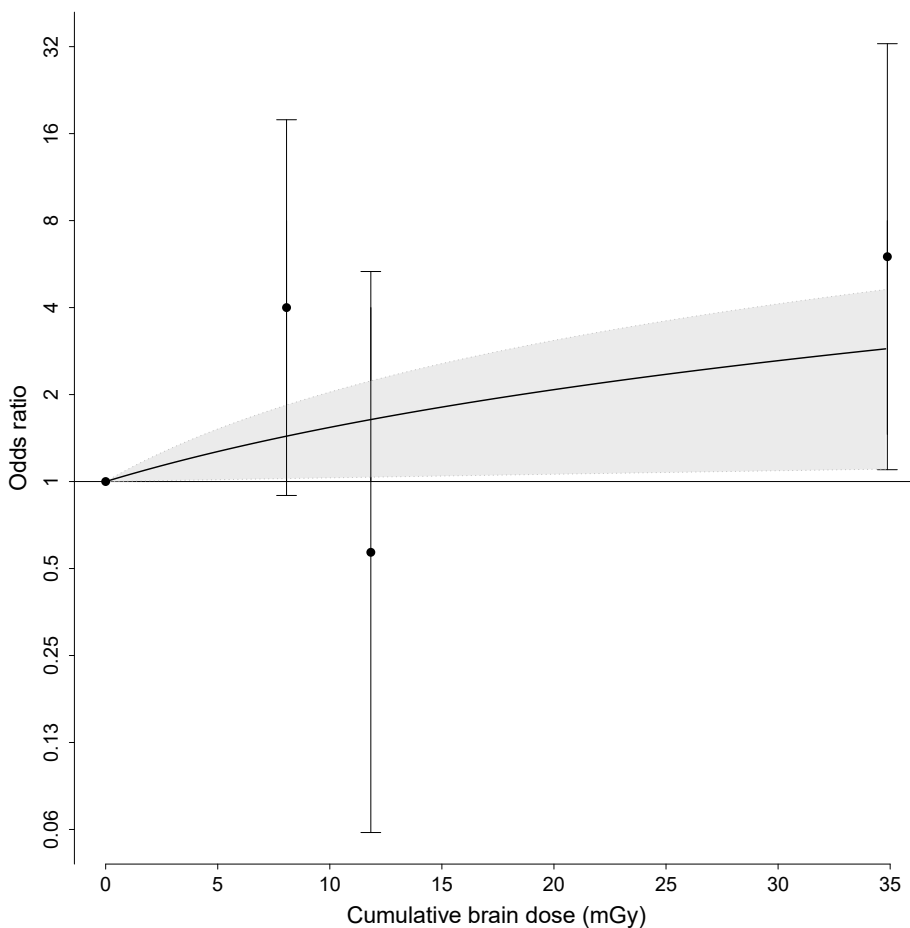
5.4 CNS tumor risk in children exposed to radiation

For the case-control analysis, we included 1,067 childhood brain tumor cases diagnosed between 1990 and 2016, along with 3,200 matched controls (Figure 2). A 5-year lag period was applied, and individuals with CPS (n=97) or a history of previous malignancy (n=8) were excluded. Only CT examinations of the head or neck were considered. In total, 9 cases (0.9%) and 10 controls (0.4%) had undergone at least one head/neck CT scan. The mean absorbed brain dose per head/neck CT scan was 16.7 mGy (standard deviation (SD)=11.8). The mean cumulative absorbed brain dose was 22.0 mGy (SD=27.6) among all exposed participants, 31.2 mGy (SD=38.5) among exposed cases, and 13.6 mGy (SD=6.4) among exposed controls (Table 14). Approximately 78% of cases and 70% of controls were between 0 and 5 years old at the time of their first head/neck CT scan.

Participants who underwent one or more head/neck CT scans had a higher risk of developing brain tumors compared to those without a history of CT imaging (odds ratio (OR)=2.84, 95% CI 1.12, 7.19) (Table 15). No significant differences in ORs were observed by age group at index date (likelihood-ratio test, $p=0.97$) or sex ($p=0.91$). The excess odds ratio (EOR) per 100 mGy of cumulative brain dose was 5.50 (95% CI 0.31, 10.95) for all brain tumors. For gliomas, the OR for any (versus none) head/neck CT exposure was 1.31 (95% CI 0.32, 5.36), with an EOR of 1.06 (95% CI -6.55, 9.30) per 100 mGy. For malignant brain tumors, the OR for any (versus none) head/neck CT exposure was 2.64 (95% CI 0.65, 10.76), and the EOR was 3.48 (95% CI -2.33, 9.64) per 100 mGy. When cumulative brain doses were categorized into tertiles (3.5–8.7, 10.6–20.1, and 20.2–126.2 mGy) with zero dose as the reference, a significant increase in risk (OR=6.00, 95% CI 1.10, 32.76) was observed in the highest tertile (Figure 4).

CT scans were performed more frequently in patients with CPS (5.6%) compared to those without such syndromes (0.5%), and the average number of scans per patient was also higher among predisposed patients (3.7 vs. 1.7 scans, respectively). In sensitivity analyses that included participants with CPS or previous malignancies, the OR for any (versus none) head/neck CT exposure was 5.15 (95% CI 2.27, 11.68), and the EOR per 100 mGy of cumulative brain dose was 7.80 (95% CI 2.45, 13.42) (Table 15). Adjusting for maternal socioeconomic status minimally impacted the OR for any (versus non) head/neck CT exposure (adjusted OR=2.69, 95% CI 1.06, 6.85) and the EOR per 100 mGy (adjusted EOR=5.27, 95% CI 0.08, 10.72). Similar minor changes were observed after adjusting for paternal socioeconomic status.

Figure 4. Dose-response curve for brain tumor risk in relation to cumulative brain dose from exposure to CT imaging.



Each data point corresponds to the odds ratio at the median dose within each tertile, with vertical lines indicating the associated 95% confidence intervals. The solid line depicts the fitted linear dose-response relationship, while the shaded area represents the 95% confidence band. The vertical axis uses a base-2 logarithmic scale. The reference value (OR=1) is shown as a dashed line. Reproduced from Abuhamed, J., Nikkilä, A., Raitanen, J., Lohi, O., & Auvinen, A. (2024). Risk of childhood brain tumors after exposure to CT radiation: A nationwide population-based case-control study in Finland. *International Journal of Cancer*, 156(11), 2148–2157. <https://doi.org/10.1002/ijc.35318>, under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0).

Table 14. Numbers of brain tumor cases and controls with cumulative absorbed brain doses from exposure to head/neck CTs.

	Cases	Controls
All brain tumors		
Number of participants (exposed)	967 (9)	2895 (10)
Mean brain dose mGy (SD)	31.2 (38.5)	13.6 (6.4)
Median brain dose mGy (IQR)	15.3 (8.1, 39.5)	11.3 (8.1, 20.2)
Gliomas		
Number of participants (exposed)	554 (3)	1657 (7)
Mean brain dose mGy (SD)	15.3 (13.0)	16.1 (6.2)
Median brain dose mGy (IQR)	8.1 (7.5, 30.3)	12.4 (11.3, 20.2)
Malignant brain tumors		
Number of participants (exposed)	492 (4)	1475 (5)
Mean brain dose mGy (SD)	42.2 (57.2)	15.3 (7.8)
Median brain dose mGy (IQR)	19.5 (6.1, 78.3)	11.3 (10.6, 20.2)

Note: Participants with cancer predisposition syndromes or previous malignancies were excluded and a 5-year lag period was applied. Abbreviations: IQR=interquartile range, SD=standard deviation.

Table 15. Odds ratios and excess odds ratios per 100 mGy of cumulative absorbed brain dose for brain tumors associated with exposure to head/neck CTs.

	OR for any head/neck CT vs. none (95% CI)	EOR per 100 mGy (95% CI)
All participants		
All brain tumors	5.15 (2.27, 11.68)	7.80 (2.45, 13.42)
Gliomas	3.25 (1.08, 9.75)	4.57 (-1.16, 10.63)
Malignant brain tumors	3.36 (0.89, 12.73)	3.49 (-2.30, 9.62)
Participants excluding CPS or previous malignancies		
All brain tumors	2.84 (1.12, 7.19)	5.50 (0.31, 10.95)
Gliomas	1.31 (0.32, 5.36)	1.06 (-6.55, 9.30)
Malignant brain tumors	2.64 (0.65, 10.76)	3.48 (-2.33, 9.64)

Note: Risk estimates were calculated using conditional logistic regression with a 5-year lag period. Abbreviations: CPS=cancer predisposition syndromes, EOR=excess odds ratio, OR=odds ratio.

6 DISCUSSION

6.1 Overview of key findings

This dissertation aimed to quantify the utilization of CT imaging in children, estimate incidence trends of childhood CNS tumors, and evaluate the risk of these tumors following exposure to radiation from CT imaging. The nationwide population-based case-control study included 1142 childhood CNS tumor cases and 3425 matched controls, with CT data collected from multiple Finnish hospitals and radiation doses estimated using consistent dosimetric methods.

CT utilization among children in Finland increased between 1996 and 2002, with an APC of 4.9% (95% CI 3.5%, 6.3%) and a peak of 59 examinations per 10,000 children. After 2002, utilization declined significantly until 2006 (APC=-6.9%, 95% CI -10.4%, -3.2%), followed by a stabilization from 2006 to 2010 (APC=-1.0%, 95% CI -3.6%, 1.6%). The decline was observed in both academic and central hospitals, reflecting broader efforts to reduce pediatric radiation exposure. The ASR of childhood CNS tumors in Finland was 4.30 per 100,000 child-years, with the highest incidence in children aged 0–4 years and in boys. Pilocytic astrocytoma (30%) and medulloblastoma (10%) were the most common tumor types. Between 1990 and 2017, the overall incidence of childhood CNS tumors increased by 0.8% per year (95% CI 0.2%, 1.4%). The increase was mainly driven by low-grade tumors (APC=1.0, 95% CI 0.1%, 2.0%), while other tumor grade, location, and histology groups showed no major changes.

In the main analysis, we excluded patients with cancer predisposing syndromes or previous malignancies and applied a lag period excluding CT scans conducted within five years prior to the index date. Our findings demonstrated a significant association between exposure to radiation from CT imaging and the risk of childhood brain tumors. Participants who underwent at least one head/neck CT scan had a higher risk of developing brain tumors compared to those without a history of CT imaging (OR=2.84, 95% CI 1.12, 7.19). A dose-response relationship was observed, with an excess OR of 5.50 (95% CI 0.31, 10.95) per 100 mGy of cumulative brain dose. The highest-dose group (>20 mGy) had a significantly elevated risk (OR=6.00, 95% CI 1.10, 32.76). Sensitivity analyses confirmed that including patients with

cancer predisposition syndromes biased the risk estimates upwards, underscoring the importance of controlling for confounding by indication in radiation-related cancer risk assessments.

6.2 Interpretations in the context of existing literature

6.2.1 Computed tomography imaging

Our findings are consistent with previous studies reporting an increase in pediatric CT utilization during the 1990s and early 2000s. The decline and then stabilization in CT use in Finland occurred after 2002 in both academic and central hospitals, earlier than in some other countries (Bosch de Basea et al., 2016; Meulepas et al., 2016; Smith-Bindman et al., 2019). CT scan rates in infants remained stable throughout our study period, and the steepest decline was observed among children under the age of six years. Our estimates of CT imaging rates per unit population were comparable to those reported in the UK and the Netherlands but substantially lower than the rates observed in the United States (Miglioretti et al., 2013; Pearce et al., 2012a). These observations likely reflect heightened awareness among healthcare professionals in Finland regarding the risks associated with medical radiation exposure. Since 2004, STUK, the Radiation and Nuclear Safety Authority in Finland, has issued guidelines aimed at optimizing pediatric CT procedures (STUK, 2012). This initiative is part of STUK's broader mandate, which includes licensing of CT scanners and conducting national surveys of medical radiation exposure (Pastila, 2017).

Furthermore, Finland's publicly funded universal health system delivers care without financial incentives for service provision and is oriented towards cost containment and optimized testing (Teperi et al., 2009). The integrated nature of this system also reduces care fragmentation, leading to fewer unnecessary, redundant, or duplicate imaging procedures (Kern et al., 2017). In contrast, the fee-for-service reimbursement model in the United States has been associated with increased imaging utilization, as financial incentives may drive higher procedure volumes (Hendee et al., 2010; Miglioretti et al., 2013). Additionally, the pervasive concern about medical malpractice litigation in the U.S. has contributed to the practice of "defensive medicine," where physicians opt for lower diagnostic thresholds, leading to a greater reliance on imaging as a precautionary measure to exclude even unlikely differential diagnoses (Studdert et al., 2005).

Several studies have reported that declines in pediatric CT use occurred earlier in academic hospitals, particularly those with a pediatric focus, compared to general hospitals (Hoshiko et al., 2014; Meulepas et al., 2016; Ukwuoma et al., 2021). This is likely attributable to heightened awareness among pediatric radiologists and pediatricians and increased institutional capacity to implement alternative imaging modalities such as MRI and ultrasound. However, in our study, the decline in pediatric CT utilization occurred simultaneously in both academic and general hospitals, suggesting a more uniform shift in imaging practices across healthcare settings and a high degree of compliance with the Finnish Current Care Guidelines (Duodecim, 2024).

While MRI is a valuable radiation-free alternative in pediatric diagnostics, its clinical utility can be limited by longer examination times, potential need for sedation in young children, higher operational costs, and limited availability, particularly in emergency and resource-limited settings (Geethanath & Vaughan, 2019; Marin et al., 2024). These logistical and infrastructural barriers have contributed to the continued reliance on CT imaging, especially for critically ill and injured patients, even when non-ionizing alternatives might be preferable. In addition to systemic factors, variations in imaging utilization and modality choice may also be influenced by individual-level factors, including patient characteristics and preferences. Parental anxiety, the quality of clinician-patient communication, and broader cultural attitudes toward medical interventions can shape healthcare-seeking behavior and diagnostic choices (Bulas et al., 2009; Marin et al., 2021; Martinez-Rios et al., 2019).

Head CT was the most frequently performed examination in this study, consistent with findings from other countries. However, its use declined more than any other CT type. Head injury was the most common associated clinical diagnosis, followed by headache, convulsions, and migraine, with all decreasing in parallel with the decline in CT utilization. This trend aligns with patterns in the U.S., where head CT use for head injuries decreased or stabilized after 2008, except in nonteaching hospitals (Ohana et al., 2018; Ukwuoma et al., 2021). The decline is largely attributed to improved clinical decision-support tools, particularly the Pediatric Emergency Care Applied Research Network (PECARN) rules introduced in 2009, which have promoted more selective imaging in cases of pediatric head trauma (Kuppermann et al., 2009; Lorton et al., 2016). Additionally, the increased use of MRI has provided a non-ionizing alternative. In Finland, pediatric MRI utilization rose 1.75-fold from 2008 to 2018, mirroring a fourfold increase in Canada between 2000 and 2016 (Ruonala, 2019; Smith-Bindman et al., 2019).

Similarly, abdominal CT usage in our study began declining after 1998, earlier than other CT types, and by 2010, it had decreased by more than half, becoming one of the least common CT examinations. In Finland, appendicitis is typically diagnosed clinically, with CT rarely used for acute abdominal conditions (STUK, 2012). Instead, abdominal ultrasound has been widely utilized, with pediatric ultrasound examinations increasing by 38% between 2008 and 2018 (Ruonala, 2019). This shift toward ultrasound is also evident in the U.S., where the use of abdominal CT for abdominal pain remained stable, but ultrasound for the same indication significantly increased in emergency departments between 2003 and 2010 (Menoch et al., 2012).

Concerns about cumulative radiation doses arising from repeated CT scans have garnered substantial attention, especially following alerts by the International Atomic Energy Agency (IAEA) (Brambilla et al., 2020). It was reported that approximately 1.33% of patients undergoing repeated CT examinations accumulated more than 100 mSv of effective dose over a period of 1–5 years. We found that 1.2% of pediatric patients underwent ten or more CT scans between 1996 and 2010. The cumulative effective dose from the three most frequently performed CT examination types ranged from 1.4 to 61 mSv per patient, with a median cumulative dose of 6.2 mSv. International bodies have advocated for dose tracking initiatives, such as the Smart Card project, which aims to compile and track patients' cumulative radiation exposure across time and healthcare facilities (Rehani & Kushi, 2013). However, debate is ongoing regarding its necessity, with concerns regarding potential misinterpretation, unjustified restrictions, and increased costs (Frush et al., 2025). Some experts argue that optimizing imaging protocols and minimizing unnecessary exposures are more effective strategies than tracking individual dose histories.

