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Special Focus on Hypertension, Myocardial Infarction and Gastrointestinal Stromal Tumors

Niina Loponen

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ABSTRACT

Neurofibromatosis type 1 (NF1) is a dominantly inherited multiorgan genetic condition caused by pathogenic variants of the *NF1* gene. NF1 is characterized by café au lait macules, axillary and inguinal freckling, and cutaneous neurofibromas. The syndrome also predisposes affected persons to both benign and malignant tumors. Cognitive and behavioral problems are also common in NF1. The birth incidence of NF1 is approximately 1/2,000, and the mean prevalence is 1/4,000 owing to compromised survival.

In this thesis, a Finnish nationwide cohort of NF1 individuals was used in three population-based analyses. The data were linked with multiple national administrative health registers to study the distribution of gastrointestinal tumors, gastrointestinal stromal tumors (GISTs) as a cause of death, essential and secondary hypertension, and the risk and prognosis of myocardial infarction in individuals with NF1.

The site-specific register analysis of 1,410 NF1 patients revealed a markedly high hazard ratio (HR) of 15.6 for tumors of the small intestine, and the analysis of death certificates demonstrated substantial morbidity related to GISTs in NF1. Cardiovascular outcomes showed that NF1 patients had significantly elevated hazard for both secondary (HR 3.76) and essential hypertension (HR 1.73), with essential hypertension being predominant and occurring an average of six years earlier compared to matched controls. NF1 patients also had an increased risk of myocardial infarction and their survival after myocardial infarction was worse than in controls.

The results highlight the importance of early and accurate diagnosis of NF1-related comorbidities, surveillance, multidisciplinary care, and risk reduction to improve patient outcomes. The study has clinical relevance and it may help in formulating the national guidelines of treatment and follow-up of NF1 patients.

KEYWORDS: gastrointestinal tumor, gastrointestinal stromal tumor, hypertension, myocardial infarction, neurofibromatosis type 1

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TIIVISTELMÄ

Tyypin 1 neurofibromatoosi (NF1) on vallitsevasti periytyvä monielinsairaus, joka aiheutuu *NF1*-geenin muutoksista. NF1:n tavallisimpia löydöksiä ovat ihon neurofibroomat, maitokahviläiskät ja kainaloiden ja nivusten kesakot. Lisäksi oireyhtymä altistaa sekä hyvän- että pahanlaatuisille kasvaimille. Myös kognitiiviset ja käyttäytymiseen liittyvät ongelmat ovat yleisiä. NF1 todetaan noin yhdellä 2000 syntyvästä lapsesta, mutta keskimääräinen esiintyvyys on noin 1/4 000, mikä selittyy lisääntyneellä kuolleisuudella.

Väitöskirjassa käytettiin suomalaista valtakunnallista NF1-potilaiden kohorttia kolmessa väestöpohjaisessa analyysissä. NF1 kohortti yhdistettiin useisiin kansallisiin terveysrekistereihin. Tutkimuksessa selvitettiin ruoansulatuskanavan kasvainten paikkajakaumaa, ruoansulatuskanavan stroomakasvainta (GIST) kuolinsyynä, essentiaalisen ja sekundaarisen verenpainetaudin esiintyvyyttä sekä sydäninfarktin riskiä ja ennustetta NF1-potilailla.

Rekisteripohjainen 1410 NF1-potilaan tietojen analyysi osoitti merkittävästi kohonneen uhkasuhteen (HR 15,6) ohutsuolen kasvaimille. Kuolinsyyanalyysi toi esiin GIST:iin liittyvän NF1-potilaiden kuolleisuuden. Sydän- ja verisuonisairauksien osalta havaittiin, että NF1-potilailla vaikutti olevan suurentunut riski sekä sekundaariseen (HR 3,76) että essentiaaliseen verenpainetautiin (HR 1,73). Essentiaalinen verenpainetauti oli näistä yleisempi ja ilmeni keskimäärin kuusi vuotta aikaisemmin kuin verrokkiryhmässä. NF1-potilailla todettiin myös kohonnut sydäninfarktin riski sekä huonompi eloonjääminen infarktin jälkeen.

Tulokset korostavat NF1:ään liittyvien liitännäissairauksien varhaisen ja tarkan diagnostiikan, seurannan, moniammatillisen hoidon ja riskien vähentämisen merkitystä potilaiden ennusteen parantamisessa. Tutkimuksella on kliinistä merkitystä, ja se voi osaltaan tukea NF1-potilaiden hoitoa ja seurantaa koskevien kansallisten suositusten laatimista.

AVAINSANAT: neurofibromatoosi tyyppi 1, ruoansulatuskanavan kasvain, ruoansulatuskanavan stroomakasvain, sydäninfarkti, verenpainetauti

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Abbreviations

ATC	Anatomical Therapeutic Chemical classification of drugs
CALM	Café au lait macule
CI	Confidence interval
CNS	Central nervous system
CT	Computed tomography
CVD	Cardiovascular disease
DOG-1	Discovered on GIST 1, also called Anoctamin-1 (ANO-1)
FDA	Food and Drug Administration
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
HE	Hematoxylin and eosin
HER2	Human epidermal growth factor receptor 2
HILMO	The Finnish Care Register for Health Care
HR	Hazard ratio
ICC	Interstitial cells of Cajal
ICD-9	International Classification of Diseases, 9th edition
ICD-10	International Classification of Diseases, 10th edition
ISCED	International Standard Classification of Education
JMML	Juvenile myelomonocytic leukemia
LAD	Left anterior descending artery
MEK	mitogen-activated protein kinase kinase
MI	Myocardial infarction
MPNST	Malignant peripheral nerve sheath tumor
MRI	Magnetic resonance imaging
NCD	Non-communicable disease
NCR-RisC	NCD Risk Factor Collaboration
NF1	Neurofibromatosis type 1
NF2	Neurofibromatosis type 2
NIH	National Institutes of Health
OMIM	Online Mendelian Inheritance in Man
ORPHA	Orphanet nomenclature of rare diseases

OPG	Optic pathway gliomas
OR	Odds ratio
PMR	Proportionate mortality ratio
PDGFRA	Platelet derived growth factor receptor alpha
Ras	Rat sarcoma, a family of small GTPases
RCA	Right coronary artery
RR	Rate ratio
SDH	Succinate dehydrogenase
SD	Standard deviation
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
TIA	Transient ischemic attack

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Heli Ylä-Outinen, Niina Loponen, Roope A. Kallionpää, Sirkku Peltonen, Juha Peltonen. Intestinal tumors in neurofibromatosis 1 with special reference to fatal gastrointestinal stromal tumors (GIST). *Molecular Genetics & Genomic Medicine*, 2019; 7(9): e927.

II Niina Loponen, Heli Ylä-Outinen, Roope A. Kallionpää, Mikko Valtanen, Kari Auranen, Hannu Järveläinen, Sirkku Peltonen, Juha Peltonen. Hypertension in NF1: A closer look at the primacy of essential hypertension versus secondary causes. *Molecular Genetics & Genomic Medicine*, 2024; 12(1): e2346.

III Niina Loponen, Roope A. Kallionpää, Heli Ylä-Outinen, Mikko Valtanen, Kari Auranen, Hannu Järveläinen, Sirkku Peltonen, Juha Peltonen. Risk and prognosis of myocardial infarction in patients with neurofibromatosis type 1: Evidence of compromised survival. *Genetics in Medicine*, 2025; 27(11): 101571.

1 Introduction

Neurofibromatosis type 1 (NF1; OMIM #162200; ORPHA:636) is an autosomal dominant genetic disorder caused by pathogenic variants in the *NF1* gene, which encodes neurofibromin and is located on chromosome 17q11.2 (Wallace et al., 1990; Xu et al., 1990; Gutmann et al., 2017). Individuals with NF1 are predisposed to developing both benign and malignant tumors affecting the skin, nervous system, and other organs, including the gastrointestinal tract (Ferner and Gutmann, 2013).

Diagnosis of NF1 is based on clinical and molecular criteria (National Institutes of Health Consensus Development Conference, 1988; Legius et al., 2021). Café au lait macules and cutaneous neurofibromas are the hallmark features of NF1. Café au lait macules are the first detectable clinical finding of NF1 syndrome, and these pigmented macules may be visible at birth while cutaneous neurofibromas start to grow during puberty (DeBella et al., 2000). The manifestations of NF1 also include optic pathway tumors and plexiform neurofibromas, and skeletal abnormalities and neurocognitive impairments are frequently observed in children with NF1. Notably, NF1 exhibits complete penetrance but its clinical manifestations are highly variable, including differences in the number and type of tumors, ranging from few to numerous lesions, their cosmetic impact, and whether the tumors are benign or malignant. As a result, affected individuals may experience anything from mild dermatological findings to severe complications such as malignant peripheral nerve sheath tumors, reflecting the broad spectrum of phenotypic expression (Jouhilahti et al., 2011a; Ferner and Gutmann, 2013).