6.2.2 Tumors of the central nervous system

Our analysis showed that the mean age-standardized incidence rate of childhood CNS tumors in Finland was 4.3 per 100,000 child-years, exceeding the rates reported in France, Canada, Germany, and Great Britain (Desandes et al., 2014; Larouche et al., 2020; Stiller et al., 2019; Wellbrock et al., 2024). Multiple factors may contribute to the higher incidence in Finland, including potential genetic predispositions and robust diagnostic and registration practices (Leinonen et al., 2017; Uusimaa et al., 2022).

A marked increase in CNS tumor incidence was observed in the late 20th century, particularly during the mid-1980s, coinciding with the rapid advances in imaging

technology (Peris-Bonet et al., 2006; Smith et al., 1998). The widespread adoption of MRI, characterized by higher sensitivity, is frequently highlighted as a pivotal contributor to this rise. Enhanced detection capabilities likely identified previously occult or asymptomatic lesions, contributing to a transient spike in reported incidence as earlier undiagnosed cases entered the registries (diagnostic catch-up). However, one hypothesis is that if imaging improvements alone fully explained this observed increase, incidence rates would eventually plateau once accumulated undiagnosed cases were exhausted. Contrary to this, we found a continued upward trend in childhood CNS tumor incidence between 1990 and 2017, similar to the trends reported in the United States and Germany (Ostrom et al., 2018; Wellbrock et al., 2024).

The sustained increase in childhood CNS tumor incidence beyond the diagnostic catch-up period suggests that factors beyond imaging advancements might contribute to these trends. Established risk factors for CNS tumors (such as high dose ionizing radiation exposure and CPS) explain only a small fraction of cases. It seems improbable that these particular factors drove the observed increase in incidence. The utilization of radiation therapy has significantly declined over recent decades across various pediatric cancer types (Jairam et al., 2013). Familial cancer syndromes, including tuberous sclerosis and neurofibromatosis, are associated with substantially elevated risks of CNS tumors. However, the prevalence of these genetic conditions is very low, stable over time, and thus insufficient to explain the observed upward trends in incidence. Beyond these factors, ongoing research continues to investigate numerous potential risk factors implicated in childhood CNS tumor etiology (Johnson et al., 2014). Emerging evidence points to positive associations with maternal dietary supplement intake, advanced parental age at childbirth, pesticide exposure, and higher birth weight.

Due to the largely uncertain etiology of CNS tumors, it remains critical to consider that unknown or poorly characterized risk factors may also play a role in influencing childhood CNS tumor incidence. If the increase in incidence was attributable to specific causes, epidemiological reasoning implies that these exposures would have likely accumulated gradually over several decades, rather than arising from a sudden shift. The slight but statistically significant increase in childhood CNS tumor incidence in our study may thus reflect a genuine increase in risk. However, ongoing and gradual improvements in detection as a contributor cannot be ruled out. Supporting this hypothesis, our findings showed a consistent increase in the incidence of grade 1 CNS tumors throughout the study period. These tumors typically exhibit slow growth and are more likely to be detected with advanced imaging techniques like MRI

(Vagvala et al., 2022). Additionally, the annual rate of pediatric head MRI scans in Finland increased substantially between 2008 and 2018 (Ruonala, 2019).

Evaluating the potential impact of temporal changes in registration practices on incidence trends is challenging, though such an effect on overall rates in Finland would likely be minimal. The Finnish Cancer Registry (FCR) has maintained a consistently high level of completeness, registering both malignant and non-malignant CNS tumors since 1953 (Leinonen et al., 2017). From the late 1980s onward, the introduction of automated pathological reporting has ensured nearly comprehensive coverage of histologically confirmed cases. Additionally, rigorous cross-checking against the hospital discharge register and the national cause of death database, facilitated by Finland's unique personal identity codes, helps eliminate duplicates and capture missed cases. The other source of case ascertainment is clinical notifications from hospitals, which transitioned from manual forms to a simplified electronic format in 2020 (Pitkaniemi et al., 2020). Although these notifications have decreased in number relative to pathological reports, this decline is unlikely to materially affect incidence estimates, as clinical notifications primarily provide detailed information on tumor staging, localization, and treatment. Key data for incidence analysis, such as diagnosis date, histological type, and child's age and sex, are reliably captured through electronic pathology reports.

Coding and classification modifications, however, can influence incidence patterns within specific tumor histology groups. The FCR transitioned from the ICD-7 classification system to ICD-O-3 in 2008, accompanied by multiple retrospective recoding efforts (E. Hirvonen, personal communication, October 5, 2021). The recoding process reduced the frequency of nonspecific histological codes, exemplified by glioma malignant not otherwise specified (NOS) (code 9380), which represented only 2% of all tumors in our dataset, substantially lower than the 14% observed in the United States and 15% in Canada (Larouche et al., 2020; Ostrom et al., 2018). More than half of these tumors were recoded into pilocytic astrocytoma, which could explain the higher proportion of pilocytic astrocytomas in our dataset (30%) compared to studies in France (22%) and the UK (21%) (Desandes et al., 2014; Stiller et al., 2019). A U.S. study reported stable overall incidence rates of childhood CNS tumors from 1998 to 2013 yet observed slight but statistically significant trends for specific histological subtypes: gliomas exhibited an increasing trend, while embryonal tumors declined (Withrow et al., 2018). Furthermore, between 1981 and 2009, an increase in the incidence of pilocytic astrocytomas was accompanied by a decline in astrocytomas NOS (McKean-Cowdin et al., 2013). In contrast, our study did not identify statistically significant temporal trends within tumor

histology groups, a finding likely attributable to limited sample sizes and low statistical power to detect modest temporal variations.

6.2.3 Radiation exposure and cancer risk

Several studies have demonstrated an association between CT scans and an increased risk of childhood brain tumors, although the magnitude of this risk has varied considerably across the literature. Such variability likely reflects differences in study design, follow-up duration, methods for dose estimation, and approaches to confounder control. In our study, which incorporated a five-year lag, we observed a higher radiation-related risk per unit dose than that reported in previous large cohort studies (Hauptmann et al., 2023; Mathews et al., 2013; Pearce et al., 2012b). This comparatively elevated estimate may be attributable, at least in part, to statistical instability arising from our relatively small sample size.

We also found that the mean absorbed brain dose per CT scan in our cohort was lower than the averages reported in earlier research. This discrepancy suggests that our study may have underestimated cumulative radiation exposure. Potential reasons include reliance on contemporary scan parameters that may not accurately reflect historically higher administered doses, as well as possible underascertainment of early CT exposures resulting from incomplete historical records. Nevertheless, given the relatively infrequent use of pediatric CT scans during the early adoption period, any exposure misclassification due to missing historical data is likely to have only a modest effect on our risk estimates.

The excess odds ratio for gliomas observed in our study was not statistically significant, a result that is most plausibly explained by limited statistical power and a relatively short follow-up period. By contrast, the EPI-CT study reported a significantly increased risk of glioma, a finding that aligns with long-term follow-up studies of childhood cancer survivors. These studies have demonstrated clear dose–response relationships and elevated glioma incidence persisting for decades following radiotherapy exposure (Hauptmann et al., 2023; Heymer et al., 2024; Neglia et al., 2006).

We observed that children with CPS, such as neurofibromatosis and tuberous sclerosis, underwent more frequent CT imaging than children without such syndromes. This likely reflects the need for routine cancer surveillance in these individuals, including the use of CT scans, particularly prior to the widespread adoption of whole-body MRI for pediatric CPS screening. Similar patterns have been

reported in studies from France and the Netherlands, supporting the view that CPS status can confound analyses of CT-related cancer risk, given its association with both increased imaging and elevated baseline cancer incidence (Journey et al., 2015; Meulepas et al., 2019).

In our study, the excess odds ratio per unit dose decreased by nearly one-third after excluding children with CPS. Comparable reductions have been reported in previous investigations, suggesting that including CPS patients may lead to an upward bias in risk estimates (Berrington de Gonzalez et al., 2016; Journey et al., 2015; Meulepas et al., 2019). Nevertheless, after adjustment for CPS, the association between radiation exposure from CT imaging and brain tumor risk remained statistically significant in most studies, including our own. It is noteworthy that some studies did not adjust for CPS, often due to limited clinical information in registries, and argued that the low prevalence of CPS and relatively infrequent CT imaging among affected children would have minimal impact on risk estimates (Hauptmann et al., 2023; Mathews et al., 2013; Smoll et al., 2023).

Another important consideration is the potential role of CPS as an effect modifier rather than solely a confounder. In the French CT cohort study, statistically significant increases in CNS tumor risk were observed among children without predisposing conditions, with hazard ratios closely resembling those for the entire cohort (Foucault et al., 2022). In contrast, no clear dose-response relationship was detected among children with CPS. The authors interpreted these findings as evidence that CPS may modify, rather than substantially confound, the association between CT-related radiation exposure and subsequent brain tumor risk. This effect modification could be due to differing baseline hazards or distinct biological responses to radiation in children with versus without CPS. In our study, the small number of CPS patients precluded a separate analysis of risk in this subgroup, limiting our ability to explore potential effect modification directly.

A five-year lag period is commonly employed in studies of pediatric radiation exposure, informed by evidence from long-term research such as the Life Span Study of atomic bomb survivors, which demonstrated that solid tumors generally require at least five years to manifest following ionizing radiation exposure (Preston et al., 2007). Additionally, investigations into diagnostic intervals for childhood brain tumors have reported median times from symptom onset to diagnosis ranging from several weeks to months, with considerably longer delays observed for low-grade tumors (Kehoe et al., 2023; Weile et al., 2024). By excluding exposures occurring within five years prior to tumor diagnosis, studies aim to reduce the risk of reverse causation, the possibility that CT scans are performed in response to early symptoms of an

undiagnosed tumor rather than representing exposures that contribute causally to tumor development.

Although some studies have employed shorter lag periods, such approach may lead to overestimation of the exposure-outcome association by including scans performed as part of the diagnostic process. Conversely, applying a substantially longer lag could exclude tumors causally related to radiation and diminish statistical power by reducing the number of informative cases. In this study, the selection of a five-year lag period was based on epidemiological precedent and biological plausibility, representing a balance between established latency intervals and the need for sufficient case ascertainment to ensure the validity of dose-response analyses for these rare pediatric tumors.

6.3 Approach to study design

To quantify CT-related cancer risk, we employed a nationwide population-based case-control design. This approach was chosen due to the rarity of childhood CNS tumors, which makes a retrospective cohort study less practical in Finland's relatively small population. A cohort design would require the assembly and long-term follow-up of a very large population to accrue a sufficient number of cases. In contrast, the Finnish healthcare system, offering near-complete coverage of pediatric CT imaging and CNS tumor diagnoses, provided comprehensive, register-based data on both exposure and outcome, with unambiguous linkage and minimal exposure misclassification and selection bias. Under these conditions, a nationwide case-control study represented the optimal strategy for investigating this rare outcome.

We selected three controls per case, matched on birth month, year, and sex. Although register-based data could feasibly support a higher control-to-case ratio (e.g., 1:4), methodological literature demonstrates diminishing returns in statistical power beyond a ratio of 1:3. The most substantial gain occurs when increasing from a 1:1 to a 1:2 ratio, with progressively smaller improvements thereafter (Hennessy et al., 1999; Taylor, 1986). Consequently, our choice of a 1:3 ratio reflects a well-established balance between statistical power and analytical efficiency.

Our case-control design included both children who had and had not undergone CT scans prior to diagnosis, distinguishing it from many cohort studies that are often restricted to exposed populations. This allowed us to estimate relative risks across the full exposure spectrum, but also introduced greater potential for confounding by socio-economic status (SES), as CT use may correlate with SES-related differences

in healthcare access or referral patterns. While restricting analyses to exposed individuals can reduce SES confounding by design, such an approach was not feasible here due to the rarity of childhood CNS tumors and the relatively low prevalence of CT exposure, particularly in earlier calendar periods, which limited statistical power for exposed-only analyses.

Multi-country collaborations hold clear promise for studying rare childhood tumors, offering a stronger statistical basis by pooling patient data across national boundaries. This approach can substantially bolster sample size and improve precision, allowing for more refined dose-response analyses and the detection of small effect sizes and subtle risk differences among tumor subtypes. By encompassing multiple healthcare systems, pooled analyses can also highlight cross-national variations in imaging practices and radiation protocols, information that single-country studies may not capture. These insights can foster international standards for pediatric CT use, reduce redundant scans, and ultimately contribute to evidence-based dose optimization globally.

However, multi-country consortia face some logistical and methodological hurdles. Data harmonization is one major challenge. Different registries and hospitals may adopt varied dose recording practices and coding for CT scan types or tumor classifications, complicating consistent exposure and outcome definitions. Moreover, the harmonization process often necessitates adopting the smallest common denominator across studies, standardizing variables based on the most limited dataset as the common model, which can result in loss of the granularity and accuracy of more comprehensive datasets. Differences in record linkage quality or health information systems across countries can also result in exposure misclassification or incomplete follow-up. Furthermore, ethical and privacy regulations, which vary widely by jurisdiction, can further delay or limit data sharing.

In comparison, single-nation, register-based studies with unified personal identity code systems can at best yield high-quality, nearly complete coverage of both exposures and outcomes. While sample sizes may be smaller overall, consistent data collection protocols and standardized linkage procedures minimize several forms of bias. This internal consistency can increase validity, albeit at the expense of statistical power and global generalizability.

6.4 Strengths and limitations

A major strength of this study is its robust, nationwide, population-based design, which leveraged comprehensive data systematically collected from validated high-quality national registries. The individual-level integration of data from the Finnish Cancer Registry, known for its consistent recording of both malignant and benign CNS tumors, and hospital-based CT imaging records spanning multiple decades ensured near-complete ascertainment of childhood CNS tumor cases and detailed exposure histories. This level of registry coverage and interoperability not only reduced potential selection bias but also enhanced the external validity of the findings by ensuring that the study population is representative of the entire pediatric population of Finland.

The CT dataset, which was assembled through systematic hospital data collection, captured the majority of pediatric CT examinations in Finland during a period of substantial technological and clinical change in imaging practices. A national coding system provided standardized and reliable categorization of CT scans, while the low likelihood of duplicate records, facilitated by a unique personal identity code system, minimized the risk of overestimating utilization rates and exposure doses. This comprehensive approach, which avoided reliance on self-reported data or manual medical record reviews, enabled consistent and robust exposure assessment and reduced the risk of misclassification bias. Furthermore, CT scanner model and manufacturer information were combined with expert-defined scan parameters and processed using NCICT program, yielding a tailored and reliable method for estimating organ-specific radiation doses from pediatric CT imaging in Finland.

The CNS tumor dataset, covering a 27-year period, enabled the accrual of substantial case numbers across the major CNS tumor groups. The centralized organization of pediatric cancer care in five university hospitals facilitated uniform and comprehensive case ascertainment and minimized selection bias. Cases and controls were matched by sex and birth cohort, and the analysis adjusted for parental socioeconomic status to mitigate potential confounding and enhance comparability. Moreover, ascertainment of relevant cancer predisposition syndromes through three national registers allowed for identification and exclusion of high-risk individuals, minimizing confounding by indication and improving etiologic specificity.

The availability of this integrated, nationwide dataset, linking diagnostic imaging, validated cancer outcomes, and individual-level health and demographic data, is exceptional by international standards. Only a small number of countries maintain

such longitudinal, population-wide infrastructures with proven data quality and complete follow-up. This study provides methodologically rigorous epidemiologic evidence on the association between low-dose radiation exposure from CT imaging and subsequent risk of CNS tumors in children, offering valuable insights and adding to the global evidence base on cancer risks associated with pediatric diagnostic imaging.

Despite these notable strengths, several limitations warrant consideration when interpreting the study's findings. While initiatives such as the Image Gently campaign and early safety reports likely contributed to the decline in pediatric CT use observed in Finland, it is unclear whether this downward trend continued following the publication of the high-profile studies by Pearce et al. (2012b) and Mathews et al. (2013), which quantified cancer risks associated with childhood CT exposure. As our analysis was limited to data up to 2010, further research using more recent data would be of interest to examine subsequent changes in CT utilization.

Our count and dose estimates for the older CT dataset may be underestimated, as they were based on scan parameters and national survey data collected after 2000, reflecting more contemporary practices. However, pediatric CT use during the early period of CT adoption was relatively uncommon. Additionally, older CT scanners did not provide protocol-specific dose metrics such as CT dose index volume (CTDIvol) and dose-length product (DLP), which are outputs more commonly available from newer-generation CT scanners. The absence of these parameters reduces the precision of dose estimates and increases the potential for exposure misclassification, albeit one constrained by the historical availability of data.

Limited clinical data represent another limitation. Diagnostic information around CT examinations was available for only a subset of the study population, restricting our analysis of clinical conditions associated with CT use and their temporal trends. Specific CT referral indications were also unavailable. The concern is the potential inclusion of head CT scans performed for prodromal symptoms of undiagnosed brain tumors, which could introduce reverse causation if diagnostic delays occurred. Nevertheless, this scenario is less likely, as we excluded all CT scans conducted within five years prior to a brain tumor diagnosis. This lag period is generally considered sufficient to reduce the risk of reverse causation.