NF1 is classified as a rare disease, with an estimated average prevalence ranging from 1/4,500 to 1/2,000 individuals (Huson et al., 1989; Evans et al., 2010; Kallionpää et al., 2018). Importantly, its prevalence is age-dependent, decreasing in older age groups and leading to a shortened lifespan among affected individuals (Kallionpää et al., 2018). In Finland, the birth incidence of NF1 has been reported to be approximately 1/2,000 (Uusitalo et al., 2015).

The most significant contributor to excess mortality in NF1 is malignant peripheral nerve sheath tumor (MPNST) (Rasmussen et al., 2001; Uusitalo et al., 2015). Other causes include vascular complications, such as cardiovascular and hypertension-related events, and cerebrovascular diseases, as well as increased risks

of breast cancer and brain tumors (Zöller et al., 1995; Evans et al., 2011; Uusitalo et al., 2015).

This thesis comprises three original nationwide, population-based epidemiological studies, utilizing data linked from multiple national health registers. The studies investigate selected comorbidities of NF1, including the sites of gastrointestinal tract tumors, gastrointestinal stromal tumors (GISTs) as a cause of death, essential and secondary hypertension, and the risk and prognosis of myocardial infarction (MI) in individuals with NF1.

2 Review of the Literature

2.1 Neurofibromatosis type 1 (NF1)

2.1.1 History of NF1

The earliest descriptions of NF1 can be traced to Ancient Egypt (1500 BC) and the Ebers Papyrus, one of the oldest surviving medical documents. Possible neurofibromas are visible on a statuette from Smyrna dating to the Hellenistic period (323–331 BC) (Ruggieri et al., 2018). Nodular skin lesions are also portrayed on coins of the Parthian Empire (247 BC to AD 228) in ancient Persia (Todman, 2008).

Rudolf Ludwig Virchow (1821–1902), regarded as the father of modern pathology, first concentrated on the pathology of peripheral nerve tumors (Ruggieri et al., 2018). Friedrich Daniel von Recklinghausen (1833–1910) was a German pathologist and a student of Virchow. In 1882, he provided a comprehensive description of two cadavers with dermal tumors and pigmented spots on their skin. Von Recklinghausen identified the neural connection of these dermal fibromas and named them as neurofibromas. He also recognized that the pigmentation of the skin was not a separate feature, but rather one symptom of a syndrome, thereafter called as von Recklinghausen's neurofibromatosis. Peripheral neurofibromatosis is an additional term for this condition to make a distinction between two different syndromes, the other previously called the central neurofibromatosis (=bilateral acoustic neurofibromatosis) as reviewed by Reynolds et al. (2003), Brosius (2010) and Ruggieri et al. (2018).

Frank Crowe (1919–1987) emphasized the diagnostic importance of café au lait macules in neurofibromatosis and recognized that neurofibromatosis followed an autosomal dominant trait with full penetrance, thus affecting approximately 50% of offspring as reviewed by Carey et al. (1986). In 1987, the National Institutes of Health (NIH) consensus conference named the peripheral and central neurofibromatosis as NF1 and NF2, respectively (National Institutes of Health Consensus Development Conference, 1988).

In 1990, two independent research groups (Wallace et al., 1990; Xu et al., 1990) identified the sequence of a large gene on the long arm of chromosome 17 harboring

pathogenic variants in patients with NF1. This gene was subsequently named the *NF1* gene.

2.1.2 Diagnostic features of NF1

Diagnosis of NF1 is based on clinical and molecular criteria (Table 1). The diagnostic criteria were established by National Institutes of Health (NIH) Consensus Development Conference in 1987 (National Institutes of Health Consensus Development Conference, 1988) and were updated in 2021 (Legius et al., 2021).

The 1987 NIH clinical criteria are highly sensitive and specific for adults with NF1 (Friedman, 2002; Gutmann et al., 2017). Diagnosing especially young children can be challenging, because they do not yet meet the NIH Diagnostic Criteria with two observed clinical findings required for NF1 diagnosis. It has been estimated that 95% of children with NF1 fulfill the diagnostic criteria by the age of six and that all patients can be recognized by the age of twenty (DeBella et al., 2000). Advances in gene testing led to the inclusion, in 2021, of detection of a heterozygous pathogenic NF1 variant as a diagnostic criterion (Legius et al., 2021). Genetic testing is particularly useful in confirming the diagnosis of young children and in patients with atypical presentations.

Café au lait macules (CALMs) and cutaneous neurofibromas are the hallmarks of NF1 (Figure 1). Typical CALMs are flat, oval or round patches of skin, about 1–3 cm in size with regular and well-defined borders. Their coloration varies from light to dark brown (Ozarslan et al., 2021; Albaghdadi et al., 2022) depending on the patient´s skin tone. CALMs are usually the first detectable clinical manifestation of NF1. Some children may have CALMs visible at birth, but they are present in 95% of the NF1 patients by the age of one (DeBella et al., 2000) and in >99% of the patients by adulthood (Ferner and Gutmann, 2013). The macules are distributed all over the body, mostly (>50%) on the thorax, but not on the palms, soles, or head (Nasi et al., 2023).

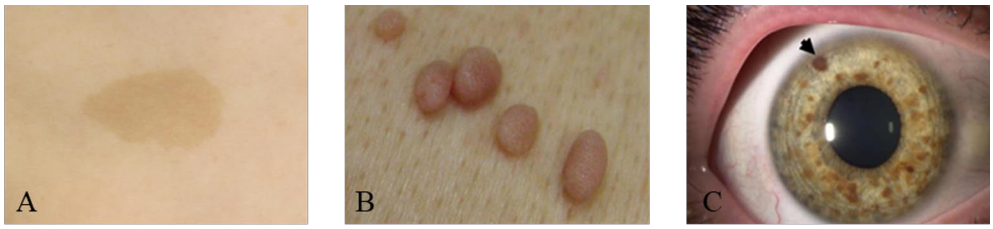

Figure 1. Typical clinical findings of NF1. **A**) Café au lait macules; **B**) Cutaneous neurofibromas; and **C**) Lisch nodules (arrowhead). Photo courtesy of Sirkku Peltonen (**A**, **B**) and Vesa Aaltonen (**C**).

Table 1. Diagnostic criteria for neurofibromatosis type 1 (NF1). The National Institutes of Health (NIH) consensus development conference statement 1987 and revised criteria[a] by Legius et al. in 2021.

A. The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:

1. Six or more café au lait macules of over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals.
2. Freckling in the axillary or inguinal region[b].
3. Two or more neurofibromas of any type or one plexiform neurofibroma.
4. Optic pathway glioma.
5. Two or more iris Lisch nodules or **two or more choroidal abnormalities.**
6. A distinctive osseous lesion such as sphenoid dysplasia[c], **anterolateral bowing of the tibia,** or pseudarthrosis of a long bone.
7. **A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells.**

B. **A child of a parent** who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present.

[a] Revisions made to original criteria are shown in bold.

[b] If only café au lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least 1 of the 2 pigmentary findings (café au lait macules or freckling) should be bilateral to exclude mosaicism.

[c] Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.

Freckling in intertriginous areas is diagnostic for NF1. Freckles are small (1–2 mm), pigmented spots which are clustered in skin folds typically in axillary and inguinal regions. These benign skin pigmentation changes usually appear between 3 and 5 years of age, though axillary freckling may be visible at birth (Korf, 2002).

Lisch nodules are small, pigmented lesions of the iris with nodular appearance. They are benign and do not impact vision. Multiple Lisch nodules are found in more than 90% of adult NF1 patients and typically these yellow or brown lesions are detectable by the age of 6 (Lubs et al., 1991; Friedman and Birch, 1997; Midena and Cosmo, 2025).

Cutaneous neurofibromas are the most frequently occurring benign tumor type in NF1, with an estimated lifetime cumulative incidence of 99% (Friedman, 2022). Neurofibromas are peripheral nerve sheath tumors. Histologically, they are composed of a subpopulation of Schwann cell precursors, mast cells, fibroblasts, perineurial cells, T- and B-lymphocytes and macrophages (Peltonen et al., 1988; Jouhilahti et al., 2011b; Kallionpää et al., 2024). Cutaneous neurofibromas typically become clinically apparent during puberty and tend to grow in size and number with

age (DeBella et al., 2000). Their growth accelerates and their number increases during pregnancy (Duong et al., 2011a; Well et al., 2020). Neurofibromas are mostly located on the trunk and limbs and vary in number, colour and size. The number of cutaneous neurofibromas ranges from a few lesions to thousands (Duong et al., 2011a) and they typically grow up to size of 2–3 cm (Jouhilahti et al., 2011b). It is noteworthy that cutaneous neurofibromas never turn malignant. Pruritus as a clinical symptom is associated with neurofibromas and has been reported in 20% of NF1 patients (Brenaut et al., 2016). In addition, high tumor burden causes significant cosmetic discomfort and affects quality of life and interferes with daily activities of NF1 individual (Lin et al., 2024; Cieza Rivera et al., 2024). Subcutaneous neurofibromas are firm and distinct nodules located in deep dermis or subcutaneous area. The typical age of onset is during adolescence, and these lesions occur in about 20% of patients (Duong et al., 2011a).

Plexiform neurofibroma affect about 20–50% of individuals with NF1 and this most complex subtype of neurofibroma is typically congenital (Mautner et al., 2008; Nguyen et al., 2012). Plexiform neurofibromas arise within nerve plexuses and grow along the course of the nerve branches, involving multiple fascicles (Fisher et al., 2022). Tumors can be superficial or deep. In the case of asymptomatic internal plexiform neurofibroma, computed tomography (CT) or magnetic resonance imaging (MRI) examination is needed to detect the tumor (Mautner et al., 2008). Some plexiform tumors may grow into large masses, invade surrounding structures, and compress organs and nerves. Surgical excision of the tumor is the first-line treatment but it can be very challenging due to adjacent tissues and anatomical structures (Fisher et al., 2022). In 2020, the FDA approved the MEK inhibitor (mitogen-activated protein kinase kinase) selumetinib for the treatment of pediatric patients with inoperable plexiform neurofibromas (Casey et al., 2021). Mirdametinib, a selective MEK1 and MEK2 inhibitor, was approved by FDA for the treatment of adults with NF1-associated plexiform neurofibromas in 2025 (Oztosun et al., 2025). Plexiform neurofibromas carry a risk of malignant transformation. Patients with NF1 have a lifetime risk of 8-16% to develop MPNST (Evans et al., 2002; Uusitalo et al., 2016).

Optic pathway gliomas (OPGs) are the most common central nervous system tumors in NF1. OPGs are found in 15–20% of NF1 patients and are typically diagnosed before age of 7 (Listernick et al., 1994). OPGs are classified as low-grade pilocytic astrocytomas (Louis et al., 2021) and may affect any part of the optic pathway (Listernick et al., 1995). Most tumors (>75%) are located in the anterior part of the visual pathway in optic nerves or optic chiasm, but they can also arise from optic tracts and optic radiations in the posterior visual pathway (Prada et al., 2015; Sellmer et al., 2018). Clinical symptoms depend on tumor location, and about 30–50% of NF1 patients with OPG present with tumor-related symptoms such as decreased visual acuity, proptosis, diplopia, and precocious puberty (Campen and

Gutmann, 2018; Katz et al., 2024). MRI imaging and neuro-ophthalmological examinations are recommended for children with NF1-related OPG annually to monitor tumor growth and possible progression (Carton et al., 2023; Evans et al., 2022). In addition, if the tumor is chiasmatic or hypothalamic, a detailed endocrinological evaluation should be performed (Shofty et al., 2020). Chemotherapy with vincristine and carboplatin is the first-line treatment for children with clinically progressive tumors, while radiotherapy is not recommended, due to the risk of secondary malignancies (Sharif et al., 2006; Kebudi et al., 2024).

NF1 patients can develop several skeletal manifestations, the most severe being pseudarthrosis of tibia and dystrophic scoliosis, both of which represent challenging orthopedic problems. Congenital dysplasia of long bones is relatively specific to children with NF1 and this osseus defect is most typically developed unilaterally in tibia (Elefteriou et al., 2009). Tibial dysplasia presents as anterolateral bowing of the bone, and cortical thickening or thinning of the tibia as well as medullary canal narrowing is observed radiographically in affected children. This condition can lead to a pathologic fracture of bone and the formation of pseudarthrosis (false joint).

Scoliosis is a common orthopedic problem and 10% of NF1 children are diagnosed with scoliosis (Toro et al., 2021). Scoliosis appears in lower cervical or upper thoracic region in NF1 individuals and it can be classified in two types: non-dystrophic and dystrophic types. Non-dystrophic scoliosis is most typical type in NF1 and it has similar clinical appearance and rate of progression as idiopathic scoliosis but it has an earlier onset of skeletal changes. Scoliosis is often associated with vertebral defects and sometimes scoliosis may progress to the dystrophic type (Kaspiris et al., 2022). Dystrophic scoliosis can develop rapidly and lead to severe deformity of the spine and affect pulmonary function. Therefore, regular follow-up of NF1 children, usually at 6-month intervals, is recommended (Feldman et al., 2010).

Sphenoid wing dysplasia is a cranial defect of sphenoid bone and found in up to 11% of NF1 individuals (Friedman and Birch, 1997). The defect is usually present at birth, typically unilateral, and involves thinning or absence of the greater sphenoid wing. Sometimes sphenoid wing dysplasia is associated with orbital plexiform neurofibroma and the lesion can thus be a secondary response of bone. Alterations in facial appearance of children must be observed. Affected eye may appear asymmetric or proptotic, ocular motility may be impaired, and pulsating exophthalmos is also rarely possible (Arrington et al., 2013; Chauvel-Picard et al., 2020).

2.1.3 Findings associated with NF1

Bone mineralization is frequently impaired among NF1 individuals, and osteopenia or osteoporosis are more common than in general population. It has been reported that bone mineral density is decreased in up to 50% of patients with NF1 (Kuorilehto

et al., 2005; Elefteriou et al., 2009). In addition, NF1 patients have up to 5-fold risk of bone fractures (Heervä et al., 2012).

Neurocognitive impairments such as learning disabilities and cognitive or behavioral disorders are common in NF1. Up to 75% of children with NF1 experience learning difficulties at school (Krab et al., 2008). Impairments in gross and fine motor functions (Pardej et al., 2022), speech and language deficits (Alivuotila et al., 2010; Vogel et al., 2017) are also frequent in children with NF1. Also, attention deficit hyperactivity disorder, autism spectrum disorder, and other psychiatric conditions such as depression and anxiety are common findings in children and adolescents with NF1 (Vogel et al., 2017).

Glomus tumors are rare, benign tumors which are associated with NF1 (Brems et al., 2009; Harrison et al., 2013). These tumors originate from the glomus body which is a small arteriovenous anastomosis in dermis controlling peripheral blood circulation and thus regulating body temperature (Stewart et al., 2010). Glomus tumors are small and painful tumors and they are most typically located in the nail beds and digital pulps of fingers and toes where glomus bodies are abundant. Tumors associated with NF1 are more likely to be multiple and tend to appear at a younger age, while sporadic tumors are typically solitary. Furthermore, NF1-related glomus tumors do not express neurofibromin (Kumar et al., 2014).

2.1.4 Heredity and molecular background of NF1

Neurofibromatosis type 1 is an autosomal dominant genetic condition caused by pathogenic variants in the *NF1* gene. These pathogenic variants always manifest clinically as NF1, i.e., the penetrance of the variants is 100% (Crowe et al., 1956; Huson et al., 1989). Mutation frequency (1/10 000 gametes) of the *NF1* gene is among the highest known in humans. Consequently, about half of all individuals with NF1 harbor a new pathogenic variant in the *NF1* gene (Huson et al., 1989). About 80% of these new sporadic germline mutations are paternally derived (Jadayel et al., 1990). Because of the dominant inheritance and full penetrance, there are no skipped generations, and a child of healthy parents cannot inherit NF1 from grandparents. A person is either born with NF1 or does not have NF1.

The *NF1* gene (OMIM *613113) was cloned and published simultaneously in 1990 by two research groups (Wallace et al., 1990; Xu et al., 1990). Located on chromosome 17q11.2, the gene spans approximately 280 kb and comprises about 60 exons (Wallace et al., 1990).

The *NF1* gene encodes the tumor suppressor protein neurofibromin (DeClue et al., 1991; Gutmann et al., 1991). Neurofibromin is ubiquitously expressed in different cell types and tissues in adults and during development. Vascular expression of neurofibromin is localized to the endothelial cells of the renal and

cerebral arteries and aorta. In addition, smooth muscle cells of the aorta express neurofibromin (Norton et al., 1995; Kuorilehto et al., 2006).

Neurofibromin is involved in tumor suppression, and it functions as a negative regulator of the Ras signal transduction pathway. Ras pathway is a molecular switch controlling key cell functions, such as cell growth, proliferation, and differentiation (Basu et al., 1992; Mo et al., 2022). Neurofibromin protein normally accelerates the conversion of active Ras-GTP to inactive Ras-GDP. However, pathogenic *NF1* variants lead to impaired neurofibromin function and to the upregulation of Ras activity and increased cell growth (Xu et al., 1990; Gutmann et al., 2017). Somatic alterations in *NF1* and in genes encoding Ras proteins are common in many cancers (The Cancer Genome Atlas Research Network, 2014; Krauthammer et al., 2015). The expression of neurofibromin can be regulated at transcriptional, translational, and protein levels (Jouhilahti et al., 2011a).

2.1.5 Incidence and prevalence of NF1

The incidence of a disease is the number of new occurrences of the disease within a defined population and timeframe. For a fully penetrant genetic disease such as NF1, incidence can be defined as the proportion of persons born with the condition during a defined time period out of all persons born during the same time period. Thus, birth incidence of NF1 is a useful term (Uusitalo et al., 2015).

The prevalence of a disease is defined as the proportion of persons having the condition at a specified prevalence date or period. The prevalence of NF1 can be calculated for the whole population or for specific subgroups. Since the survival of NF1 persons is inferior compared to the general population, the prevalence of NF1 decreases by increasing age (Kallionpää et al., 2018).