An a priori power calculation was not conducted, as the case-control analysis was designed to include all eligible childhood CNS tumor cases recorded in Finnish health registers between 1990 and 2016. Rather than relying on sampling, the study population was fixed by the total number of cases nationwide. In this context, a preliminary sample size calculation would not have been meaningful. Nevertheless,

statistical power remains an important consideration, particularly for conducting or interpreting subgroup analyses. Although the study had nationwide coverage, the number of cases exposed to head/neck CTs was small after applying a 5-year lag and excluding individuals with cancer predisposition syndromes. In the primary analysis of all brain tumors, only nine cases were exposed, with even fewer in subgroups such as gliomas. The limited number of informative events reduced our statistical power to detect modest associations and restricted our ability to assess variation in risk by age at exposure or time since exposure.

Minor discrepancies existed in the parameters for the incidence and case-control analyses. Specifically, the age ranges differed (0–14 years for the incidence analysis vs. 0–15 years for the case-control analysis), as did the final year of case inclusion (2017 for the incidence analysis vs. 2016 for the case-control analysis). These differences arose primarily from the phased nature of this doctoral project, where data for the different publications were requested from the Finnish Cancer Registry at separate times. This resulted in slightly different data cut-off dates for each analysis. Finally, the generalizability of our findings on pediatric CT utilization and associated CNS tumor risks should be interpreted in the context of Finland's specific healthcare model and socioeconomic environment. While the results may be relevant to other high-income countries with similar healthcare infrastructures and regulatory environments, their applicability to settings with different health systems, resource levels, or diagnostic practices may be limited.

6.5 Public health implications

Our findings underscore the importance of carefully weighing the clinical benefits of pediatric CT imaging against the need for heightened vigilance regarding radiation-related risks. CT imaging delivers substantially higher doses of ionizing radiation than conventional radiography, raising particular concern for pediatric populations. Children are especially vulnerable to radiation exposure due to their developing organs and extended lifespans, providing more time for radiation effects to develop (UNSCEAR, 2013).

Our study, providing evidence of a dose-response relationship between radiation exposure from CT and childhood brain tumor risk, highlights an essential moment for healthcare systems to rigorously balance diagnostic accuracy with radiological protection and long-term risk. Although the absolute risk from an individual pediatric

CT scan might be small, cumulative exposure from multiple scans across a large population translates into a public health concern (UNSCEAR, 2021).

While we found that pediatric CT imaging rates have declined in Finland, it remains essential to implement and regularly update pediatric-specific diagnostic reference levels. These benchmarks help detect and correct deviations from optimized radiation dosing, particularly as imaging technology and clinical practices continue to evolve. Additionally, CT manufacturers and radiology departments must systematically record dosimetric parameters through standardized dose-reporting mechanisms, enabling more accurate assessment of patient radiation doses. In clinical practice, strict adherence to the core radiological protection principles of justification and optimization is essential, including evidence-based imaging decisions, avoiding low-value examinations, and reducing defensive medicine (ICRP, 2018). Radiology departments should require detailed clinical indications from referring physicians, as this supports decision-making, facilitates research, and enables periodic review and auditing of imaging use.

Enhanced interdisciplinary collaboration among radiologists, pediatricians, emergency physicians, and other clinicians, alongside the active involvement of families through transparent communication regarding risks and benefits, support informed decision-making and patient safety (WHO, 2016). To translate scientific findings into safer clinical practices, educational initiatives and policy measures must target multiple layers within the healthcare system. Raising awareness among healthcare providers and caregivers about radiation dose metrics, clinical decision-support tools, and the rationale behind choosing non-ionizing alternatives such as MRI or ultrasonography can help the efforts to optimize CT use in children and reduce unnecessary radiation exposure.

Furthermore, comprehensive population-based cancer surveillance systems are essential, particularly given our findings of increasing incidence rates of childhood CNS tumors. The recording of benign CNS tumors should be adopted universally by cancer registries, given their impact on pediatric morbidity. Cancer registries should also incorporate diverse data sources and routinely cross-verify entries to minimize missed cases or duplications. Accurate and timely incidence data are indispensable for detecting shifts in tumor epidemiology and guiding clinical and public health responses. Robust surveillance, anchored in standardized tumor classification and thorough case ascertainment, supports efforts to distinguish genuine changes in disease burden from diagnostic or reporting artifacts, enabling evidence-based interventions.

6.6 Recommendations for future research

Extending the follow-up of existing pediatric CT cohorts is essential for capturing the longer-term effects of radiation exposure on CNS tumor risk. Such prolonged follow-up would enable tracking of subsequent exposures and incidence rates for specific subtypes like gliomas and yield more definitive estimates of how cumulative radiation exposure and latency influence the manifestation of malignancies. Accurate exposure assessment is equally important. Future studies should prioritize prospective data collection in which key CT dosimetric parameters are systematically recorded in real time rather than reconstructed retrospectively. These measures would improve the precision of dose estimation and allow for the quantification of uncertainties linked to different reconstruction methods. Refined outcome ascertainment is also crucial. This includes continuous monitoring of CNS tumor incidence trends, comprehensive registry linkages, and cross-checks to ensure all cases are captured and to detect any changes in incidence, tumor subtypes, or age at diagnosis that might be related to changing CT utilization patterns or evolving radiation exposure levels.

Future research should move beyond reliance on average whole-brain dose estimates. Instead, studies should utilize advances in computational phantom models and voxel-level dosimetry to quantify radiation doses to smaller intracranial structures. This more precise, region-specific dosimetry is crucial for accurately assessing risk, as uniform brain dose metrics may mask variations in exposure and potentially misrepresent the true risk for tumor subtypes that develop in higher-dose regions.

Attention must also be directed toward confounding by indication, beginning with better identification of cancer predisposing factors. Where ethically permissible, researchers should integrate information from genetic databases and standardize diagnostic criteria for CPS ascertainment to ensure that individuals at elevated risk are recognized. Subsequent stratified or dedicated analyses, especially among those with syndromes such as neurofibromatosis and tuberous sclerosis, can help clarify how genetic vulnerabilities might influence the relationship between pediatric CT scans and the risk of childhood CNS tumors.

Research into the biological mechanisms contributing to the risk of radiation-induced CNS tumors may provide valuable insights into why some children are particularly susceptible. Incorporating genetic susceptibility data, for instance through genome-wide association studies or targeted genetic testing, could facilitate the identification of individuals with heightened radiosensitivity and help develop

polygenic risk scores for predicting radiation-related malignancies. Parallel efforts to investigate biomarkers in blood samples, such as DNA damage markers or gene expression profiles, may reveal early biological signals associated with increased cancer risk. By linking such biomarkers with quantified radiation doses and long-term clinical outcomes, it may be possible to identify early indicators of radiation-induced carcinogenesis and enhance risk stratification models.

Investigations should also evaluate how effectively pediatric-specific CT protocols, iterative reconstruction, and greater reliance on MRI or ultrasound can achieve meaningful dose reductions while preserving, or even enhancing, diagnostic accuracy. Tracking integrated longitudinal dose data for individual exposures, alongside measures of diagnostic yield, is necessary to clarify the full impact of these interventions. Clinical decision support tools, such as those informed by the PECARN guidelines, also warrant ongoing assessment to ensure they continue to reduce unnecessary scans and risks.

Addressing health disparities is essential to ensuring that all children benefit equally from safer imaging practices. Research that stratifies data by socioeconomic status and geographic location is critical for identifying subpopulations that may face barriers to diagnostic access or experience a disproportionate reliance on radiation-based imaging. Findings from such studies could guide targeted interventions aimed at improving equity in healthcare utilization and minimizing avoidable risks.

Finally, future research should investigate potential risk factors for childhood CNS tumors beyond ionizing radiation. This includes examining environmental exposures (e.g., air pollutants, specific chemicals), infectious agents, and immune-related conditions. Study designs may include case-control studies, prospective cohorts, and analyses leveraging existing biobanks and geocoded environmental databases. Identifying modifiable risk factors, even those with small individual effects, could meaningfully contribute to prevention strategies.

7 SUMMARY AND CONCLUSIONS

The key findings of this research provide insights into pediatric CT use in Finland, CNS tumor incidence, and radiation risks. CT use among children increased from 1996 to 2002 but significantly declined thereafter, stabilizing by 2010, likely reflecting increased radiation protection awareness. Head scans were the most common CT type but showed the largest decrease. The average CNS tumor incidence (1990–2017) was 4.30 per 100,000 child-years, with the highest rates in younger children and boys. A slight but significant overall incidence increase (APC 0.8%) was observed, driven mainly by low-grade tumors (APC 1.0%). The increase may be attributable to improved ascertainment or real minor changes. With a 5-year lag period and the exclusion of participants with cancer predisposition syndromes or previous malignancies to mitigate reverse causation and confounding by indication, a significant association between head CT exposure and brain tumor risk was observed. Exposed children had nearly triple the odds of developing a brain tumor (OR=2.84), with a significant dose-response relationship (EOR=5.50 per 100 mGy of cumulative brain dose). Including patients with predisposing factors inflated the risk estimates, suggesting confounding by indication.

This dissertation benefited from its nationwide, population-based design, utilizing comprehensive, high-quality Finnish registers with near-complete case ascertainment and CT exposure data, improving comparability and minimizing selection bias and non-differential misclassification. Strengths also include consistent dosimetry and careful handling of bias through matching, lag periods, and confounder adjustment. Limitations involve potential underestimation of historical doses, low statistical power for subgroup analyses, and incomplete clinical data. This research confirms an association between radiation exposure from CT and brain tumor risk in children after accounting for key biases, reinforcing the importance of justification and optimization principles in pediatric radiation protection. The decline in pediatric CT use in Finland since 2002 is encouraging; nevertheless, continued vigilance is needed, including the use of pediatric protocols, regular updates to diagnostic reference levels, and consideration of non-ionizing alternatives such as MRI and ultrasound whenever clinically appropriate. Continued surveillance of CNS tumor incidence trends and rigorous epidemiological evaluation are critical to distinguish

genuine incidence shifts from diagnostic or reporting artifacts. Future research should focus on extended follow-up, improved dosimetry, better quantification of confounders, exploration of biological mechanisms and genetic susceptibility, optimization of imaging protocols, and addressing healthcare disparities. This comprehensive approach will inform evidence-based strategies, balancing diagnostic needs with long-term pediatric safety.

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Trends of computed tomography use among children in Finland

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ABSTRACT

Objectives: CT is an essential diagnostic tool in health care. However, CT delivers relatively high levels of radiation which has been associated with an increased risk of childhood cancer. To address this, we evaluated patterns and time trends of CT use among children in Finland during the period in which changes in pediatric CT imaging practices were reported in several countries.

Methods: Data on CTs performed on children younger than 15 years were obtained from Finland's largest eight hospitals. CT data included the period 1996–2010 with an estimated coverage of more than 80 % of pediatric CT imaging in Finland. Joinpoint regression was used for trends analysis. CT radiation doses were estimated based on a Finnish dosimetry survey.

Results: A total of 48,807 pediatric CTs were performed in 1996–2010. More boys (55.5 %) were scanned than girls (42.8 %). CT numbers increased up to 2002, then decreased significantly (-6.9 % per year, 95 % CI: -10.4 to -3.2) towards 2005 and to a lesser extent thereafter, particularly among younger children. All CT types decreased in recent years, except for chest, spine, and extremities. The frequency of head CTs related to the diagnoses of intracranial injury, migraine and headache decreased towards the end of the study period. The estimated annual average effective dose from the three most common CT examinations was 0.004 mSv per child in the population.

Conclusions: The frequency of pediatric CTs in Finland started to decrease after 2002. Apart from chest and orthopedic CTs, the utilization of pediatric CT imaging declined in recent years, most likely explained by improved awareness of medical radiation risks and reliance on alternative modalities such as MRI and ultrasound.

1. Introduction

The benefits of computed tomography (CT) in the field of pediatrics are undeniable. However, CT use in children has been a topic of concern and debate for several reasons. In the 1990s and early 2000s, CT utilization in children increased in many countries, and several studies showed that children who have undergone CT imaging have a higher risk of malignancy such as leukemia and brain cancer [1–6]. The risk of cancer after exposure to pediatric CT radiation might be relatively small in absolute terms, yet it is a public health concern because of the large population of children exposed [7].

Several campaigns and international programs have been launched to raise awareness of the need to optimize CT dose and use among

children. Although pediatric CT trends have been reported to be leveling off or decreasing in some studies, particularly in academic hospitals, these findings might not reflect a general trend across all settings, where children are exposed to CT radiation [8–12]. Hence, following CT rates overtime on the national level aids in clarifying imaging use patterns and guide radiation protection measures. This study evaluates CT utilization among children in Finland from 1996 to 2010, during which changes in pediatric CT imaging practices were reported in several countries. Evaluating CT use in this period is important to assess current and future health effects of radiation from CT. We analyzed CT data from eight large hospitals by age, CT type, recurrent use, institution type, and estimated CT radiation doses. The data covered more than 83 % of pediatric CT imaging performed in Finland.

Abbreviations: APC, annual percentage change; CTDIvol, volume computed tomography dose index; DLP, dose length product; mGy, milligray; mSv, millisievert; PECARN, pediatric emergency care applied research network; person-Sv, person-sievert; RBM, red bone marrow; STUK, Radiation and Nuclear Safety Authority.

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2. Materials and methods

Data on CT examinations performed on children aged 0–15 years were obtained from radiological databases from the ten largest Finnish hospitals for another study [5]. In Finland, primary healthcare is provided through municipal health centers. For secondary and tertiary medical care, Finland is divided into twenty hospital districts, each with a central hospital. The districts are grouped into five catchment areas with five university hospitals for highly specialized medical care.

The time period covered by CT data varied between hospitals, as radiological databases were introduced at the hospitals at different times. Thus, for the period 1996–2010, all five university hospitals and three of the central hospitals were included in the analysis (Table 1). According to a survey by STUK (Radiation and Nuclear Safety Authority), these eight hospital districts covered 83 % of all pediatric CT imaging performed in Finland in 2015 [13]. Data on each CT examination included personal identity code, examination date, examination code, child's date of birth, and child's sex. CT examination types were derived using a national coding system [14]. Moreover, three of the university hospitals (Tampere, Oulu and Kuopio) provided ICD-10 clinical diagnosis codes that were registered for children up to seven days before the CT examination. We evaluated these diagnoses in order to better understand the clinical paths that might have led to performing the CT examination.

CT examinations were categorized into seven groups: head/neck, chest, abdomen/pelvis, spine, extremities, combined, and miscellaneous/unknown. CT of combined regions included examinations of more than one anatomical region such as chest/abdomen/pelvis and abdomen/pelvis/lower extremity. The miscellaneous/unknown group included CT examinations labeled "others", and unknown CT examinations (167 or 0.3 % of all examinations). Participants were categorized into four age groups: under one year, 1–5 years, 6–10 years, 11–15 years. We stratified CT examinations by sex, hospital type, CT examination type, age group, and undergoing recurrent examinations. For analysis by sex and recurrent examinations, 818 CT examinations (1.6 % of all examinations) were excluded because of incomplete personal identity code or unknown sex.

To estimate CT radiation doses, we employed CT dose data collected in a Finnish survey between 2011 and 2013 [15]. Data (1049 CT examinations) were obtained from four university hospitals and included patients' information and scanning parameters such as the CT dose index (CTDIvol) and dose length product (DLP). We used NCICT software to assign organ and effective doses to three CT types: head, chest, and abdomen [16].

We employed joinpoint regression to evaluate CT trends. In the analysis, data are fitted into several lines connected at joinpoints. Monte Carlo calculations are used to determine the minimum number of points needed to adequately describe the trend. The output of regression is the annual percentage change (APC) for each segment between two

joinpoints. Joinpoint software was used for trends analysis (Joinpoint Regression Program, Version 4.7.0.0. February 2019; Statistical Research and Applications Branch, National Cancer Institute) and Stata software for other analyses (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). The study was exempt from ethical committee review and written informed consent in accordance with the Finnish regulation on register-based research.

3. Results

Over 15 years, from 1996 to 2010, 48,807 CT examinations were performed on patients younger than 15 years (Table 1). For all CT examination types, there were more examinations among boys (55.5 %) than girls (42.8 %). Older children underwent more CT examinations than younger children, with those under one year of age undergoing 8.1 % (4036) of the total examinations (Table 2). There were 31,643 head/neck CTs (63.5 %), 5196 chest CTs (10.4 %), and 3311 abdomen/pelvis CTs (6.7 %).