Multiple studies have been carried out in order to estimate the incidence and prevalence of NF1. The estimates have been highly variable mainly due to differences in study settings. The population to be investigated can be hospital-based or population-based and ascertainment methods can be different. Huson et al. (1989) reviewed medical records of hospitalized patients and examined first-degree relatives of affected individuals in South East Wales during years 1983–1986. In this study, 135 NF1 patients were found, yielding estimated prevalence of 1/4,510 and incidence of 1/2,558 (Huson et al., 1989). In the Manchester region of North West England (population 4.1 million), genetic registers were searched. As a result, 979 patients with NF1 diagnosis confirmed according to NIH clinical criteria were found, yielding a prevalence of 1/4,560 and birth incidence of 1/2,712 (Evans et al., 2010). In Northern Finland (population 733,037), Pöyhönen (2000) reported a prevalence of 1/4,436 and birth incidence of 1/3,647. Later, a birth incidence of approximately 1/2,000 for NF1 was reported in a total population study in Finland (Uusitalo et al.,

2015) and an overall observed prevalence of 1/4,088 for NF1 (Kallionpää et al., 2018). A systematic review and meta-analysis by Lee et al. (Lee et al., 2023) reported pooled NF1 prevalence of 1/3,164 and birth incidence of 1/2,662.

2.1.6 Mortality in NF1

Comorbidities such as cancers are causing excess mortality throughout the lifetime of the affected individuals (Figure 2). Consequently, the life expectancy is reduced markedly in NF1 compared to the general population (Evans et al., 2011; Uusitalo et al., 2015). Particularly, MPNSTs which have a poor prognosis have the greatest influence on premature mortality (Rasmussen et al., 2001). Also, cerebrovascular diseases, hypertension-related events, high-grade gliomas and OPGs with aggressive behavior contribute to mortality in NF1 (Zöller et al., 1995; Evans et al., 2011).

Studies on mortality in NF1 are often based on data obtained from national death registers. Studies solely based on death certificates are dependent on the information recorded on the death certificate. Unfortunately, NF1 is not always marked on the death certificate as the underlying cause of death or otherwise mentioned, thus leading to poor sensitivity of identifying individuals with NF1. In studies with clinical patient cohorts, NF1 diagnosis may be verified but hospital-based ascertainment of individuals with NF1 may bias the cohort toward those with more severe disease manifestations and leaving out mild cases.

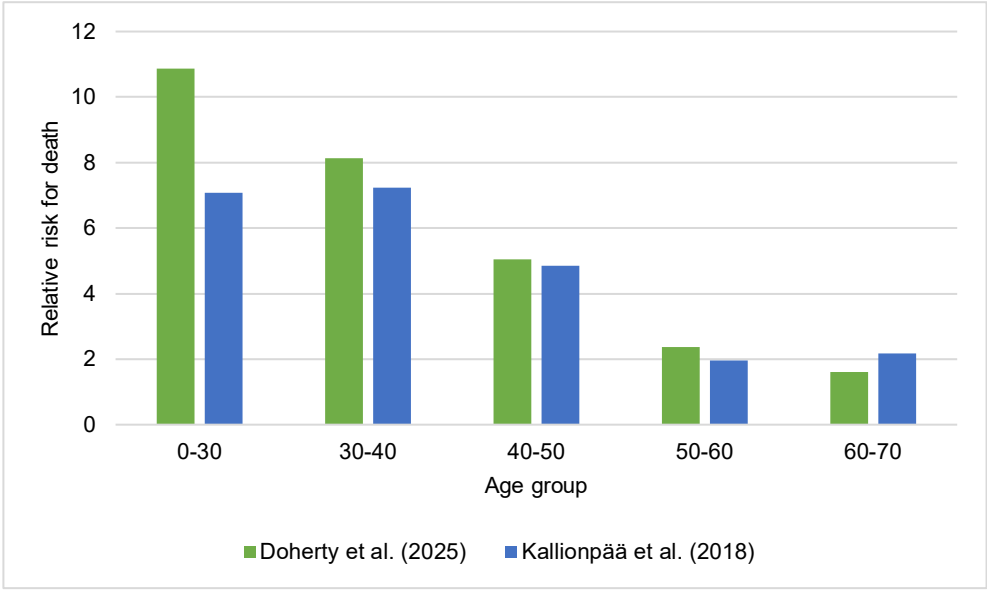

Figure 2. Age group-specific relative risk for death in NF1 compared to general population in two Nordic cohorts (Kallionpää et al., 2018; Doherty et al., 2025).

A Finnish study analyzed 214 death certificates of NF1 patients from years 1987–2012 (Uusitalo et al., 2015). The NF1 diagnosis was confirmed by reviewing a total of 1,471 patient records. Standardized mortality ratio (SMR) was used to present the ratio of observed death to expected deaths in the study group (SMR 3.22, 95% CI 2.81–3.68). Excess mortality found in this cohort was mainly due to malignancies at a relatively young age. The mean age at death was 52.3 years for men with NF1 and 51.9 years for women with NF1, compared to 68.8 and 78.0 years in the general population. In other words, NF1 decreased mean age at death by 16.5 years in men and by 26.1 years in women (Uusitalo et al., 2015).

Death certificates from the United States from years 1983–1997 were reviewed by Rasmussen et al. (2001) in order to analyze mortality in NF1. They found 3,770 deaths of individuals with presumed NF1 among over 32 million deaths. The number of identified NF1 deaths in this study was clearly underestimated due to the missing NF1 diagnosis on death certificates. Malignant neoplasms of connective and other soft tissue, and neoplasms of the brain were reported more frequently than expected and these were the main factors that decreased life expectancy by 15.7 years. In numbers, the mean age at death was 54.4 years in NF1 and 70.1 years in the general population (Rasmussen et al., 2001).

An Italian study by Masocco et al. (2011) examined death certificates from years 1995–2006. The search revealed 632 deaths with NF1 diagnosis. They observed 22-fold rate of deaths in NF1 individuals compared to general population for connective and other soft tissue malignant neoplasms (PMR 22.3, 95% CI 15.50–30.95), and a 4-fold rate of deaths for brain malignant neoplasms (PMR 4.2, 95% CI 2.69–6.15). Furthermore, the mean age at death in patients with NF1 was 55.5 years, compared to 76.2 years in general population. Specifically, one third of the deaths occurred before 40 years.

Evans et al. (2011) performed a population-based study in North West England. A total of 1,186 individuals with NF1 were identified and 131 of them died during the years 1957–2009. The most common cause of death was MPNST (34/131 = 26%), glioma being the second most common (14/131 = 9%). Furthermore, most of the excess mortality in NF1 occurred before 50 years of age. As a conclusion, median survival for NF1 patients was 71.5 years and life expectancy for both men and women were reduced by approximately 8 years compared to the general population (Evans et al., 2011).

NF1-associated mortality was also studied in France by Diaz et al. (2023). They identified 11,425 NF1 patients admitted to hospital during the years 2013–2019 and an SMR of 4.14 (95% CI 3.71–4.56) was observed. In this study cohort, cancer accounted for 37% of deaths. The next two most common causes of death were diseases of the respiratory system (15%) and diseases of the circulatory system (12%).

2.2 Cancer and NF1

2.2.1 Cancer risk in NF1

NF1 predisposes patients to benign and malignant tumors. An example of a benign tumor is cutaneous neurofibroma. Another example of a usually benign tumors is GIST which, however, may sometimes undergo malignant transformation. The age-standardized incidence of cancer is at least four-fold in individuals with NF1 compared to the general population (Zöller et al., 1997; Seminog and Goldacre, 2013). A French study by Diaz et al. (2023) reported a standardized incidence ratio (SIR) of 10.3 (95% CI 9.6–11.1) for cancer in individuals with NF1. Cancers of the central nervous system and small intestine largely accounted for this elevation (Diaz et al., 2023). OPG is the most common type of brain tumor, but also brainstem gliomas are found in children with NF1 (Peltonen et al., 2019). The lifetime risk of cancer has been estimated as high as 60% in NF1 (Uusitalo et al., 2016). Cancers in NF1 can be categorized into NF1-specific cancers (MPNST and intracranial gliomas) and NF1-related cancers (GIST and breast cancer). Also, pheochromocytomas (reviewed in section 2.3.2) and juvenile myeolomonocytic leukemia have been shown to be associated with NF1. Several studies have estimated the risk and incidence of specific cancer types in NF1 (Table 2).

MPNSTs are the leading cause of excess mortality in NF1 (Duong et al., 2011b; Evans et al., 2011). MPNST is an aggressive soft tissue sarcoma and 30–50% of all MPNSTs are found in individuals with NF1. MPNSTs most typically develop from pre-existing plexiform neurofibromas in young adults aged 20–30 years (Evans et al., 2002). They can also arise as second malignant neoplasms after chemotherapy with alkylating agents and irradiation (Coffin et al., 2004; Sharif et al., 2006). Individuals with NF1 have a cumulative lifetime risk of 8-16% for MPNST (Evans et al., 2002; Uusitalo et al., 2015). The majority (70%) of MPNSTs are high-grade tumors that metastasize early and therefore have a poor prognosis (Ferner and Gutmann, 2002; Martin et al., 2020). Evans et al. (2002) have reported a 5-year survival of 21% after MPNST diagnosis in NF1 compared to 42% sporadic MPNST. Lately, survival has increased perhaps due to improvements in early identification and recognition of symptoms suggestive of malignant transformation (Ingham et al., 2011). Suspicion for MPNST should arise if a plexiform neurofibroma is growing rapidly, becomes firm or tumor is causing pain and neurological symptoms. To confirm the location of MPNST, imaging with positron emission tomography (PET) is the most sensitive and specific diagnostic method, because it can differentiate benign and malignant tumors (Warbey et al., 2009). The first-line treatment for MPNST is complete surgical excision with tumor-free margins when possible (Carton et al., 2023). In addition, neoadjuvant

chemotherapy with ifosfamide and epirubicin can also be used to reduce the size of the tumor and to facilitate surgical removal (Hirbe et al., 2017).