Overall, CT numbers increased significantly (APC 4.9, 95 % CI: 3.5–6.3) between 1996 and 2002, then started to decrease after 2002 (APC -6.9, 95 % CI: -10.4 to -3.2) and to a lesser extent after 2005 (APC -1, 95 % CI: -3.6 to 1.6) (Fig. 1). The decline in CT imaging was observed in both academic and central hospitals. The rate of pediatric CT imaging in 2010 was 43.5 examinations per 10,000 children, which is slightly higher than 42.5 in 1996. The peak was in 2002 with 59 examinations per 10,000 children

CT numbers among children in their first year of life exhibited a slightly decreasing trend throughout the study period (Fig. 2). In older age groups, however, CT use increased in the early period and started decreasing later, with the largest decrease in children aged 1–5 years (APC -10.2, 95 % CI: -17.3 to -2.6). Head/neck CT was the most common type of examination, with numbers decreasing or stabilizing in recent years across all age groups (Fig. 3). Similarly, abdomen and combined regions CTs started to decrease later, whereas chest, spine, and extremities CTs continued to increase throughout the study period (Fig. 4). Most patients (88.8 %) underwent one or two CT examinations (Fig. 5), while 373 children (1.2 %) had ten or more CT examinations, of which almost half were head/neck examinations (46.2 %). Intracranial injury, headache, convulsions, hearing loss and migraine were the most common diagnoses related to head CT. The frequency of head CT examinations related to these diagnoses significantly decreased towards the end of the study period (Fig. 6). For abdomen CT, the most common related diagnoses were injury of intra-abdominal organs and abdominal and pelvic pain.

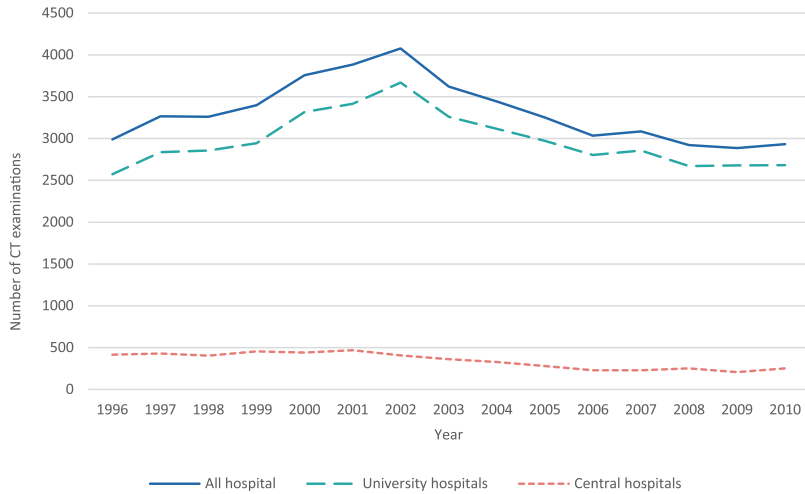
The average estimated brain dose was 17.7 mGy from head CT. Average red bone marrow (RBM) dose was 4.4 mGy from head CT and

Table 1
Number of CT examinations by hospital, sex and time period.

		CT examinations N	%
Hospitals	Helsinki University Hospital	21,733	43.6 %
	Tampere University Hospital	6945	13.9 %
	Oulu University Hospital	6654	13.4 %
	Turku University Hospital	5358	10.8 %
	Kuopio University Hospital	3957	7.9 %
	Central hospitals	5160	10.4 %
Sex	Boys	27,660	55.5 %
	Girls	21,329	42.8 %
Time period	1996–2000	16,673	33.5 %
	2001–2005	18,276	36.7 %
	2006–2010	14,858	29.8 %

Table 2
Number of CT examinations by examination type and age group.

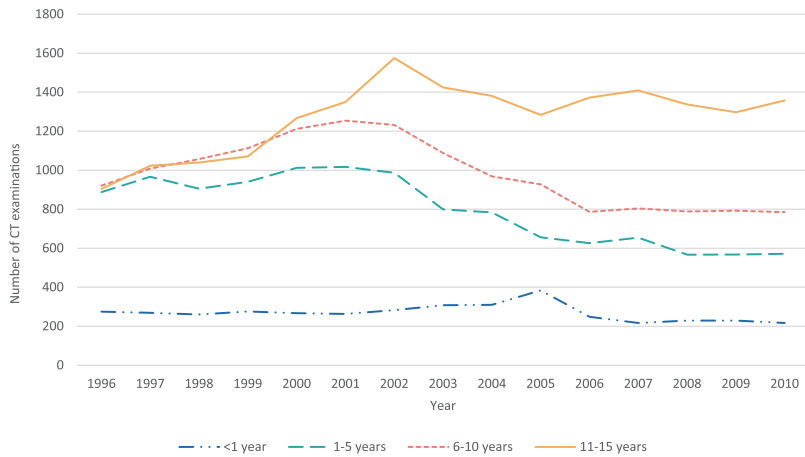
CT examination	N (%)				
	<1y	1–5y	6–10y	11–15y	0–15y
Head/Neck	2653 (65.7)	7823 (65.5)	9890 (67.1)	11,277 (59.1)	31,643 (63.5)
Chest	621 (15.4)	1603 (13.4)	1336 (9.1)	1636 (8.6)	5196 (10.4)
Combined regions	369 (9.1)	1003 (8.4)	912 (6.2)	1078 (5.7)	3362 (6.8)
Abdomen/Pelvis	290 (7.2)	773 (6.5)	935 (6.3)	1313 (6.9)	3311 (6.7)
Extremities	23 (0.6)	162 (1.4)	732 (5)	2214 (11.6)	3131 (6.3)
Spine	64 (1.6)	452 (3.8)	741 (5)	1268 (6.6)	2525 (5.1)
Miscellaneous/Unknown	16 (0.4)	126 (1.1)	191 (1.3)	306 (1.6)	639 (1.3)
Total	4036 (8.1)	11,942 (24)	14,737 (29.6)	19,092 (38.3)	49,807 (100)



All hospitals			University hospitals			Central hospitals		
Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI
1996-2002	4.9*	3.5 to 6.3	1996-2002	5.6*	4 to 7.2	1996-2001	2.7	-1.3 to 6.8
2002-2006	-6.9*	-10.4 to -3.2	2002-2005	-7	-14.7 to 1.4	2001-2006	-12.5*	-17.8 to -6.9
2006-2010	-1	-3.6 to 1.6	2005-2010	-1.9	-3.9 to 0.2	2006-2010	-0.4	-7.5 to 7.3

* Indicates that the annual percentage change (APC) is significantly different from zero (P<0.0.5)

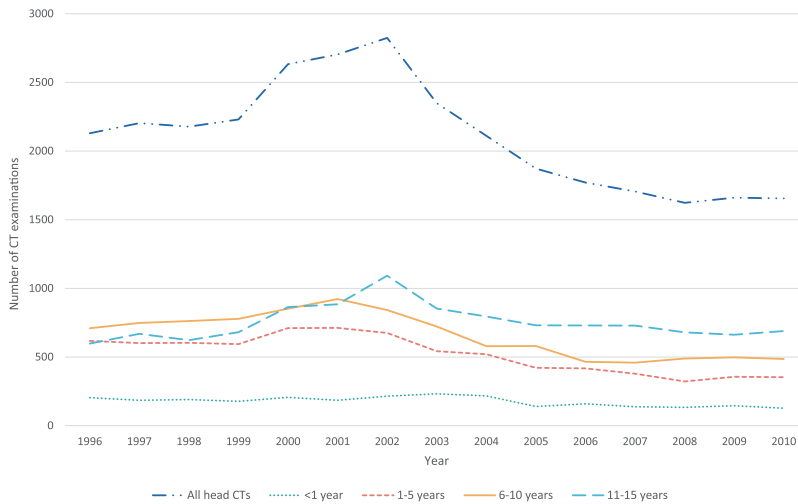
Fig. 1. Frequency trends of CT examinations by hospital type.



<1 year			1-5 years			6-10 years			11-15 years		
Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI
1996-2002	-1	-3 to 1.2	1996-2001	3	-0.5 to 6.7	1996-2001	6.9*	5.5 to 8.5	1996-2002	8.4*	6 to 10.8
			2001-2005	-10.2*	-17.3 to -2.6	2001-2006	-8.8*	-10.6 to -7	2002-2010	-1.4*	-2.6 to -0.1
			2005-2010	-3.7	-7.9 to 0.6	2006-2010	-1.1	-3.3 to 1.2			

* Indicates that the annual percentage change (APC) is significantly different from zero (P<0.0.5)

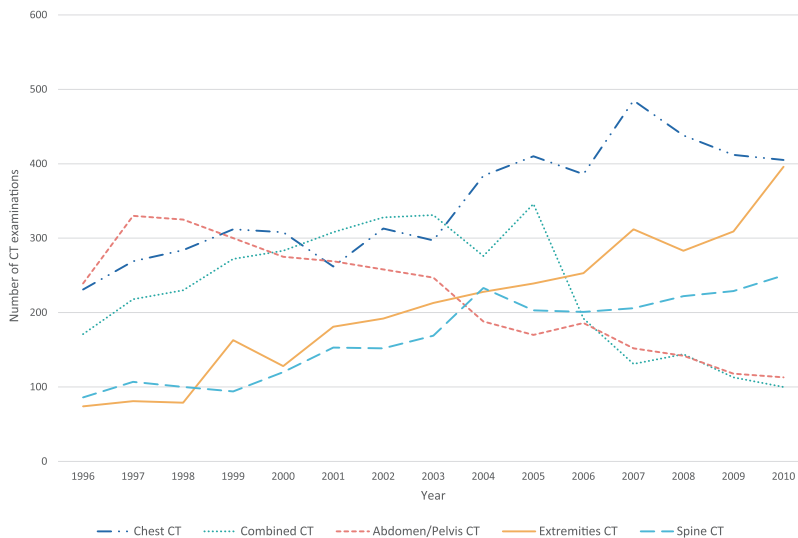
Fig. 2. Frequency trends of CT examinations by age group.



All head CTs			<1 year		1-5 years		6-10 years			11-15 years	
Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI
1996-2002	5.2*	2.8 to 7.7	1996-2003	1.7	-2.5 to 6.1	1996-2001	3.9	-0.7 to 8.7	1996-2001	5.7*	2.7 to 8.8
2002-2005	-13.3*	-24.8 to -0.1	2003-2010	-7.7*	-12 to -3.2	2001-2008	-10.4*	-13.8 to -6.8	2001-2006	-12.3*	-16.0 to -8.4
2005-2010	-2.4	-5.8 to 1.2				2008-2010	4.5	-20.5 to 37.4	2006-2010	0.7	-4.4 to 6.2
									2002-2005	-10.4	-26.4 to 9
									2005-2010	-1.4	-5.9 to 3.4

* Indicates that the annual percentage change (APC) is significantly different from zero (P<0.05)

Fig. 3. Frequency trends of head/neck CT examinations by age group.



Chest CT		Combined CT		Abdomen/Pelvis CT		Extremities CT		Spine CT			
Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI
1996-2010	4.4*	3 to 5.9	1996-2003	9.9*	3.4 to 16.7	1996-1998	15.8	-4.9 to 41	1996-2010	10.6*	8.4 to 12.8
			2003-2010	-17.4*	-23.1 to -11.1	1998-2010	-8.6*	-9.9 to -7.3			

* Indicates that the annual percentage change (APC) is significantly different from zero (P<0.05)

Fig. 4. Frequency trends of CT examinations by examination type excluding head/neck CTs.

1.7 mGy from Abdomen CT. Average breast dose among girls was 1.9 mGy from chest CT and 3.3 mGy from abdomen CT. Average effective doses for head, chest, and abdomen CTs were 1 mSv, 1.1 mSv, and 2.8 mSv, respectively. The annual average collective dose from these

three CT types (81 % of all CT examinations) was 3.7 person-Sv, translating into an annual effective dose of 0.004 mSv per child in the population.

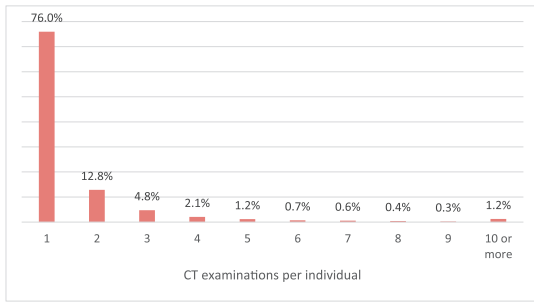


Fig. 5. Numbers of CT examinations per individual.

4. Discussion

This study evaluated CT utilization patterns over 15 years with a coverage of more than 80 % of pediatric CTs performed in Finland. Data from the eight largest Finnish hospitals showed that CT use in children increased by a third from 1996 through 2002, and then decreased towards 2010, particularly among younger children. Over the study period, the Finnish pediatric population showed little change. Several other studies have also reported declining or flattening trends, but starting later than in our study [8,9]. An Australian study found, however, that pediatric CT imaging rates leveled after 2000, whereas the numbers of CT examinations continued to increase towards 2012 in the Netherlands [10,11]

Concerns over the expanding use of pediatric CT in the 1990s and the associated cancer risks were expressed by Brenner et al. in 2001 [17]. Additional studies reported that children received unnecessarily high radiation doses, as scan parameters were not adjusted for pediatric patients [18]. Decreasing trends of pediatric CT imaging after 2002 in Finland likely reflect these concerns. In 2004, STUK (Radiation and Nuclear Safety Authority) started publishing guidelines for pediatric CT examinations [19]. STUK also regulates licensing of CT scanners and conducts surveys on the use of medical radiation in the country [13,20].

Head CT was the most common examination in this study, similar to findings from other countries. We observed a decrease in head CT use across all age groups in recent years. Head CT is often used in the management of children presenting with traumatic brain injury (TBI). In the US, it is estimated that 20–60 % of these children undergo CT

imaging [21]. Improved clinical prediction tools, such as the pediatric emergency care applied research network (PECARN) guidelines, have led to a better-targeted CT use in children presenting with TBI [22,23]. Other clinical conditions leading to a head CT include headache, convulsions and migraine. The frequency of head CTs related to these conditions decreased towards the end of our study period. The utilization of MRI has been expanding as an alternative to head CT. In Finland, between 2008 and 2018, the annual number of head MRI examinations performed on children increased from 4185 to 7315 [24]. MRI has shortcomings in children as it usually requires sedation and the child to stay motionless for a few minutes. However, the development of faster MRI sequences might facilitate even a broader utilization of MRI in the field of head imaging. A recent study showed that fast MRI is accurate and feasible relative to CT in clinically stable patients with TBI [25].

Abdominal pain is a common presentation in pediatric patients, and the diagnosis might be challenging because of the wide range of possible etiologies [26]. The utilization of pediatric abdomen CT in the US has been stabilizing or decreasing in recent years; however, imaging rates are still considerably higher than two decades ago [8,9]. In our study, rates of abdominal CT started to decrease significantly after 1998, earlier than other CT types. The number of abdomen CTs decreased by more than half to become one of the least frequent examinations in 2010. In Finland, appendicitis is usually diagnosed based on clinical findings, and CT is seldom used in the assessment of acute abdomen [19]. Instead, abdominal ultrasound is widely utilized. Between 2008 and 2018, the annual number of pediatric abdominal ultrasound examinations in Finland increased from 10,690 to 14,735 [24]. Point-of-care ultrasound (POCUS) is an emerging addition to traditional radiology, where pediatricians perform the ultrasound and rapidly incorporate the findings into their clinical decision [27]. One study found that the utilization of POCUS in the emergency department reduced CT use in children presenting with appendicitis [28].

Unlike head and abdomen CT, chest CT rate continued to increase throughout the study period, particularly among children younger than five years. According to an expert in pediatric radiology, chest CT in Finland is still the preferred option to scan the lung parenchyma with a partial shift towards MRI (K. Lauerma, personal communication, 4 December 2019). Moreover, chest CT angiography is replacing conventional invasive angiography, particularly in younger children. We also found that extremities and spine CT examinations continued to increase throughout the study period, mainly for children aged 10–15 years. As orthopedic CTs are primarily performed for surgery planning, one explanation for this finding might be the increasing frequency of

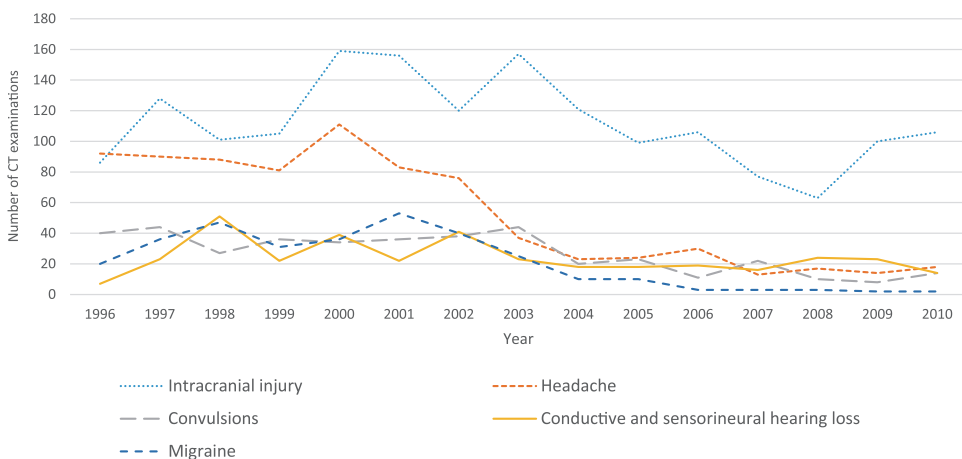


Fig. 6. Frequency trends of head/neck CT examinations by related clinical diagnosis (data from three university hospitals).

sports injuries among Finnish adolescents [19,29]. A number of studies also showed that the rate of operative management of fractures in children has increased in several countries, including Finland [30]. A provisional analysis of pediatric CT trends in three Finnish university hospitals showed that orthopedic and chest CTs kept increasing towards 2018 compared to declining trends of abdomen and head CTs (unpublished data).