Juvenile myelomonocytic leukemia (JMML) is a rare and aggressive hematological malignancy of early childhood with an incidence of 0.7–1.3 per million (Passmore et al., 2003). Allogeneic hematopoietic stem cell transplantation is the first-line treatment. Without stem cell transplantation, the 10-year survival after diagnosis of JMML is less than 10% (Yoshimi et al., 2010). NF1 predisposes children to JMML. It has been estimated that children with NF1 have approximately a 200-fold risk of developing JMML compared to the general population (Stiller et al., 1994), and an even higher estimate of a 350-fold risk has been reported (Niemeyer et al., 1997). Although JMML is overrepresented in children with NF1, some studies have not reported any JMML cases (Uusitalo et al., 2016; Peltonen et al., 2019). Consequently, the absolute risk remains low, and specific screening or surveillance strategies are not currently recommended (Carton et al., 2023).

Women with NF1 have an increased risk of breast cancer, especially before the age of 50. The SIRs reported for breast cancer in NF1 range from 2 to 5 (Frayling et al., 2019). The population-based study by Uusitalo et al. (2016) reported a SIR of 3.04 for breast cancer in NF1 women overall, and a SIR of 11.1 in NF1 women younger than 40. In addition, the lifetime risk of breast cancer has been estimated to be 18% in women with NF1 (Uusitalo et al., 2017). Furthermore, survival of NF1 patients with breast cancer is worse compared to general population (Uusitalo et al., 2016, 2017). The 10-year disease specific survival was 64.2% in NF1 compared with 91.2% in control group in a five-country study (Evans et al., 2020). NF1-related breast cancers often show unfavorable prognostic factors. These cancers are often hormone receptor negative and have HER2 amplification (Uusitalo et al., 2017). Due to the early onset of breast cancer and poor prognosis, current guidelines recommend annual mammograms starting at age 30 for women with NF1 (Carton et al., 2023).

Table 2. Studies reporting cancer risk in neurofibromatosis type 1.

Cancer	Walker et al. (2006)	Seminog and Goldacre (2013)	Uusitalo et al. (2016)	Landry et al. (2021)	Diaz et al. (2023)
CNS	SIR 22.6	RR 58.3	SIR 37.5		SIR 195
MPNST			SIR 2,056	OR 2,186	
Adrenal medulla		RR 304	SIR 74.3	OR 126	
Digestive organs	SIR 2.2	RR 2.9	SIR 1.83		
Small intestine		RR 14.5			SIR 103
GIST			SIR 34.2	OR 272	
Breast	SIR 1.87	RR 2.3	SIR 3.04	OR 3.8	SIR 4.9
Respiratory organs	SIR 0.54	RR 3.0	SIR 1.25		
Melanoma		RR 3.6	SIR 1.58		

CNS: central nervous system; GIST: gastrointestinal stromal tumor; MPNST: malignant peripheral nerve sheath tumor; OR: odds ratio; RR: rate ratio; SIR: standardized incidence ratio.

2.2.2 Gastrointestinal tumors

Gastrointestinal (GI) tumors accounted for 26% of new cancer cases and 35% of all cancer-related deaths worldwide in 2018 (Arnold et al., 2020). Tumors of colorectum were the most common, followed by tumors of stomach, liver, esophagus and pancreas (Arnold et al., 2020). Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors of GI tract and approximately 1–2% of GISTs arise in patients with NF1 (Miettinen and Lasota, 2013).

An incidence of 10–20 new GISTs per million per year has been reported for GISTs in the general population (Nilsson et al., 2005; Søreide et al., 2016). The incidence of GISTs in NF1 patients is markedly higher (Table 2). Uusitalo et al. (2016) reported a SIR of 34.2 for GISTs in NF1. Miettinen et al. (2006) have reported up to 45-fold higher prevalence of NF1 in patients with GIST than expected. A recent meta-analysis shows that the prevalence of small intestinal GISTs is 3% in NF1 while it is 0.002% in general population (Mantalovas et al., 2025). On the other hand, previous studies have estimated that GISTs occur in up to 6–7% of NF1 patients (Zöller et al., 1997; Nishida et al., 2016a), while autopsy studies have revealed that GISTs are found in one-third of NF1 patients (Andersson et al., 2005). Importantly, all GISTs are never diagnosed, especially if they are asymptomatic.

GISTs are thought to originate from interstitial cells of Cajal (ICCs). These pacemaker cells are located particularly between the circular and longitudinal muscle layers in the walls of the GI tract (Al-Shboul, 2013). GISTs can occur throughout the GI tract as solitary or multiple tumors. NF1-associated GISTs are typically multiple and located in the small intestine (Miettinen and Lasota, 2006; Salvi et al.,

2013), whereas half of GISTs in the general population are found in the stomach and are typically solitary (Søreide et al., 2016; Wada et al., 2016; Mehren and Joensuu, 2018). In addition, NF1 patients with GISTs are slightly younger at the time of diagnosis with a mean age of 50 years compared to 60 years in the general population (Miettinen and Lasota, 2006; Salvi et al., 2013).

The majority of GISTs of the general population are sporadic tumors, with approximately 75% harboring an activating mutation in the *KIT* gene, which encodes mast/stem cell growth factor receptor tyrosine kinase. In 10% of cases, the platelet derived growth factor receptor alpha (*PDGFRA*) gene is mutated (Mehren and Joensuu, 2018). These two transmembrane receptors are molecular targets for the tyrosine kinase inhibitor imatinib, which is the first-line chemotherapy for the treatment of GISTs harboring *KIT* or *PDGFRA* mutations. Also, mutations of succinate dehydrogenase (SDH) complex subunits are found in 13% of GISTs. In individuals with NF1, the inactivation of both alleles of the *NF1* gene leads to the development of GIST (Maertens et al., 2006; Schaefer et al., 2022). GISTs of the NF1 patients do not depend on the KIT or PDGFRA (Kinoshita et al., 2004; Maertens et al., 2006) and, consequently imatinib is ineffective in the treatment of GISTs in NF1 (Mehren and Joensuu, 2018; Casali et al., 2022).

The diagnosis of GIST is based on morphology and immunohistochemistry. The morphology of GISTs is characterized on hematoxylin-eosin (HE) staining (Nishida et al., 2016b). GISTs can be divided into three groups based on their histological morphology: spindle cell type (70%), epitheloid cell type (20%), and mixed type (10%) (Nishida et al., 2016b). The distribution of these different types depends on location in GI tract, but spindle cell morphology is the most common throughout the whole tract. NF1-associated GISTs also most often have spindled morphology (Miettinen and Lasota, 2011).

The immunohistochemical analysis of a tumor sample establishes the definitive diagnosis of GIST (Wu et al., 2019). The most important immunohistochemical marker is KIT. Positive staining for KIT (CD117) is observed in approximately 95% of GISTs (Miettinen and Lasota, 2006; Wu et al., 2019). Moreover, 98% of GISTs are positive for DOG-1 (Discovered on GIST 1, also called Anoctamin-1 (ANO-1)) (West et al., 2004). DOG-1 is a calcium activated chloride channel protein, which is expressed ubiquitously in gastrointestinal stromal tumors regardless of *KIT* or *PDGFRA* mutation status (West et al., 2004). Notably, the KIT-negative GISTs are usually identified by positive staining for anoctamin (DOG-1/ANO-1), although small intestinal tumors may remain negative. In addition, 70–80% of GISTs are positive for CD34 (Miettinen and Lasota, 2006). NF1-associated GISTs lack *KIT* mutations, however they are strongly positive for KIT.

The clinical manifestations of GISTs are variable. Patients may be quite asymptomatic, or present with GI bleeding, which can be insidious or chronic,

leading to anemia. Bleeding can also be a life-threatening acute complication with hematemesis or melena. Other symptoms include abdominal pain, gastrointestinal discomfort after eating, intestinal obstruction, or palpable abdominal mass (Sorour et al., 2014). Endoscopy is a useful method in the evaluation of gastric or colorectal GISTs and GI bleeding. However, CT scanning or imaging with MRI is needed to detect GISTs in NF1 patients because tumors are frequently located in the small intestine and grow intramurally (Casali et al., 2022).

The first-line treatment for all patients with localized and resectable GISTs larger than 2 cm is complete surgical removal. In the general population, if the complete removal of the tumor is not possible in locally advanced disease, imatinib can be used as neoadjuvant therapy to reduce tumor size before resection. If the tumor is unresectable or if it has metastasized, treatment with tyrosine kinase inhibitors is recommended. The use of imatinib is preferred, followed by sunitinib in imatinib-resistant mutations (Demetri et al., 2010). Regorafenib, a multitarget tyrosine kinase inhibitor, is the third-line therapy (Casali et al., 2022). There is currently no standard treatment for NF1-associated GISTs except surgery. A case report of Fujimi et al. (2019) described a therapeutic response to regorafenib in NF1-associated GIST. Mutational analysis is recommended for all GISTs to identify the underlying mutation and to aid the planning of the appropriate treatment for each patient (Casali et al., 2022).

2.3 Cardiovascular diseases and NF1

2.3.1 Cardiovascular diseases

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide (Roth et al., 2020). CVDs accounted for 28% of deaths in the United States in 2021 (Martin et al., 2024). In the Finnish general population, cardiovascular diseases caused 31.0% of deaths in 2022. Specifically, MI was the underlying cause in 10.3% of all deaths (Causes of death | Statistics Finland). Excess overall mortality has been reported in NF1 compared to the general population. This is mainly explained by malignancies, but increased mortality due to circulatory system diseases has been documented with an SMR of 1.82 (Uusitalo et al., 2015).

The CVDs affect the heart and blood vessels and present with different clinical manifestations. The most common presentation is coronary heart disease, in which decreased blood flow due to stenosis of the coronary arteries can lead to MI. Clinical manifestations of cerebrovascular disease include strokes and transient ischemic attacks (TIAs), whereas peripheral artery disease presents as claudication of the lower limbs due to decreased blood circulation. Furthermore, aortic disease involves thoracic and abdominal aortic aneurysms (Tasouli-Drakou et al., 2025).

Well recognized modifiable risk factors for coronary heart disease include smoking, dyslipidemia, hypertension, diabetes mellitus, obesity, unhealthy diet, and physical inactivity. A family history of early atherosclerotic heart disease is a significant non-modifiable risk factor (Sagris et al., 2022). Additionally, chronic kidney disease (Sarnak et al., 2019), rheumatoid arthritis (Crowson et al., 2013), and obstructive sleep apnea (Sert Kuniyoshi et al., 2008) are linked to increased risk for coronary heart disease. Furthermore, low socioeconomic status, low income, and low education have been shown to contribute to the risk of MI (Kucharska-Newton et al., 2011; Petrelli et al., 2022; Xiao et al., 2022).

Blood vessel walls consist of three different layers: the tunica intima is the innermost layer with endothelial cells lining the lumen of the blood vessel. The intermediate layer, the tunica media, is mainly composed of smooth muscle cells, which regulate vascular tone. The outermost, principally supporting tissue, is called the tunica adventitia. This layer contains, for instance, small vasa vasorum arteries and nerves (Seidelmann et al., 2014).

Neurofibromin is normally expressed by endothelial and smooth muscle cells of blood vessels. Loss of neurofibromin expression in these cells is considered a key factor in the pathogenesis of vasculopathy in NF1 (Norton et al., 1995). NF1-associated vasculopathy can affect arteries, and various vascular abnormalities can be observed in patients with NF1. Vasculopathy in NF1 can present with stenosis or occlusion of an artery, aortic coarctation, and aneurysms (Bergqvist et al., 2020). In addition, abnormalities in intracranial vessels may cause Moya-Moya syndrome (Scott and Smith, 2009).

2.3.2 Hypertension

The global age-standardized prevalence of hypertension was 32% in women and in men 34% among adults aged 30–79 years in year 2019 (NCD Risk Factor Collaboration (NCD-RisC), 2021). Hypertension can be classified into two main types: essential hypertension and secondary hypertension. According to clinical guidelines, blood pressure is considered elevated if systolic pressure is ≥ 130 mmHg or diastolic pressure is ≥ 80 mmHg, and drug treatment should be initiated if blood pressure is ≥140/90 mmHg (Mancia et al., 2023; Jones et al., 2025).

Secondary hypertension can be caused by a variety of renal and endocrine disorders. Secondary hypertension is diagnosed in 5–10 % of hypertensive patients in the general population (Charles et al., 2017). The prevalence of secondary hypertension varies with age, and about 30% of patients are diagnosed under age of 40 (de Freminville et al., 2024). The most common endocrine cause of hypertension in the general population is primary aldosteronism, the prevalence of which increases along with the severity of hypertension (Reincke et al., 2021). Screening for

aldosteronism is currently performed on only a subset of those for whom it would be potentially beneficial. Primary aldosteronism is likely to occur in at least 5% of patients with hypertension (Jaffe et al., 2020).

Although essential hypertension is common in the general population, epidemiological studies on its association with NF1 are sparse (Kenborg et al., 2020), and current knowledge is mainly based on case reports describing consequences of essential hypertension (Faris et al., 2021). Collectively, these reports suggest that hypertension is a common finding in patients with NF1. Hypertension may also develop during childhood in NF1 (Bergqvist et al., 2020). Up to 16% of children and adolescents with NF1 have been reported to show blood pressure values suggestive of hypertension (Lama et al., 2004; Dubov et al., 2016). A Danish analysis of diagnoses associated with hospitalizations reported a relative risk of 1.5 (95% CI 1.1–2.0) for hypertensive disorders other than renal vascular hypertension in NF1 compared to the control population (Kenborg et al., 2020). In addition to essential and secondary hypertension, pulmonary arterial hypertension should be recognized as a distinct and severe vascular complication of NF1, as evidenced by its unique phenotype and poor outcomes (Jutant et al., 2020). Annual monitoring of blood pressure is recommended for individuals with NF1 (Bergqvist et al., 2020; Merker et al., 2022; Carton et al., 2023).

Secondary hypertension is more common in individuals with NF1 than in the general population. NF1-associated vasculopathy may manifest as a renal artery stenosis leading to renovascular hypertension (Ferner et al., 2007; Gutmann et al., 2017). Therefore, children with elevated blood pressure and young adults with refractory hypertension should be carefully screened for renal artery stenosis (Fossali et al., 2000; Patel and Cahill, 2021). In addition, renovascular hypertension may also result from aortic coarctation or middle aortic syndrome in children with NF1 (Dubov et al., 2016).

Pheochromocytoma is a rare endocrine cause of secondary hypertension in the general population. However, it should be suspected as a potential cause of NF1-associated hypertension, especially if hypertension is resistant to antihypertensive therapies and if symptoms include paroxysmal hypertension, palpitations, tachyarrhythmias, sweating, or headache. Pheochromocytoma is a catecholamine-producing tumor originating from chromaffin cells of the adrenal medulla. Occasionally, these tumors are also found outside the adrenal gland in the paravertebral sympathetic ganglia, in which case they are called paragangliomas. The prevalence of pheochromocytoma in systematically screened individuals with NF1 has been reported to be as high as 7.7–14.6% (Zinnamosca et al., 2011; Képénékian et al., 2016). Currently, screening for pheochromocytoma and functional paraganglioma is recommended for NF1 patients who have elevated blood pressure unexplained by other medical reasons. Biochemical screening is also

recommended for all women with NF1 who are contemplating pregnancy or are already pregnant (Stewart et al., 2018; Carton et al., 2023). Measurement of plasma-fractionated or urinary-fractionated metanephrines is recommended initial screening test for pheochromocytoma, and the localization of the tumor is confirmed by CT or MRI before surgery (Lenders et al., 2014; de Freminville et al., 2024).

2.3.3 Myocardial infarction

MI is a severe vascular complication and can occasionally lead to immediate death. It is mainly caused by insufficient oxygen supply to the heart muscle. The primary mechanism of ischemic coronary heart disease is atherosclerosis. This process begins to develop in large arteries during early adulthood, but clinically significant changes occur primarily in older individuals. Atherosclerotic changes in vessel walls start with the formation of a fatty streak. These lesions develop in the subendothelial space as a result of turbulent flow at the sites of shear stress. Lipoproteins circulating in the bloodstream enter the intima, aggregate, and become oxidized. This cascade leads to the activation of endothelial cells, followed by leukocyte recruitment and inflammation. Macrophages in the fatty streak lesions take up oxidized low-density lipoproteins and develop to foam cells. These cholesterol rich cells frequently undergo apoptosis or necrosis and form the necrotic core of an atherosclerotic lesion with accumulated cell debris (Björkegren and Lusis, 2022).

The fibrous cap of an atherosclerotic plaque is built when smooth muscle cells proliferate and migrate to the region beneath the endothelial cells, and secrete collagen. The main function of the fibrous cap is to protect the lesion from rupture. It has been observed that lesions with a thick fibrous cap are more stable and resistant than those lesions containing lipids and abundant macrophages, which maintain chronic inflammation (Libby, 2021).

The calcification of coronary arteries occurs in both the intimal and medial layers of the vessel, where calcium-phosphate deposits start to accumulate and form calcified sheets or plates. Computed tomography can be used as an imaging modality to evaluate the extent and localization of coronary calcification in patients with coronary artery disease (Mori et al., 2018). Specifically, an advanced atherosclerotic lesion can rupture and lead to MI if the thrombus occludes the coronary artery (Björkegren and Lusis, 2022). It is clinically important to note that atherosclerosis or calcification is rarely observed in the internal thoracic artery, thus making this vessel suitable as a graft in bypass surgery (Otsuka et al., 2013).