Several studies have shown that CT imaging rates at general hospitals tended to decrease later than at academic hospitals and that ultrasound was utilized more frequently in pediatric-focused emergency departments [10,31,32]. However, in this study, trends of CT at central hospitals decreased concurrently with those at university hospitals. This might imply a collective awareness of medical radiation risks and commitment to radiation safety across various types of Finnish health-care facilities.

Pediatric CT imaging rates in our study peaked at 59 examinations per 10,000 children in 2002, which is comparable to rates in the UK (51 in 2002) and the Netherlands (68 in 2012), but substantially below those in the United States (200 in 2005) [8,10,33]. Differences in imaging rates and trends may indicate higher awareness of medical radiation risks, but they may also reflect variances across healthcare systems. In the United States, financial incentives in fee-for-service health models can contribute to the overutilization of medical imaging [8,9,34]. Besides, concerns over medical malpractice litigation have led to “defensive medicine” with a low threshold for diagnostic testing, including imaging [35]. On the other hand, in a universal health system, such as in Finland and the UK, health services are primarily funded through public expenditure, and care is provided without direct benefit to health professionals but rather an inclination to contain costs and limit tests [36]. There is also less fragmentation in patient care, which minimizes imaging rates, particularly duplicate examinations [37]. The overuse of imaging might also involve patients’ characteristics and preferences.

Dose estimations in this study were based on a Finnish dose survey conducted between 2011 and 2013 [15]. Generally, organ and effective dose estimates were lower than those reported in other countries such as Spain, the UK, Germany and the US [8,12,38,39]. Breast doses from chest CT were particularly low (1.4–2.7 mSv) relative to breast doses from abdomen CT (0.5–5.6 mSv). Scan lengths for abdomen CT were 15 cm longer on average than chest CT and consequently had higher DLPs. Alongside declining CT numbers, the annual average collective effective dose from the three most common CT types decreased from 4.7 person-Sv in 2002 to 2.9 person-Sv in 2010. Based on these estimates, the pediatric population in Finland received an annual effective dose of 0.004 mSv per capita, a tiny fraction of the 3.2 mSv mean annual effective dose for the Finnish population [40]. One limitation in our estimation is that the applicability of the dose estimates to scans from older periods is uncertain. Our dose estimates source was a survey performed at university hospitals and, thus, these estimates might not entirely reflect practice at central hospitals. However, we believe it is safe to assume that dose optimization measures are reasonably similar at university and central hospitals since CT radiation exposure reference levels are mandated nationally by law [41].

The variations in CT utilization and radiation doses across countries and institutions indicate that there is room for improvement. In many instances, doses can be lowered with minimal effect on image quality. In the UK, the absorbed dose for the brain from head CTs decreased after 2000 from 62 mGy to 30 mGy in children under 20 years of age [38]. These changes were the result of using pediatric protocols to adjust scan parameters. In one Finnish hospital, the percentage of justified CT examinations in patients under 35 years increased from 71 % to 87 % after improving the capacity of MRI and promoting guidelines and education on radiation protection [42].

Concerns over radiation dose from recurrent CT exposure have been recently raised by the International Atomic Energy Agency (IAEA) [43]. One study estimated that 1.33 % of patients undergoing recurrent CTs received more than 100 mSv of cumulative effective dose (CED) over a

period of 1–5 years [44]. In our study, 1.2 % of patients underwent ten or more CT examinations. CED from the three most common CTs ranged between 1.4 and 61 mSv with a median of 6.2 mSv. The IAEA endorsed, among other measures, the Smart Card project, which aims to track the patient’s radiation exposure history through summing effective doses as CED [43].

Clinical diagnoses registered before the CT examination were available only for part of the cohort and were utilized to infer the most common clinical conditions related to a CT examination and their trends over time, though direct information on indications as given in referrals was not available for us. A recent survey by STUK showed that the total number of pediatric CT examinations in Finland increased slightly in 2018 compared to 2015 [24]. Although this finding might not indicate a returning increasing trend of pediatric CTs in Finland, it is crucial to continuously evaluate adherence to national and institutional guidelines. Further research into the appropriateness of pediatric CT examinations is essential. The indications and clinical path that lead to the CT scan are worth investigating, coupled with the extent to which other imaging modalities like MRI and ultrasound had been utilized. This study has several strengths. The CT data covered the majority of pediatric CT imaging performed in Finland during the period in which CT use trends in children started to change in several countries. Grouping of CT examinations was reliable, as we used a national coding system. Moreover, numbers of recurrent examinations were reasonably accurate, as the repetition of imaging studies is not a significant issue in Finland.

5. Conclusions

CT imaging utilization in children started to decrease in Finland after 2002, particularly among children under five years of age. Numbers of all CT types decreased in recent years except for chest, extremities, and spine CTs. Our study suggests that there is a high level of awareness of medical radiation risks in Finnish hospitals. Further studies should evaluate the appropriateness of various pediatric CT examinations in an effort to standardize practices and minimize children’s unnecessary exposure to medical radiation.

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Ethical statement

Written informed consent was not required for this study because the Finnish legislation allows register-based research without informed consent.

CRedit authorship contribution statement

Jad Abuhamed: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Project administration. **Atte Nikkilä:** Investigation, Data curation, Writing - review & editing. **Olli Lohi:** Writing - review & editing, Supervision. **Anssi Auvinen:** Conceptualization, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors report no declarations of interest.

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PUBLICATION II

Incidence trends of childhood central nervous system tumors in Finland 1990-2017

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RESEARCH

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Incidence trends of childhood central nervous system tumors in Finland 1990–2017

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Abstract

Introduction: Central nervous system (CNS) tumors are a leading cause of cancer-related morbidity and mortality in children. Our aim is to characterize incidence trends of pediatric CNS tumors in Finland over the last three decades.

Methods: Data on all benign and malignant incident CNS tumors diagnosed in children aged 0–14 years in 1990–2017 were extracted from the Finnish Cancer Registry and classified according to the 2016 WHO classification of CNS tumors. We analyzed age-standardized incidence rates (ASR) for pediatric CNS tumors overall and by sex, age, tumor histology, grade, and location using Poisson regression. We used joinpoint regression to evaluate changes in trends.

Results: Overall, 1117 pediatric CNS tumor cases were registered in Finland with a 1.2:1 male to female ratio. The average annual ASR was 4.3 per 100,000 person-years (95% CI 4.26, 4.34). The most common tumor type was pilocytic astrocytoma (30% of tumors), followed by medulloblastoma (10%) with incidence rates of 1.30 and 0.45 per 100,000 person-years, respectively. The overall incidence of pediatric CNS tumors increased by an annual percentage change (APC) of 0.8% (95% CI 0.2, 1.4). We observed no major changes in incidence trends of tumor histology groups or tumor location groups. The ASR of benign tumors increased by an APC of 1.0 (95% CI 0.1, 2.0).

Conclusions: Utilizing the high-quality and completeness of data in the Finnish Cancer registry, we found that the incidence of pediatric CNS tumors in Finland has increased slightly from 1990 until 2017. Although variations in diagnostic and registration practices over time might have affected the rates, the trend may also reflect a true increase in incidence.

Keywords: Incidence, CNS tumors, Childhood cancer, Trends, Cancer register

Introduction

Central nervous system (CNS) tumors are the second most common group of childhood neoplastic diseases after leukemia and a leading cause of cancer-related death among children [1]. The global incidence of CNS tumors in children is estimated at 2.8 per 100,000 person-years [1]. These tumors constitute a heterogeneous group of pathologic entities with different biology, and

their incidence, histologic type, and prognosis in children are distinct from those in adults [2]. Between the 1970s and 1990s, the incidence of pediatric CNS tumors increased in several European countries and the United States [3, 4]. Recent studies from Canada and France reported stable incidence rates of pediatric CNS tumors, while a study from the US showed a small but significant increase [5–7]. As the etiology of CNS tumors is still largely unknown, monitoring changes in cancer incidence is critical for instigating hypothesis-based research on potential environmental risk factors, as well as assessing the public health burden [8].

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However, the characterization of CNS tumor incidence and temporal trends involves several challenges. The coding and classification of CNS tumors have been amended and updated over the years, reflecting the evolving pathological and clinical knowledge as showcased lately by the incorporation of molecular parameters into the 2016 WHO classification of CNS tumors [9]. Another example is downgrading the tumor behavior of pilocytic astrocytoma from malignant to uncertain in the 2000 edition of ICD-O-3 [10]. Moreover, cancer registers vary in completeness and inclusion of benign CNS tumors, which can be premalignant and potentially life-threatening. In the US, registration of benign CNS tumors was mandated by law in 2004 compared to 1953 in Finland [11, 12]. The completeness of the Finnish Cancer Registry (FCR) for childhood tumors was estimated as 94% for 2009–2013 [13].

In this study, we evaluate incidence trends of childhood CNS tumors during 1990–2017 by sex, age, tumor histology, grade, and location utilizing the population-based high-quality data of benign and malignant childhood tumors in Finland based on the 2016 WHO classification of CNS tumors.

Materials and methods

Data on all benign and malignant CNS tumors cases registered in children aged 0–14 years between 1990 and 2017 were extracted from the FCR based on the topographical categories: brain, meninges, and central nervous system (ICD-10 codes C70–72, D32–33, and D42–43). We included only first primary cancers. CNS lymphomas were excluded. Tumors were coded using ICD-O-3 (first and second revision) and grouped by the 2016 WHO classification of central nervous system tumors [9] into six histology groups (Table 1): 1) diffuse astrocytic and oligodendroglial tumors, 2) other astrocytic tumors (low-grade gliomas), 3) ependymal tumors, 4) neuronal and mixed neuronal-glioma tumors, 5) embryonal tumors, and 6) other tumors which included choroid plexus tumors, other gliomas, tumors of the cranial and paraspinal nerves, meningiomas, mesenchymal tumors, melanocytic tumors, germ cell tumors, malignant glioma not otherwise specified (NOS), and unclassified tumors.

The following morphology codes were appended to the 2016 WHO classification: 9381 (gliomatosis cerebri, growth pattern); 9423 (polar spongioblastoma); 9380 (malignant glioma NOS); 8800, 8963, 8990 (other sarcomas); and 9081 (teratocarcinoma). We excluded ten cases of recurrent tumors from the study. The population size was retrieved from Statistics Finland by single-year age and sex for each year of the study period [14]. The mean annual population size was 924,605 for children aged 0–14 years. Incidence rates were age-standardized using

the 2013 European standard population and calculated per 100,000 person-years stratified by sex, age group, tumor histology, tumor grade, and tumor location [15].

The differences in incidence rates between the groups were estimated by incidence rate ratios (IRR). We used joinpoint regression to evaluate changes in incidence trends as annual percentage change (APC) (Joinpoint Regression Program, Version 4.7.0.0. February 2019; Statistical Research and Applications Branch, National Cancer Institute). Stata software was used for other analyses (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). *P*-values below 0.05 were considered statistically significant, and all tests were two-tailed.

Results

During 1990–2017, 1117 pediatric CNS tumors were registered in Finland, 614 in boys and 503 in girls (Table 2). Tumors were most frequent in the age group 0–4 years (428 tumors). The predominant tumor location was the infratentorial area with an age-standardized incidence rate (ASR) of 1.80 (95% CI 1.77, 1.83) per 100,000 person-years, followed by the supratentorial brain (ASR 1.34, 95% CI 1.32, 1.37), and the spinal cord (ASR 0.25, 95% CI 0.24, 0.26). Tumors registered with an unspecified location comprised 19% of all tumors. Overall, 96% of the tumors were histologically verified. Gliomas accounted for half of the tumors, with low-grade gliomas comprising the largest tumor group in the study. Pilocytic astrocytoma was the most common tumor (ASR 1.30, 95% CI 1.28, 1.33) followed by medulloblastoma (ASR 0.45, 95% CI 0.43, 0.46), constituting 30 and 10% of all tumors, respectively. Most embryonal tumors and low-grade gliomas were infratentorial (71 and 52%, respectively). Benign tumors (grade I) comprised 48% of the tumors (ASR 2.05, 95% CI 2.02, 2.08), and highly malignant (grade IV) comprised 22% (ASR 0.95, 95% CI 0.93, 0.97). Overall, 32% of the infratentorial and 17% of supratentorial tumors were grade IV tumors. Of the 66 tumors in the spinal cord, 18% were pilocytic astrocytomas, and 12% ependymomas.

The average annual ASR of all pediatric CNS tumors combined was 4.30 (95% CI 4.26, 4.34) per 100,000 person-years (Table 2). The ASR in boys was higher than in girls (IRR = 1.17, 95% CI 1.04, 1.32) with a 1.2:1 male to female cancer ratio. Male predominance in incidence was most marked in embryonal tumors (IRR = 1.76, 95% CI: 1.31, 2.34). The incidence rate of CNS tumors decreased with age, as the highest incidence rate was in children aged 0–4 years (5.08, 95% CI 4.60, 5.56) and the lowest in children aged 10–14 (3.70, 95% CI 3.30, 4.10). Older children aged 10–14 years had the highest proportion (35%) of benign tumors (grade I), while the youngest age

Table 1 Modified classification of the central nervous system (CNS) tumors based on the 2016 World Health Organization Classification of Tumors of the CNS [9]

Tumor group	Morphology code
(1) Diffuse astrocytic and oligodendroglial tumors	
Diffuse astrocytomas grade II-III	9400, 9401
Oligodendrogliomas, grade II-III	9450, 9451
Mixed oligo-astrocytoma, grade II-III	9382
Glioblastoma	9440, 9441
Diffuse midline glioma, H3 K27M-mutant	9385
Gliomatosis cerebri (growth pattern)	9381
(2) Other astrocytic tumors (low-grade gliomas)	
Pilocytic astrocytoma	9421
Pilomyxoid astrocytoma	9425
Subependymal giant-cell astrocytoma	9384
Pleomorphic xanthoastrocytoma	9424
(3) Ependymal tumors	
Subependymoma	9383
Ependymomas grade II-III	9391, 9392, 9394
Ependymoma, RELA fusion-positive	9396
(4) Neuronal and mixed neuronal-glial tumors	
Dysembryoplastic neuroepithelial tumor	9413
Gangliocytoma	9492
Ganglioglioma	9505
Dysplastic gangliocytoma of cerebellum	9493
Desmoplastic infantile ganglioglioma	9412
Central neurocytoma	9506
(5) Embryonal tumors	
Medulloblastoma	9470, 9471, 9474
Central neuroblastoma	9500
Ganglioneuroblastoma	9490
CNS embryonal tumor NOS	9473
Atypical teratoid/rhabdoid tumor	9508
(6) Other tumors	
Choroid plexus tumors	9390
Other gliomas	9431, 9430, 9423
Tumors of the cranial and paraspinal nerves	9560, 9540, 9550
Meningiomas	9530, 9537, 9531, 9538, 9539
Mesenchymal, non-meningothelial tumors	9120, 9364, 9150, 8800, 8963, 8990
Melanocytic tumors	8728
Germ cell tumors	9064, 9080, 9084, 9081
Malignant glioma NOS	9380
Unclassified tumors	8000, 8982

group had the highest proportion (42%) of highly malignant tumors (grade IV). Most tumors located in the spinal cord and meninges were diagnosed in the age group 10–14 years.