Despite the fact that MIs are relatively common in the general population, studies of MI in NF1 are limited. Corona-Rivera et al. (2023) presented an overview of 17 published cases of obstructive and/or aneurysmal coronary artery disease in NF1 patients. MI was the cardiac manifestation in 11 of these 17 individuals, with the

most prevalent site of aneurysm in the left anterior descending artery (LAD). The youngest patient was 13 years old and the oldest 80 years. In addition, Corona-Rivera (2023) reported, for the first time, aneurysmal coronary artery disease in a neonate with NF1 diagnosed at birth (Corona-Rivera et al., 2023). Recently, a case report described MI in a 25-year-old NF1 patient with an ectatic right coronary artery (RCA) and LAD with significant stenosis (van Gelder et al., 2024).

2.4 Registers and data sources

Epidemiological studies can reveal associations between certain diseases and risk factors, such as having a genetic condition like NF1. Nationwide registers are useful data sources for epidemiological studies and enable retrospective studies on rare diseases. The success of such studies depends on the accuracy of disease diagnoses in the registers and patient coverage.

During the years 1964–1968, unique personal identity code was created for each Finnish resident. The code includes the date of birth and sex, and remains unchanged over lifetime. The health care centers, hospitals and administrative registers use the code to identify persons. The personal identity code also enables cross-linking data from different databases as well as lifelong follow-up of each person. This practically eliminates the loss to follow-up.

The Finnish Care Register for Health Care (HILMO) (https://thl.fi/en/statistics-and-data/data-and-services/register-descriptions/care-register-for-health-care) collects comprehensive patient information from health care providers using International Standard Classification of Diseases (ICD) codes to record diagnoses. Importantly, validation studies have shown that the data from the Finnish Care Register for Health Care is reliable (Sund, 2012). Another administrative register relevant for the epidemiology of life-threatening diseases is the Causes of Death Register (Lahti and Penttilä, 2001; Tolonen et al., 2007) (https://stat.fi/en/statistics/ksyyt). Specifically, the diagnoses on coronary heart disease events were shown to be reliable both in the Finnish Care Register for Health Care and in the Causes of Death Register (Pajunen et al., 2005).

3 Aims

The thesis had four specific aims:

1. To study the site distribution of tumors in the gastrointestinal tract in NF1. (Study I)
2. To evaluate the clinical course of fatal GISTs in NF1 patients. (Study I)
3. To analyze the occurrence of primary and secondary hypertension in NF1. (Study II)
4. To evaluate the risk and prognosis of myocardial infarction in NF1. (Study III)

4 Materials and Methods

4.1 Ethical considerations

The study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital District of Southwest Finland (66/180/2012). Research permits were obtained from the Finnish Social and Health Data Permit Authority Findata, Ministry of Social Affairs and Health, the Finnish Institute for Health and Welfare, the Finnish Social Insurance Institution, Statistics Finland, and all participating hospitals. The study was register-based and retrospective and therefore exempt from obtaining informed consent from the participants.

Academic proofreading and refinement of language of this thesis were supported by artificial intelligence tools (ChatGPT-5 and Copilot).

4.2 Study populations

4.2.1 The Finnish NF1 cohort

Studies I–III were based on the total population-based Finnish NF1 cohort. The Finnish NF1 cohort was initially collected by searching all hospital visits with a diagnosis of neurofibromatosis in the 15 Central and five University Hospitals in mainland Finland during the years 1987–2011 (Uusitalo et al., 2015). The search covered the ICD-9 diagnosis code 2377A (neurofibromatosis) and the ICD-10 codes Q85 (phakomatoses, not elsewhere classified), Q85.0 (neurofibromatosis), Q85.00 (neurofibromatosis type 1), Q85.01 (neurofibromatosis type 2), and Q85.09 (other neurofibromatosis). ICD-9 has been used in Finland in 1987–1995 and ICD-10 since 1996. The search also included diagnosis codes for NF2 and unspecified neurofibromatosis to maximize the coverage. The medical records of each patient were reviewed to confirm NF1 diagnosis according to the NIH diagnostic criteria (National Institutes of Health Consensus Development Conference, 1988). Verification procedure excluded persons with insufficient data on medical records, and persons not fulfilling the diagnostic criteria. As a result, 1,471 patients with NF1 were identified. This cohort was used in Studies I–II (Table 3).

Table 3. Data sources and outcomes of interest.

Study	Register of outcomes of interest	Follow-up start	Follow-up end	Number of individuals	Follow-up time (person-years)	Event of interest
GI tumors (I)	HILMO	1987–2011	2014	1,410 NF1 14,030 controls	21,220 NF1 229,314 controls	ICD-9: 150-154, 211.0-211.4, 230.1-230.6 ICD-10: C15-21, D00.1-D00.2, D01.0-D01.3, D12.0-D12.9, D13.0-D13.3, D37.1-D37.5, D48.42
GIST characteristics (I)	Death certificates	1987	2013	1,453 NF1	NA	GIST
Hypertension in NF1 (II)	HILMO The Finnish Register of Reimbursed Drug Purchases	1996–2011	2014	1,365 NF1 13,923 controls	18,329 NF1 199,223 controls	ICD-10: I10-I15 ATC: C02, C03, C07, C08, C09 (excluding drugs commonly used primarily for indications other than hypertension)
Risk for myocardial infarction (III)	HILMO Causes of death	1987–2020	2021	1,811 NF1 18,006 controls	32,146 NF1 347,415 controls	ICD-9: 410 ICD-10: I21-I22
Survival after myocardial infarction (III)	Causes of death	1987–2021	2021	37 NF1 362 controls	NA	I21-I22 as the primary or underlying cause of death

ATC: Anatomical Therapeutic Chemical Classification; GI: Gastrointestinal; GIST: Gastrointestinal Stomal Tumor; HILMO: The Finnish Care Register for Health Care; ICD-9: International Standard Classification of Diseases, 9th revision; ICD-10: International Standard Classification of Diseases, 10th revision; NA: not available; NF1: Neurofibromatosis type 1

The Finnish NF1 cohort was recently updated to include 1,811 patients with confirmed NF1 diagnoses (National Institutes of Health Consensus Development Conference, 1988; Legius et al., 2021). This updated NF1 cohort covers an ascertainment period of 1987–2020. This updated cohort was used in Study III (Table 3).

4.2.2 Control cohort

A control cohort was formed by searching ten control persons for each individual with NF1 from the Finnish Population Register Centre. Controls were required to be alive on the cohort entry date of the respective NF1 individual. Controls were matched with the NF1 individuals by date of birth, sex and municipality of residence at the time of cohort entry. The first-degree relatives of NF1 individuals were excluded from the control cohort.

4.3 Data sources and outcomes of interest

The Finnish Population Register Center is a national authority which gathers information on all inhabitants in Finland from several institutions such as hospitals (https://dvv.fi/en/population-information-system). Dates of birth, death and emigration data were obtained from the Finnish Population Register (Studies I–III).

The Finnish Care Register for Health Care (HILMO) (Sund, 2012) (Care Register for Health Care - THL) (https://thl.fi/en/statistics-and-data/data-and-services/register-descriptions/care-register-for-health-care) is maintained by the Finnish Institute for Health and Welfare. This register collects data from health care providers and contains information on visits to specialized outpatient care and patients discharged from inpatient care. The register has information on inpatient care since 1969, while the outpatient visits have been recorded since 1998. Hospital visits are recorded using the International Standard Classification of Diseases (ICD) diagnosis codes. During the years 1987–1995, the ICD-9 was the coding system, and ICD-10 has been used since 1996. The Finnish Care Register for Health Care was used in Studies I–III.

The death certificate is written by the physician who treated the patient prior to the death, or by forensic pathologist if autopsy is required. Causes of death are recorded on the certificate using the ICD codes. The causes of death are categorized into three levels: immediate cause of death (A), intermediate and contributing causes of death (B) and underlying cause of death (C). The underlying cause of death must always be entered on the certificate. The causes of death listed on death certificate are recorded in the Causes of Death Register (Lahti and Penttilä, 2001) maintained by Statistics Finland (Causes of death | Statistics Finland) (https://stat.fi/en/statistics/ksyyt). The death certificates were searched for GIST in Study I. If the death certificate mentioned GIST, the medical history of the patient was studied in more detail using hospital records. In addition, MIs recorded in death certificates were analyzed in Study III.

The Finnish Register of Reimbursed Drug Purchases contains information of prescription drug purchases with eligibility to reimbursement. This data, collected by the Finnish Social Insurance Institution, is available since 1996. The drug purchases are recorded using the Anatomical Therapeutic Chemical (ATC) codes. This classification system divides drugs into specific groups according to which organ system they affect and based on their therapeutic use. Practically, every drug molecule has its own code. Drug purchases were analyzed in Studies II and III.