The total ASR increased from 4.12 (95% CI 4.03, 4.21) in 1990–1994 to 4.81 (95% CI 4.71, 4.91) in 2013–2017 (Table 3). The annual percentage change (APC) for all

tumors was 0.8% per year (95% CI 0.2, 1.4). The ASR increased by 0.4% per year (95% CI -0.8, 1.5) for age group 1–4 years, by 1% per year (95% CI -0.4, 2.3) for age group 5–9 years, and by 1.1% per year (95% CI -0.3, 2.4) for age group 10–14. No major changes in incidence rate trends were observed for tumor histology groups or tumor location groups, as shown by APC values in Table 3. The ASR

Table 2 Age-standardized incidence rates (ASR) per 100,000 person-years with 95% confidence intervals (CIs) of pediatric CNS tumors in Finland 1990–2017

	Total N (%)	ASR (95% CI)	Boys N (%)	ASR (95% CI)	Girls N (%)	ASR (95% CI)
Total	1117 (100)	4.30 (4.26, 4.34)	614 (100)	4.63 (4.57, 4.69)	503 (100)	3.96 (3.91, 4.02)
Age group						
0–4 years	428 (38)	5.08 (4.60, 5.56)	242 (39)	5.62 (4.91, 6.33)	186 (37)	4.51 (3.86, 5.16)
5–9 years	363 (33)	4.20 (3.77, 4.63)	200 (33)	4.53 (3.90, 5.16)	163 (32)	3.85 (3.26, 4.45)
10–14 years	326 (29)	3.70 (3.30, 4.10)	172 (28)	3.82 (3.25, 4.39)	154 (31)	3.57 (3.01, 4.13)
Tumor grade						
Grade I	531 (48)	2.05 (2.02, 2.08)	285 (46)	2.15 (2.11, 2.19)	246 (49)	1.94 (1.90, 1.98)
Grade II	155 (14)	0.60 (0.58, 0.61)	80 (13)	0.60 (0.58, 0.62)	75 (15)	0.59 (0.57, 0.61)
Grade III	99 (9)	0.38 (0.37, 0.39)	53 (9)	0.40 (0.38, 0.41)	46 (9)	0.36 (0.35, 0.38)
Grade IV	246 (22)	0.95 (0.93, 0.97)	152 (25)	1.14 (1.11, 1.17)	94 (19)	0.74 (0.72, 0.77)
Grade NA	86 (8)	0.33 (0.32, 0.34)	44 (7)	0.33 (0.31, 0.34)	42 (8)	0.33 (0.31, 0.34)
Tumor location						
Supratentorial	349 (31)	1.34 (1.32, 1.37)	178 (29)	1.34 (1.31, 1.38)	171 (34)	1.35 (1.31, 1.38)
Infratentorial	468 (42)	1.80 (1.77, 1.83)	262 (43)	1.97 (1.93, 2.01)	206 (41)	1.62 (1.59, 1.66)
Cerebellum	324 (29)	1.24 (1.22, 1.27)	185 (30)	1.39 (1.36, 1.42)	139 (28)	1.09 (1.06, 1.12)
Brain stem	138 (12)	0.53 (0.52, 0.55)	77 (13)	0.58 (0.56, 0.60)	61 (12)	0.48 (0.46, 0.50)
Spinal cord	66 (6)	0.25 (0.24, 0.26)	42 (7)	0.32 (0.30, 0.33)	24 (5)	0.19 (0.18, 0.20)
Meninges	26 (2)	0.10 (0.09, 0.11)	15 (2)	0.11 (0.10, 0.12)	11 (2)	0.09 (0.08, 0.10)
Unspecified	208 (19)	0.80 (0.78, 0.82)	117 (19)	0.88 (0.85, 0.91)	91 (18)	0.72 (0.69, 0.74)
Histology						
Diffuse astrocytic tumors	161 (14)	0.62 (0.61, 0.64)	72 (12)	0.55 (0.52, 0.57)	89 (18)	0.71 (0.68, 0.73)
Other astrocytic tumors	374 (33)	1.44 (1.42, 1.46)	192 (31)	1.45 (1.42, 1.48)	182 (36)	1.43 (1.40, 1.47)
Pilocytic astrocytoma	339 (30)	1.30 (1.28, 1.33)	176 (29)	1.33 (1.30, 1.36)	163 (32)	1.28 (1.25, 1.31)
Ependymal tumors	85 (8)	0.33 (0.31, 0.34)	54 (9)	0.40 (0.39, 0.42)	31 (6)	0.24 (0.23, 0.26)
Neuronal/glial tumors	118 (11)	0.46 (0.44, 0.47)	65 (11)	0.49 (0.47, 0.51)	53 (11)	0.42 (0.40, 0.44)
Embryonal tumors	190 (17)	0.73 (0.71, 0.74)	123 (20)	0.92 (0.89, 0.95)	67 (13)	0.53 (0.51, 0.55)
Medulloblastoma	116 (10)	0.45 (0.43, 0.46)	74 (12)	0.56 (0.54, 0.58)	42 (8)	0.33 (0.32, 0.35)
Other tumors	189 (17)	0.73 (0.71, 0.74)	108 (18)	0.81 (0.79, 0.84)	81 (16)	0.64 (0.61, 0.66)

increased in all tumor histology groups except diffuse astrocytic and oligodendroglial tumors (Fig. 1). The incidence of benign tumors (grade I) increased by an APC of 1.0% per year (95% CI 0.1, 2.0).

Discussion

In this nationwide register-based study, we estimated the incidence trends of pediatric CNS tumors in Finland during 1990–2017. We observed an increase of 0.8% per year in the overall incidence of pediatric CNS tumors. The average ASR increased from 4.12 in 1990–1994 to 4.81 in 2013–2017. We observed no major changes in incidence trends of tumor histology groups or tumor location groups.

We categorized CNS tumors into broad groups based on the 2016 WHO classification of CNS tumors, which incorporated molecular parameters for the first with the addition of newly recognized neoplasms and

removal of a few others [9]. The FCR adopted the ICD-O-3 coding system in 2008 and retrospectively recoded the tumors previously registered based on the ICD-7. The recoding reduced the number of unspecified tumor codes such as glioma malignant NOS (code 9380), which comprised 3% of all the tumors in our dataset compared to 14% in the US and 15% in Canada [5, 6]. A proportion of glioma malignant NOS was recoded into pilocytic astrocytoma, which explains the higher proportion of pilocytic astrocytomas in our dataset (30%) compared to studies in France (22%) and the UK (21%) [7, 16]. However, the frequencies of other tumor groups in our study were comparable to the study conducted in France, which reported 14% medulloblastomas, 7% ependymomas, and 9% neuronal and mixed neuronal-glial tumors [7]. Similar to earlier studies, we observed that the incidence of CNS tumors in children declined

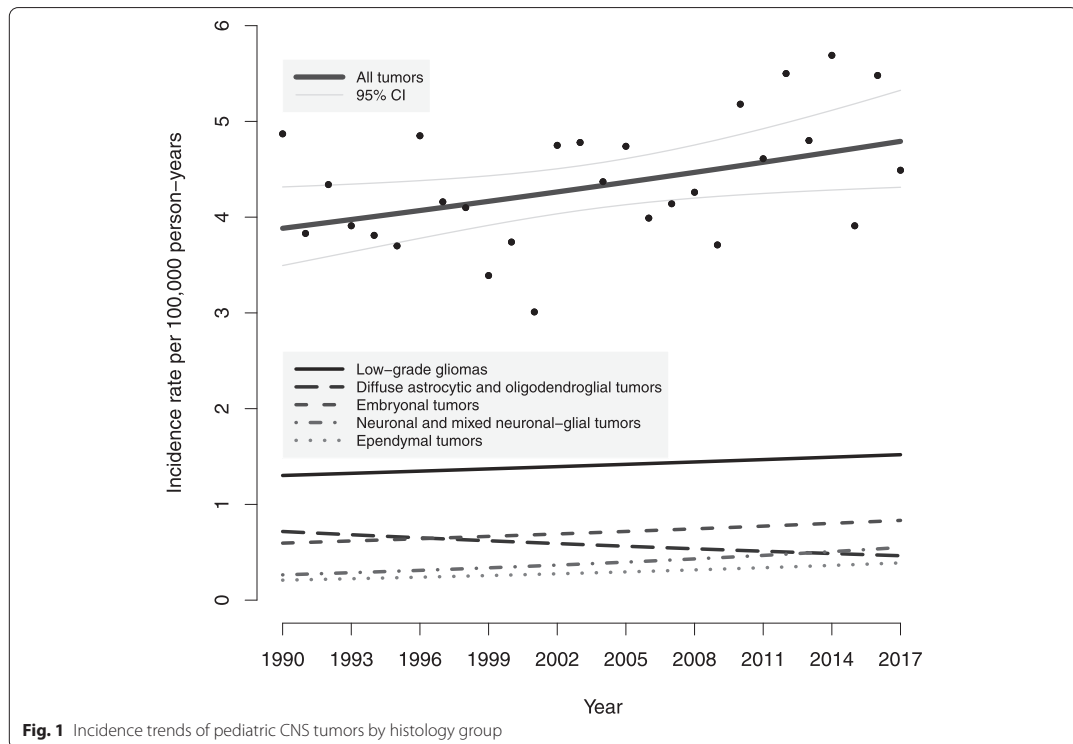
Table 3 Incidence trends and five-year age-standardized incidence rates (ASR) per 100,000 person-years with 95% confidence intervals (CIs) of pediatric CNS tumors in Finland

	1990–2017	1990–1994		2001–2005		2013–2017	
	APC (95% CI)	N	ASR (95%)	N	ASR (95%)	N	ASR (95%)
Total	0.8 (0.2, 1.4)	201	4.12 (4.03, 4.21)	195	4.25 (4.15, 4.34)	216	4.81 (4.71, 4.91)
Sex							
Boys	0.9 (0.1, 1.8)	105	4.20 (4.07, 4.32)	117	4.99 (4.85, 5.14)	117	5.09 (4.94, 5.24)
Girls	0.7 (−0.3, 1.7)	96	4.04 (3.91, 4.17)	78	3.47 (3.35, 3.60)	99	4.52 (4.37, 4.66)
Age group							
0–4 years	0.4 (−0.8, 1.5)	85	5.28 (4.16, 6.41)	68	4.78 (3.65, 5.92)	82	5.60 (4.39, 6.82)
5–9 years	1.0 (−0.4, 2.3)	61	3.81 (2.86, 4.77)	66	4.30 (3.26, 5.33)	70	4.57 (3.50, 5.64)
10–14 years	1.1 (−0.3, 2.4)	55	3.37 (2.48, 4.26)	61	3.71 (2.78, 4.65)	64	4.33 (3.27, 5.39)
Tumor grade							
Grade I	1.0 (0.1, 2.0)	80	1.64 (1.59, 1.70)	96	2.09 (2.02, 2.15)	98	2.20 (2.13, 2.27)
Grade II	−0.5 (−2.5, 1.5)	41	0.85 (0.81, 0.89)	27	0.59 (0.56, 0.63)	26	0.57 (0.54, 0.61)
Grade III	2.6 (0.0, 5.3)	13	0.27 (0.24, 0.29)	20	0.44 (0.40, 0.47)	25	0.55 (0.51, 0.58)
Grade IV	0.7 (−0.4, 1.8)	48	0.97 (0.93, 1.02)	42	0.91 (0.87, 0.96)	45	1.00 (0.95, 1.04)
Tumor location							
Supratentorial	−0.9 (−2.1, 0.4)	65	1.33 (1.28, 1.38)	74	1.61 (1.55, 1.67)	50	1.11 (1.06, 1.16)
Infratentorial	0.4 (−0.8, 1.6)	86	1.76 (1.70, 1.82)	86	1.87 (1.81, 1.93)	88	1.95 (1.89, 2.02)
Cerebellum	0.1 (−1.2, 1.4)	59	1.20 (1.15, 1.25)	59	1.28 (1.23, 1.33)	55	1.22 (1.17, 1.27)
Brain stem	1.6 (−0.4, 3.7)	26	0.54 (0.51, 0.57)	26	0.57 (0.54, 0.61)	32	0.71 (0.67, 0.75)
Spinal cord	1.0 (−1.3, 3.4)	15	0.31 (0.29, 0.34)	11	0.24 (0.22, 0.26)	14	0.32 (0.29, 0.34)
Unspecified	2.5 (−2.5, 7.8)	30	0.61 (0.58, 0.65)	20	0.44 (0.41, 0.47)	58	1.29 (1.24, 1.35)
Histology							
Diffuse astrocytic tumors	−1.7 (−3.5, 0.1)	44	0.91 (0.87, 0.95)	33	0.72 (0.68, 0.76)	23	0.52 (0.48, 0.55)
Other astrocytic tumors	0.6 (−0.6, 1.8)	63	1.30 (1.25, 1.35)	67	1.45 (1.40, 1.51)	66	1.48 (1.42, 1.54)
Pilocytic astrocytoma	0.4 (−0.9, 1.7)	56	1.15 (1.10, 1.20)	63	1.37 (1.31, 1.42)	58	1.30 (1.24, 1.35)
Ependymal tumors	1.9 (−0.5, 4.4)	13	0.27 (0.25, 0.29)	20	0.44 (0.41, 0.47)	23	0.50 (0.47, 0.54)
Neuronal/glia tumors	1.4 (−1.3, 4.2)	13	0.27 (0.24, 0.29)	23	0.50 (0.47, 0.53)	23	0.52 (0.48, 0.55)
Embryonal tumors	1.2 (−0.1, 2.6)	34	0.68 (0.65, 0.72)	27	0.59 (0.55, 0.62)	39	0.86 (0.82, 0.90)
Medulloblastoma	1.6 (−0.4, 3.6)	22	0.45 (0.42, 0.48)	14	0.31 (0.28, 0.33)	30	0.66 (0.62, 0.70)
Other tumors	1.5 (−0.0, 3.1)	34	0.69 (0.65, 0.73)	25	0.55 (0.51, 0.58)	42	0.93 (0.89, 0.98)

with age and that there was a male predominance, particularly for embryonal tumors [5–7, 17].

The observed increase in trend might be explained by a true increase in cancer incidence. However, several other factors might have led to fluctuations in overall and subgroup incidence rates over time and need to be considered before accepting such interpretation. CNS tumors comprise more than 100 histological subtypes [8]. This can lead to variations in classification and registration practices between registers and over time, complicating international incidence comparisons and time trends analysis. Studies from the US, Europe, and the Nordic countries have indicated an increasing incidence of pediatric CNS tumors from the 1970s to the 1990s [3, 4, 18–21]. This rise occurred primarily in the mid-1980s due to enhanced detection and earlier diagnosis driven mainly by the introduction of MRI [4]. It

is unclear whether the increasing availability and accessibility of MRI and the advent of advanced diagnostic techniques such as diffusion-weighted MRI and MR spectroscopy have continued to facilitate the detection and characterization of CNS tumors after 2000. In our study the incidence of benign tumors increased consistently throughout the study period, which might indicate that improved diagnostics had led to earlier detection of slow-growing tumors. A study from the US reported a significant increase of 0.6% per year for malignant CNS tumors and 2.3% per year for non-malignant tumors in children between 2000 and 2015 [6]. However, a Canadian study found a stable incidence during the same time period [5]. In Finland, the annual number of pediatric head MRIs increased from 4.1 per 1000 children in 2008 to 7.3 per 1000 children in 2018 [22]. Concurrently, the use of CT in pediatric imaging



has been declining in Finland, similar to several other Western countries [23–26].

Compared with our results (overall incidence 4.3 per 100,000), lower incidence rates have been reported in some other Western countries such as Canada (3.8/100,000), France (3.9/100,000), and Britain (4/100,000), while a higher rate was reported in the US (5.7/100,000) [5–7, 16]. Higher incidence rates have been reported in the Nordic countries than in other European countries [27, 28]. The completeness of the Finnish Cancer Registry has been shown to be very high [11]. For childhood tumors, the completeness of FCR data was estimated as 94% for 2009–2013 with registration of benign brain tumors since its establishment in 1953 [13]. Automated reporting of histologically or cytologically confirmed cases from pathological laboratories has been practically comprehensive since the late 1980s and hence the coverage of pathologically verified diagnoses is nearly complete. Clinical notifications, the other source of case ascertainment from hospitals, on the other hand, have been based on manual forms until recently (a simplified electronic format for clinical notifications was introduced in 2020) and their number relative to pathological

notifications has been declining over time [29]. During the past few decades, cross-checking with both hospital discharge register and cause of death database as independent sources of information have enabled the identification of any missed cases [11]. The comprehensive use of unique personal identifiers also allows the elimination of duplicate cases. The potential impact of any changes in coverage of cancer on the incidence of pediatric CNS tumors over time is difficult to evaluate. Clinical notifications are essential for compiling information on tumor stage, localization, and treatment, but information crucial for incidence analysis (date of diagnosis, histological type, and demographics) is available from the electronic reports by the pathology laboratories. Any incompleteness is, therefore, most likely to affect mainly the earliest part of the study period and could accentuate an increasing trend through case undercount.

Established risk factors for pediatric CNS tumors remain limited to familial cancer syndromes and high doses of ionizing radiation [8]. However, it is unlikely that these factors have contributed to the increasing incidence of pediatric CNS tumors. The use of radiation therapy has declined over time in most pediatric cancer

categories [30]. Exposure to radiation from CT imaging in children has been linked to a higher risk of malignancy such as leukemia and brain cancer [31–35]. Nevertheless, CT use in children started to decline in Finland after 2002 with increasing awareness of radiation-related risks and reliance on other imaging modalities [23]. Familial cancer syndromes such as tuberous sclerosis and neurofibromatosis can carry very high risks of brain tumors, but their prevalence is very low and stable and cannot explain the observed changes in incidence. There are several suspected risk factors for pediatric CNS tumors that are still the focus of research in the field. Growing evidence indicates a positive association with maternal dietary supplements, advanced parental age, pesticide exposure, birth weight, and birth defects [8]. As the etiology of brain cancer is still largely unknown, we also need to consider the possibility of other unknown risk factors which might have affected the incidence of pediatric CNS tumors. If the observed increase is to be explained by a specific exposure, it would be expected to be increasing gradually over several decades.

A limitation in our study is the small number of cases in some histology and topography groups, such as germ cell tumors and spinal cord tumors. Therefore, we were unable to provide a detailed analysis of incidence trends for these groups. Moreover, the statistical power to show differences in incidence trends between tumor subgroups was limited. However, our 27-year study period allowed the aggregation of relatively large numbers in the main CNS tumor groups. In addition, the centralized cancer care and quality of cancer registration in Finland contributed to the completeness of data and comparability across the entire population. Moreover, benign CNS tumors were included constantly throughout the whole study period.

In conclusion, we found a minor increase in the incidence of pediatric CNS tumors in Finland between 1990 and 2017. Although changes in registration practices and enhanced detection by improved and more available diagnostics could have driven the trend, a true increase in CNS cancer incidence and the contribution of environmental risk factors cannot be ruled out. Thus, continuous monitoring of incidence trends and further research into the etiology of childhood CNS tumors are warranted. One suggestion is a larger study with pooled Nordic data and a more detailed classification.

Abbreviations

APC: Average parentage change; ASR: Age-standardized incidence rate; CI: Confidence interval; CNS: Central nervous system; CT: Computed tomography; FCR: Finnish cancer registry; ICD: International classification of diseases; IRR: Incidence rate ratio; MRI: Magnetic resonance imaging; NOS: Not otherwise specified.

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Authors' contributions

JA: Conceptualization, Methodology, Writing - Original Draft, Data Curation, Formal analysis; AN: Formal analysis, Visualization, Writing - Review & Editing; JR: Formal analysis, Software, Data curation; WA: Visualization, Writing - Review & Editing; OL: Methodology, Writing - Review & Editing; JP: Validation, Writing - Review & Editing; HH: Methodology, Data Curation, Writing - Review & Editing; AA: Supervision, Conceptualization, Methodology, Writing - Review & Editing. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used for analyses in the current study are available in the Zenodo repository at <https://doi.org/10.5281/zenodo.5789368>

Declarations

Ethics approval and consent to participate

The requirement for ethical approval and consent to participate is waived according to Finnish legislation on register examinations in which the subjects are not in contact / are not subject to intervention. The ethics committee: Regional Ethics Committee of the Expert Responsibility area of Tampere University Hospital.

Methods: All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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III

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RESEARCH ARTICLE

Cancer Epidemiology

Risk of childhood brain tumors after exposure to CT radiation: A nationwide population-based case-control study in Finland

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Abstract

In this nationwide population-based case-control study, we assessed the risk of childhood brain tumors following exposure to radiation from CT. Brain tumors diagnosed in Finland during 1990–2016 were identified by the Finnish Cancer Registry. For each case, three age- and sex-matched controls were sampled from the Population Information System. The study population was linked to a CT dataset encompassing pediatric CTs performed in Finland during 1975–2011. We implemented a 5-year lag period and excluded participants with cancer predisposition syndromes or previous malignancies. We estimated brain doses using the NCICT program. Overall, 1067 brain tumors were diagnosed in children aged 0–15 years during 1990–2016, 58% of which were gliomas. Among eligible participants, nine cases (1%) and 10 controls (0.4%) had undergone at least one head/neck CT scan. The mean cumulative brain dose was 22 mGy for exposed participants. Participants who had undergone one or more head/neck CTs had a higher risk of developing brain tumors compared to unexposed individuals (Odds ratio [OR] = 2.84, 95% CI 1.12, 7.19). The excess OR (EOR) per 100 mGy of brain dose was 5.50 (95% CI 0.31, 10.95) for all brain tumors, and 1.06 (95% CI –6.55, 9.30) for gliomas. Our results suggest a positive association between head/neck CT imaging and the risk of childhood brain tumors. These findings contribute to the existing knowledge about the hazards of low dose ionizing radiation in pediatric populations. Further research with more precise dosimetry, including dose distribution within the brain, is needed.

KEYWORDS

brain tumors, childhood cancer, computed tomography, ionizing radiation, pediatric population

What's new?

This population-based case-control study quantifies the risk of childhood brain tumors following exposure to radiation from computed tomography scans in Finland. Leveraging comprehensive nationwide cancer and computed tomography data and addressing key limitations in previous research, including reverse causation and confounding by indication, the study provides evidence of an increased risk of brain tumors in children exposed to computed tomography

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imaging. These findings contribute to the body of evidence on the risks of low-dose ionizing radiation in pediatric populations and highlight the need for further research to refine our understanding of radiation-associated risks in children.

1 | INTRODUCTION

Children are more susceptible to the health impacts of ionizing radiation than adults, as their developing tissues and organs are more sensitive to radiation.¹ Furthermore, children's longer lifespan provides more time for radiation-induced adverse effects to manifest. Radiation from medical interventions, including computed tomography (CT) imaging, is one of the main sources of ionizing radiation exposure to the population.² Approximately 3%–10% of medical diagnostic radiation procedures are performed on children.³ CT use in children has increased globally since the 1990s, although several recent studies have reported leveling or decreasing trends.^{4–7} However, concerns persist regarding unnecessary scans and higher-than-needed radiation doses.^{8,9}

Brain tumors comprise approximately one-third of all tumors in children and are often accompanied by an unfavorable prognosis.¹⁰ Moreover, the head is the most common CT-scanned body part in the pediatric population.¹¹ Several studies have shown an increased risk of developing brain tumors in the years following a child's exposure to CT radiation.^{12,13} However, there is still inconsistency in the literature and uncertainty about the magnitude of this association and whether reverse causation or confounding by indication has contributed to the reported excess risks.^{14–16}

This nationwide population-based study aimed to quantify the risk of childhood brain tumors following exposure to radiation from head/neck CT imaging using comprehensive CT and cancer data, with efforts to limit reverse causation and confounding by indication.

2 | MATERIALS AND METHODS

2.1 | Study population

All brain tumors diagnosed in children aged 0–15 years between 1990 and 2016 in Finland were identified from the Finnish Cancer Registry (FCR).¹⁷ Extraction from the FCR was based on the topographical categories: meninges (except spinal), brain, and other parts of the central nervous system except spinal cord tumors. We included only primary tumors, both benign and malignant, and excluded central nervous system lymphomas. Tumors were coded using the ICD-O-3 (first and second revisions) and grouped into seven histology groups by the 2016 WHO classification of central nervous system tumors (Table S1).¹⁸ For each case, we sampled three controls from the Population Information System matched by month and year of birth and sex (Figure 1). One case and one control were excluded due to data usage opt-outs. Controls had to be cancer-free up to the index date, defined as the date of cancer diagnosis for the corresponding

case. The cancer-free status of controls was established through linkage with the FCR.

2.2 | Exposure assessment

CT scan data were gathered from 10 individual hospital databases, with each hospital's permission obtained separately. IT staff at each hospital extracted and securely transmitted the data, which were then combined and harmonized by our team into a unified CT dataset. This dataset contained all CT scans performed on children under the age of 16 years in all five university hospitals and the five largest central hospitals in Finland. The periods of data availability and the number of CT scans varied between hospitals (Table 1). We estimated that the CT dataset covered up to 87% of all pediatric CT scans in Finland in the later years of the period 1975–2011, with lower coverage in the earlier years.¹⁹ Each CT scan included a personal identity code, scan date, scan code, child's date of birth, and child's sex. CT scan types were derived using a national coding system for medical procedures.²⁰ After excluding nine scans in five individuals due to data usage opt-outs, 73,035 CT scans remained (Figure 2). The analysis included only head and neck CT scans.

We searched the Register of Congenital Malformations (1974–2016), the Hospital Discharge Register (1974–1993), and the Care Register for Health Care (1994–2016) for the following cancer predisposition syndromes (CPS) that increase brain tumor susceptibility: neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), tuberous sclerosis (TSC), Li-Fraumeni, nevoid basal cell carcinoma (NBCCS), Turcot, Cowden, hereditary retinoblastoma, and Rubinstein-Taybi (Table S2).²¹ To address potential confounding factors, we obtained information on maternal smoking during pregnancy and birth weight, classified as large for gestational age (LGA), from the Medical Birth Register (1987–2016), as well as data on socioeconomic status and education of the parents from Statistics Finland (1975–2016). LGA was defined as a birth weight two SD above the reference mean birth weight in Finland, adjusted for the newborn's sex, gestational age, parity, and birth plurality.²²

We estimated brain doses from CT exposure using the National Cancer Institute dosimetry system for Computed Tomography (NCICT), which employs five computational pediatric phantoms of 0, 1, 5, 10, and 15 years for both sexes.²³ NCICT requires several input parameters for each CT scan, including the child's age and sex, CT machine manufacturer and model, scan protocol, and tube potential, current, pitch, and colimitation. The Radiation and Nuclear Safety Authority (STUK) provided information on the CT machines used in the hospitals. We assumed that the latest CT machine in each hospital was the one used to perform the scans in that hospital. For two hospitals (Satakunta and Central Finland) where this information was

FIGURE 1 Flow chart of the selection of participants in the study. CPS: Cancer predisposition syndromes.

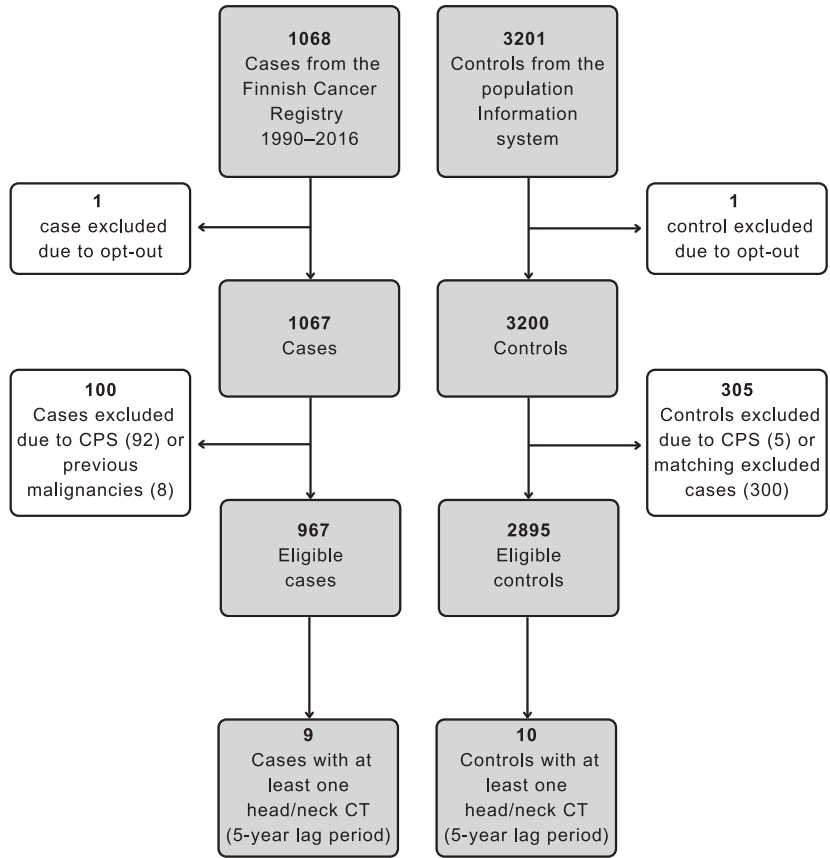


TABLE 1 Number of CT scans and the periods covered by each hospital included in the study.

Hospital	Number of CT scans	%	Period
Helsinki University Hospital	28,454	39.0	1990–2011
Tampere University Hospital	17,448	23.9	1976–2011
Oulu University Hospital	8720	11.9	1993–2011
Turku University Hospital	5806	8.0	1996–2011
Kuopio University Hospital	4115	5.6	1996–2011
North Karelia Central Hospital	3033	4.2	1993–2011
Satakunta Central Hospital	2031	2.8	1995–2011
Central Finland Central Hospital	1635	2.2	2002–2011
Seinäjäki Central Hospital	1346	1.8	1999–2011
Päijät Häme Central Hospital	447	0.6	2000–2011

missing, we assumed that the most common CT machine used in Finnish hospitals was employed. A head phantom (16 cm diameter) was selected for head and neck CT scans. Based on the scan year and child's age, an experienced hospital physicist provided estimated values of tube potential (kVp), current (mA), pitch, and collimation for CT imaging in Finland. For older scans, dating back to 1984, we used CT scan parameters estimated for the year 2002.

2.3 | Statistical analysis

We employed a 5-year lag period, meaning that head/neck CT scans performed within 5 years prior to the index date were excluded to minimize reverse causation. Analyses were conducted with and without participants who had CPS or previous malignancies, and separately for gliomas and malignant tumors. The unit of analysis was

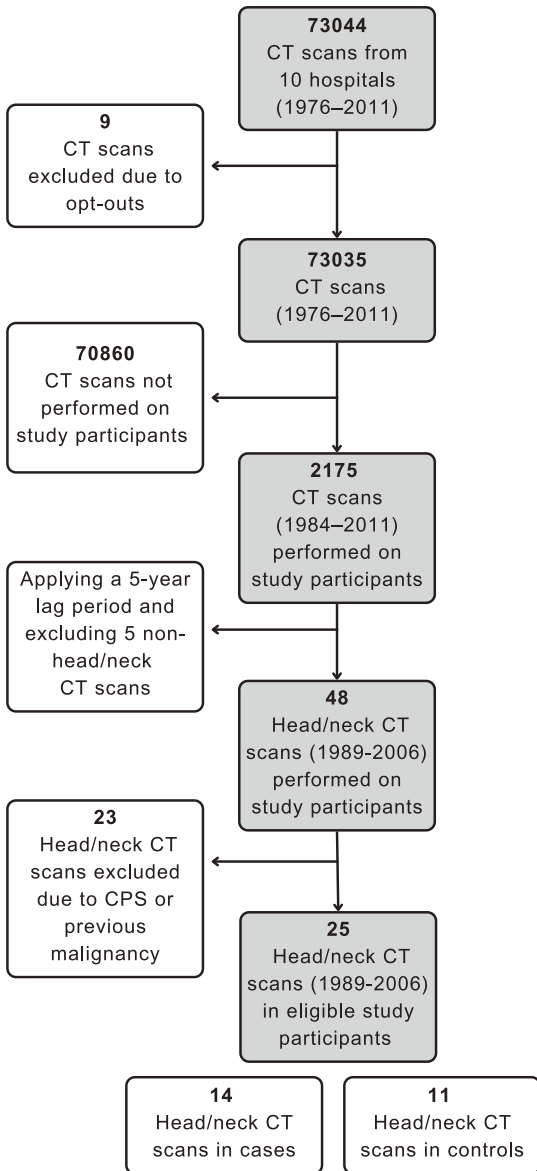


FIGURE 2 Flow chart of the selection of CT scans in the study. CPS: Cancer predisposition syndromes.

case-control sets, each consisting of one case and three matched controls. However, one case had only two controls due to a participant opt-out. Radiation exposure was analyzed as a categorical variable based on CT use (any head/neck CT vs. none) and dose levels divided into tertiles (with zero dose as the reference) or as a continuous dose variable measured in milligray (mGy). A log-linear conditional logistic regression model was applied to estimate the odds ratios (OR) and 95% confidence intervals (CIs) using the formula $OR = \exp(\beta \times \text{dose})$,

where β represents the regression coefficient per mGy of cumulative brain dose. The excess odds ratios (EOR), defined as $EOR = OR - 1$, were calculated per 100 mGy of radiation dose. The likelihood ratio test was applied to determine the significance of effects across strata of age and sex.

Parental socioeconomic status, identified as a potential confounder through Directed Acyclic Graphs (DAGs), was confirmed in our data to be associated with both child CT exposure and brain tumor risk. To account for this, we adjusted the odds ratios for maternal and paternal socioeconomic status, categorized into five groups: self-employed, upper-level employee, lower-level employee, manual worker, and other. Maternal smoking during pregnancy, infants born large for gestational age, and parental education levels were not considered as confounders due to lack of an a priori association with CT examinations. Statistical analyses were performed using Stata software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Statistical significance was defined as p values < 0.05 , with all tests being two-tailed.

3 | RESULTS

This nationwide population-based study included 1067 cases of childhood brain tumors diagnosed during 1990–2016 and 3200 controls (Figure 1). More than half of the participants were boys (53.9%) (Table 2). The three age groups at the time of diagnosis (0–4 years, 5–9 years, and 10–15 years) were comparable in size, comprising 36.5%, 30.9%, and 32.6% of the total cases, respectively. Over half (57.8%) of all brain tumors were gliomas. Cases and controls were comparable in terms of place of birth, mother tongue, birth weight, and parents' education. Cancer predisposition syndromes were more common among cases (8.8%) compared to controls (0.2%) ($p < .001$).

The majority of participants exposed to CT imaging had received only one CT, with head CT being the most common scan type. After applying a 5-year lag period, excluding participants with cancer predisposition syndromes or previous malignancies, and excluding non-head/neck CT scans, a total of nine cases (0.9%) and 10 controls (0.4%) had undergone at least one head/neck CT scan (Figure 1). Approximately 78% of cases and 70% of controls were between 0 and 5 years old at the time of their first head/neck CT scan. The mean absorbed brain dose per head/neck CT was 16.7 mGy (range: 3.5, 41.8 mGy). The mean cumulative absorbed brain dose was 22.0 mGy (range: 3.5, 126.2 mGy) for all exposed participants, 31.2 mGy (range: 3.5, 126.2 mGy) for the exposed cases, and 13.6 mGy (range: 7.9, 26.6 mGy) for the exposed controls.

Participants who had undergone one or more head/neck CT scans had a higher risk of developing brain tumors compared to those without a history of CT imaging (Odds ratio (OR) = 2.84, 95% CI 1.12, 7.19) (Table 3). No significant differences in OR were observed across age strata (likelihood-ratio test, $p = .97$) or sex ($p = .91$). The excess

TABLE 2 Characteristics of study participants before any exclusions.

	Cases		Controls		p value
	n	%	n	%	
Sex					
Boys	575	53.9	1725	53.9	
Girls	492	46.1	1475	46.1	
Age group					
0–4	389	36.5	1167	36.5	
5–9	330	30.9	990	30.9	
10–15	348	32.6	1043	32.6	
Place of birth					
Finland	1034	96.9	3110	97.2	
Outside Finland	33	3.1	90	2.8	.64
Mother tongue					
Finnish	980	91.9	2910	90.9	
Swedish	58	5.4	170	5.3	
Russian	6	0.6	22	0.7	
Other	23	2.2	98	3.1	.47
Mother's education					
Upper secondary	479	44.9	1437	44.9	
Post-secondary vocational	223	20.9	659	20.6	
Bachelor's degree	114	10.7	346	10.8	
Master's or doctoral degree	118	11.1	380	11.9	.99
Missing	133	12.5	378	11.8	
Father's education					
Upper secondary	508	47.6	1499	46.8	
Post-secondary vocational	140	13.1	408	12.8	
Bachelor's degree	85	8.0	283	8.8	
Master's or doctoral degree	130	12.2	355	11.1	.60
Missing	204	19.1	655	20.5	
Mother's socioeconomic status					
Self-employed	70	6.6	299	9.3	
Upper-level employee	177	16.6	548	17.1	
Lower-level employee	380	35.6	1252	39.1	
Manual worker	237	22.2	552	17.3	
Other	202	18.9	541	16.9	<.001
Missing	1	0.1	8	0.3	
Father's socioeconomic status					
Self-employed	137	12.8	470	14.7	
Upper-level employee	203	19.0	612	19.1	
Lower-level employee	216	20.2	546	17.1	
Manual worker	329	30.8	1023	32.0	
Other	159	14.9	484	15.1	.18
Missing	23	2.2	65	2.0	
Large for gestational age					
No	821	76.9	2475	77.3	
Yes	33	3.1	97	3.0	.89
Missing	213	20.0	628	19.6	

(Continues)

TABLE 2 (Continued)

	Cases		Controls		p value
	n	%	n	%	
Cancer predisposition syndromes					
No	973	91.2	3195	99.8	
Yes	94	8.8	5	0.2	<.001
Mother's smoking during pregnancy					
No	707	66.3	2184	68.3	
Yes	129	12.1	343	10.7	.16
Missing	231	21.7	673	21.0	

OR (EOR) per 100 mGy of cumulative brain dose was 5.50 (95% CI 0.31, 10.95) for all brain tumors. For gliomas, the OR was 1.31 (95% CI 0.32, 5.36) for any head/neck CT versus none, and the EOR was 1.06 (95% CI -6.55, 9.30) per 100 mGy of cumulative brain dose. In malignant brain tumors, the OR was 2.64 (95% CI 0.65, 10.76) for any head/neck CT versus none, and the EOR was 3.48 (95% CI -2.33, 9.64) per 100 mGy of cumulative brain dose. When brain doses were divided into tertiles (3.5–8.7, 10.6–20.1, and 20.2–126.2 mGy), with zero dose as the reference, a significant increase in risk (OR = 6.00, 95% CI 1.10, 32.76) was observed for the highest tertile (Figure 3).

In sensitivity analyses that included participants with cancer predisposition syndromes or previous malignancies, the OR for all brain tumors for any head/neck CT versus none was 5.15 (95% CI 2.27, 11.68), and the EOR per 100 mGy of cumulative brain dose was 7.80 (95% CI 2.45, 13.42) (Table 3). Adjusting for maternal socioeconomic status had a marginal impact on the OR for any head/neck CT versus none (adjusted OR = 2.69, 95% CI 1.06, 6.85) and the EOR per 100 mGy of cumulative brain dose (adjusted EOR = 5.27, 95% CI 0.08, 10.72). Similarly, adjusting for paternal socioeconomic status resulted in only minor changes in the estimates.

4 | DISCUSSION

Our nationwide population-based case-control study showed a significantly increased risk of childhood brain tumors following radiation exposure from head or neck CT imaging. To improve the robustness of results, we employed a 5-year lag period and excluded children with cancer predisposition syndromes or previous malignancies. Brain tumor cases from the Finnish Cancer Registry were linked to a CT dataset, which covered up to 87% of the annual scans performed on pediatric patients in Finland between 1975 and 2011. Radiation dose estimates for each head/neck CT scan were calculated using the NCI dosimetry system for Computed Tomography.

The estimated risk per unit dose, lagged by 5 years, was higher than that reported in previous studies. We found an excess OR of 5.5 per 100 mGy of cumulative brain dose, compared to an excess relative risk (ERR) of 1.3 in the EPI-CT study (only malignant brain

tumors), 2.1 in the Australian study, and 2.3 in the British study.^{13,24,25} The higher estimate could be the result of imprecision due to the relatively small sample size or potential underestimation of radiation doses from CT imaging. The mean absorbed brain dose per head/neck CT was 17 mGy in our study, which is considerably lower than that reported in most other studies. It's conceivable that scan parameter values derived from expert opinion reflect current practices but could potentially underestimate doses from head/neck CT scans performed during the earlier decades. Additionally, our CT dataset was prone to missing scans from earlier years, when radiation doses were likely higher. However, the annual numbers of pediatric CT scans during those early years were relatively low, as hospitals were still in the initial stages of adopting this imaging technology.

The effect of confounding by indication on risk estimates has been a debated issue in radiation epidemiology. Confounding by indication occurs when the CT scan is performed for a condition that itself increases the risk of brain tumors. To address this, we conducted a comprehensive search across three national registers for nine predisposing cancer syndromes (CPS) that increase brain tumor susceptibility.²¹ The proportion of cases with CPS in our study (9%) mirrors that of the updated British study.²⁶ However, our findings diverged as we observed that participants with CPS underwent more CT scans than those without, suggesting an association between CT imaging and CPS. This could be attributed to regular cancer surveillance in these individuals, including CT scans, particularly prior to the widespread use of whole-body MRI for screening children with CPS. Adjusting for CPS and TSC did not substantially change risk estimates in the updated British and Dutch studies, respectively, but reduced the ERR by nearly half in the much smaller French study.^{26–28} In our study, excluding participants with CPS resulted in a 29% decrease in the excess OR per 100 mGy, indicating that including children with CPS may overestimate the risk attributed to radiation exposure.

One limitation of our study is the lack of detailed clinical information regarding the indications for CT scans, especially for low-grade, slow-growing tumors. A potential concern is the inclusion of head/neck CT scans conducted due to prodromal symptoms of brain tumors, which could lead to reverse causation if there were delays in

TABLE 3 Number of cases and controls in participants older than 5 years at index date, along with odds ratios (ORs) for all brain tumors, gliomas, and malignant brain tumors by cumulative number of head/neck CT scans (any vs. none) and the excess ORs (EORs) per 100 mGy of cumulative brain dose.

	All participants	Participants excluding CPS or previous malignancies
All brain tumors		
Number of cases (exposed) ^a	678 (16)	604 (9)
Number of controls (exposed) ^a	2033 (10)	1809 (10)
Mean brain dose mGy (SD) ^b	34.0 (58.3)	22.0 (27.6)
OR for any head/neck CT vs. none (95% CI)	5.15 (2.27, 11.68)	2.84 (1.12, 7.19)
EOR per 100 mGy (95% CI)	7.80 (2.45, 13.42)	5.50 (0.31, 10.95)
Glioma		
Number of cases (exposed) ^a	401 (7)	353 (3)
Number of controls (exposed) ^a	1202 (7)	1057 (7)
Mean brain dose mGy (SD) ^b	36.5 (73.0)	15.8 (8.0)
OR for any head/neck CT vs. none (95% CI)	3.25 (1.08, 9.75)	1.31 (0.32, 5.36)
EOR per 100 mGy (95% CI)	4.57 (−1.16, 10.63)	1.06 (−6.55, 9.30)
Malignant brain tumors^c		
Number of cases (exposed) ^a	314 (5)	302 (4)
Number of controls (exposed) ^a	942 (5)	905 (5)
Mean brain dose mGy (SD) ^b	53.2 (89.6)	27.3 (38.2)
OR for any head/neck CT vs. none (95% CI)	3.36 (0.89, 12.73)	2.64 (0.65, 10.76)
EOR per 100 mGy (95% CI)	3.49 (−2.30, 9.62)	3.48 (−2.33, 9.64)

Note: Estimates were calculated using conditional logistic regression with a 5-year lag period and reported for all participants and separately for those excluding cancer predisposition syndromes (CPS) or previous malignancies.

^aParticipants older than 5 years at index date who were included in the analysis with a minimum 5-year lag period.

^bCumulative absorbed brain dose among participants exposed to radiation from CT.

^cICD-O-3 behavior code 3.

diagnosis. However, this is unlikely, given the exclusion of all CT scans performed within 5 years prior to brain tumor diagnosis. This lag period is likely long enough to rule out CT scans performed for the early symptoms of an occult low-grade brain tumor.²⁹ Previous studies have assessed the diagnostic timeline for pediatric brain tumors, with median intervals from symptom onset to diagnosis of low-grade tumors ranging from 1 to 4 months, although a few patients experienced delays of more than 2 years.^{30–32}

Another limitation is the small sample size, which results from the relatively small population size of Finland and the extreme rarity of childhood brain tumors. This restricted the number of exposed participants included in the study and precluded subanalyses of individual tumor types, such as pilocytic astrocytomas. Despite these constraints, we believe the study provides valuable insights, given the challenges inherent in researching rare diseases. Additionally, the accuracy of our brain dose reconstruction may be affected by the lack of hospital-specific scanning protocols and specific radiation output parameters, such as CT dose index-volume (CTDI-vol) and dose-length product (DLP), in the dataset. It should be noted that older CT scanners did not record these parameters, making them unavailable for earlier scans, even if we were to review individual patient records. We also lacked data on other medical radiation

exposures, such as conventional radiography. However, the contribution of radiation from x-rays to brain dose is likely to be tiny compared to CT. A single head CT delivers an absorbed brain dose approximately 95 times higher than a single conventional skull x-ray.^{13,33} Finally, the potential underestimation of dose levels for children who underwent CT scans in earlier decades may have resulted in an overestimation of the calculated risk per dose in our study.

The comprehensive coverage of our CT dataset, as opposed to relying on recall or hand-searching medical records, allowed for thorough exposure ascertainment and minimized misclassification bias. We matched cases and controls on sex and birth cohort and adjusted for parental socioeconomic status to address potential confounding. Brain tumor cases were sourced from the Finnish Cancer Registry, which has a very high level of completeness, registering both benign and malignant brain tumors since its establishment in 1953.¹⁷ The completeness for childhood tumors was estimated at 94% for 2009–2012.³⁴ The national registers covered the entire study period, except for the Medical Birth Register, which began data collection in 1987. This later start date may have resulted in some loss of information on maternal smoking during pregnancy and birth weight from earlier years.

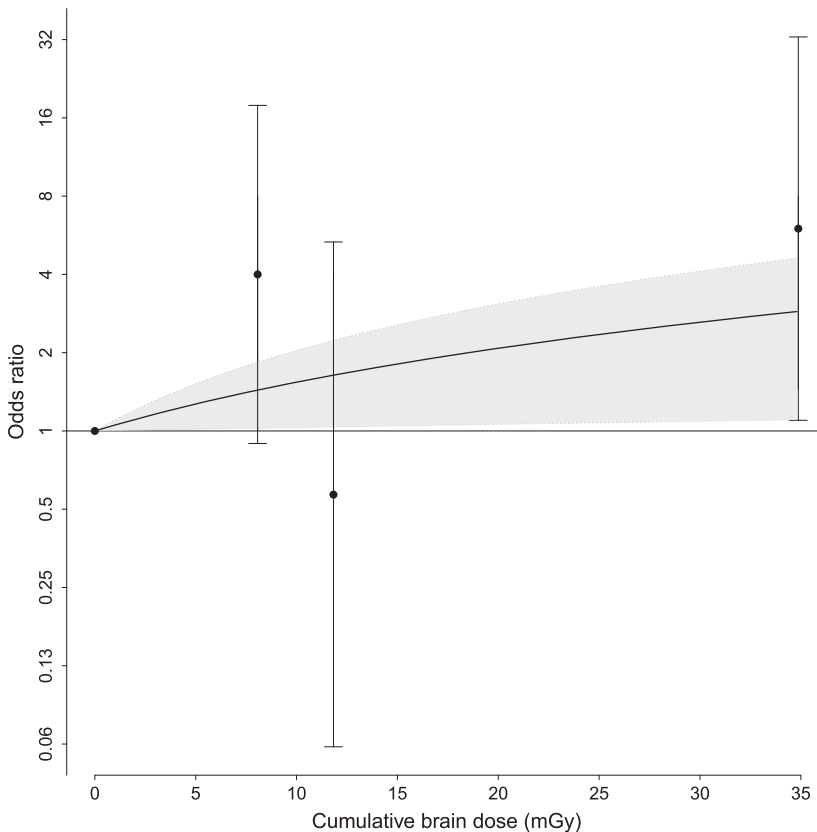


FIGURE 3 Dose–response curve of brain tumor risk by cumulative brain dose from exposure to CT radiation. The vertical axis is on a base-2 logarithmic scale. The data points and vertical lines represent the odds ratios for the median dose of each tertile and their 95% confidence intervals, respectively. The solid line and the shaded area represent the linear dose–response curve (EOR of 0.054 per mGy) and its 95% confidence band (0.003, 0.104), respectively. The reference value (1) is represented with a dashed line. EOR, excess odds ratio.

Although the frequency of pediatric CT use has been leveling off or decreasing in Finland, the population risk from exposure to CT radiation remains non-negligible.⁴ Health professionals must adhere to the principles of optimization and justification to maximize the benefit-to-risk ratio. New fast MRI modalities show promise in pediatric medical imaging, offering an alternative to CT in several settings.^{35,36} Moreover, dosimetric parameters such as CT dose index-volume and dose-length product are readily available for new CT scanners, enabling more precise CT dosimetry in future studies.

5 | CONCLUSION

In this nationwide population-based study, we reported a positive association between a history of head/neck CT imaging and the risk of brain tumors in childhood. Our findings contribute to the body of evidence on the risks of low dose ionizing radiation in pediatric populations. Further research with more precise dosimetry, including dose distribution within the brain, is needed.

AUTHOR CONTRIBUTIONS

Jad Abuhamed: Conceptualization; methodology; writing – original draft; data curation; formal analysis; visualization. **Atte Nikkilä:** Formal

analysis; visualization; writing – review and editing. **Jani Raitanen:** Formal analysis; software; data curation; writing – review and editing. **Olli Lohi:** Conceptualization; methodology; writing – review and editing. **Anssi Auvinen:** Conceptualization; methodology; validation; writing – review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest regarding the publication of this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are sourced from the Finnish registries and are available in a secure remote environment (Kapseli) controlled by the Finnish Social and Health Data Permit Authority (Findata). Access to these data is subject to the approval of Findata, as per the Finnish Act on the Secondary Use of Social and Health Data (Act 552/2019). Further information is available from the corresponding author upon request.

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SUPPORTING INFORMATION

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

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