The Finnish Cancer Registry (Leinonen et al., 2017) (Tasks - Syöpärekisteri) (https://cancerregistry.fi/information/tasks/) is a comprehensive national database which documents cancer diagnoses in Finland. Systematic cancer registration started in 1953 and was legislated as mandatory in 1961. The registry receives cancer data from hospitals and pathology laboratories. In addition, the data is supplemented with causes of death data provided by Statistics Finland. Data from the Finnish Cancer Registry was analyzed in Study III.

The educational level (Studies II and III) and annual disposable income (Study II) were retrieved from Statistics Finland. Statistics Finland obtains information on completed degrees from the providers of education and acquires the data on annual disposable income of Finnish residents. Educational level was coded using the International Standard Classification of Education (ISCED). ISCED 0–2 corresponds to ≤9 years of education, ISCED 3–4 represents ~12 years of education, and ISCED ≥5 translates to ≥15 years of education.

ATC, ICD-9 and ICD-10 codes used to identify events of interest are defined in Table 3. In Study II, patients with diagnoses for both essential and secondary hypertension were excluded from the analysis focusing on essential hypertension. In Studies II and III, factors potentially contributing to hypertension or MI were also analyzed.

4.4 Statistical analyses

For the individuals with NF1, the cohort entry date was the date when the first NF1-related hospital visit during the ascertainment period was recorded. For the matched controls, the cohort entry date was the entry date of the respective NF1 patient. The follow-up started at the cohort entry date or the beginning of the study period (Table 3) whichever was later. The follow-up ended at the first occurrence of an event of interest, death, emigration, or end of study period (Table 3) whichever occurred first.

Hazard ratios (HRs) and their 95% confidence intervals (CI) were estimated using Cox proportional hazards models (Table 4). The matching of individuals with NF1 and controls was accounted for using a frailty term. Fisher's exact test and odds ratios (ORs) were used to compare the prevalence of factors potentially contributing to hypertension or MI between the NF1 and control groups.

Table 4. Statistical analyses.

ANALYSIS	TIME SCALE	STATISTICAL ANALYSES	RESULTING ESTIMATE	STRATIFICATION	SOFTWARE
Hazard for hospital diagnosis of a GI tumor (I)	Follow-up time since cohort entry	Cox proportional hazards model with frailty term	Hazard ratio	Anatomical site	R software version 3.5.1, and package survival (version 2.42-6)
Hazard for hospital diagnosis of hypertension (II)	Age	Cox proportional hazards model with frailty term and delayed entry	Hazard ratio	Age, sex, educational level	R software version 3.6.2, and package survival (version 3.2-7)
Hazard for hospital diagnosis or death related to myocardial infarction (III)	Age	Cox proportional hazards model with frailty term and delayed entry, Nelson-Aalen estimation	Hazard ratio, cumulative risk	Age, sex, history of cancer	R software version 3.6.2, and package survival (version 3.2-7)
Survival after myocardial infarction (III)	Time since myocardial infarction	Kaplan-Meier estimation, Cox proportional hazards model	Survival probability, hazard ratio	NA	R software version 3.6.2, and package survival (version 3.2-7)

GI: Gastrointestinal; NA: not available

5 Results

5.1 Gastrointestinal tumors in NF1 (I)

The results are based on two complementary approaches: 1) a register-based analysis of hospital visits (1987–2014) by 1,410 individuals in the Finnish NF1 cohort (Uusitalo et al., 2015) to characterize the anatomical distribution of GI tumors in NF1; and 2) a review of all 232 death certificates for NF1 patients who died in 1987–2013 to identify individuals in whom GIST was the primary or major contributing factor of death.

5.1.1 Incidence and anatomical distribution of gastrointestinal tumors in NF1 (I)

Using the Finnish Care Register for Health Care, tumor related diagnoses across the esophagus, stomach, small intestine, colon, rectum, and anus were identified. Because tumor morphology was not available in the register data, all intestinal tumor types were encompassed, including GISTs. Compared with matched controls, NF1 was associated with a higher overall hazard for GI tumors (HR 2.6). The excess risk was most pronounced in the small intestine (HR 15.6), and lowest in the stomach (HR 1.2).

Based on personal experience of participation in two autopsies of two patients with NF1, benign GISTs can be more frequent in NF1 than represented in the register-based data. Both patients had died of non-GIST-related reasons and had no previous diagnosis of GIST. However, in both of them, benign GISTs were found in the autopsy.

5.1.2 Fatal GISTs in NF1: death certificate series (I)

Among the death certificates of 232 individuals with NF1, eight certificates recorded GIST; in seven, GIST was the underlying cause of death, and one patient died of MPNST. Three of the patients were men and five were women. Hospital records were available for all eight NF1 GIST patients and were reviewed for clinical and pathological characteristics of the GISTs.

The age at the diagnosis of the GIST recorded in the death certificate ranged from 35 to 74 years (median 61; 58 in women and 65 in men). All patients were symptomatic at presentation, with abdominal pain, anemia, palpable mass, weight loss or nausea. The GIST was located in the small intestine in seven NF1 patients while one GIST was retroperitoneal. Histology was predominantly spindle cell, with two mixed spindle/epithelioid cases. Six patients were also found to have other GISTs while two had solitary lesions. The diameters of the tumors ranged from 1.5 to 20 cm, and four had metastasized at diagnosis. Two patients had undergone a prior GIST resection, 11 and 27 years before the presentation of the current and fatal GIST.

Immunohistochemistry showed CD117 (c-Kit) positivity in seven NF1 GISTs and CD34 positivity in five. Four GISTs were analyzed for mutations, and were negative for *KIT* and *PDGFRA* mutations. By standard criteria (size, mitotic rate, Ki-67), six tumors were high risk and two were low risk. Notably, both low risk duodenal tumors were nevertheless fatal within one year. Initial management was surgical in all patients and five patients received post-operative systemic therapy (imatinib first-line, with sunitinib in two and later paclitaxel/sorafenib in one). Survival after GIST diagnosis ranged from 1 day to 2 years 6 months. Among these patients with fatal GISTs, the median interval from detection to death was 6 months.

5.2 Cardiovascular comorbidities in NF1 (II, III)

5.2.1 Hypertension in NF1 (II)

A total of 1,365 individuals with confirmed NF1 and 13,923 controls matched for age, sex, and municipality were analyzed. The cohorts were well matched at the beginning of the follow-up time, yet individuals with NF1 had lower educational level and smaller mean disposable income than the controls.

Across 1996–2014, hospital records identified 115 NF1 patients and 914 controls with a hypertension diagnosis (I10, I11, I12, I13, or I15), corresponding to a HR of 1.64 (95% CI 1.34–2.00) for NF1 versus controls. Nine of 115 NF1 patients had secondary hypertension (I15), yielding a HR of 3.76 (95% CI 1.77–7.95; P<0.001). The mean age at the first hospital record of secondary hypertension was 35 years (SD 30) in NF1 and 56 years (SD 19) in controls. Renovascular hypertension (I15.0) was recorded in five NF1 individuals, and adrenal etiology of secondary hypertension, pheochromocytoma (C74), adrenal neoplasm (D44.1), and/or adrenomedullary hyperfunction (E27.5) in two. In addition, the cause of secondary hypertension was unspecified in two patients. No patient had a diagnosis of primary hyperaldosteronism (E26.0) or primary hyperparathyroidism (E21.0).

A total of 98 NF1 patients had a diagnosis of essential hypertension (I10) and no diagnosis of secondary hypertension (I15). The HR for essential hypertension was

1.73 (95% CI 1.39–2.14; P<0.001) and remained unchanged in a sensitivity analysis excluding the first six months after cohort entry. Mean age at first record of essential hypertension was 63 years (SD 15) in NF1 and 69 years (SD 13) in controls. The relative hazard was higher at ages ≤50 years (HR 3.24; P<0.001) and remained elevated at >50 years (HR 1.59; P<0.001). There was no sex difference. Adjusting for education yielded a HR of 1.71 (95% CI 1.38–2.13). Adjustment for parental NF1 attenuated the estimate modestly (HR 1.53; 95% CI 1.18–1.98; P=0.001). Among those with essential hypertension, the prevalence of recorded potential contributors (sleep apnea, obesity, tobacco use, alcohol-related conditions) did not differ between NF1 and controls.

Nearly all patients with essential hypertension had purchased antihypertensive medication at least once (NF1 98.0%; controls 98.3%). However, NF1 individuals were less likely to have purchased calcium-channel blockers or agents inhibiting the renin–angiotensin system. Moreover, 24.5% of NF1 patients versus 12.4% of controls purchased drugs from only a single ATC class (P=0.003).

To capture hypertension only managed in primary care, reimbursed drug purchases were analyzed in the full NF1 and control cohorts. A total of 388 NF1 individuals and 3,563 controls had at least one antihypertensive drug purchase. Only diuretics and beta-blockers showed increased hazards in NF1; purchases of calcium-channel blockers and agents acting on the renin–angiotensin system did not differ significantly.

5.2.2 Myocardial infarction in NF1 (III)

A total of 1,811 NF1 patients and 18,006 matched controls were analyzed for the risk and prognosis of myocardial infarction during the years 1987–2021. Forty-two NF1 and 415 control patients had a diagnosis of myocardial MI, corresponding to a HR of 1.36 (95% CI 0.98–1.88; P=0.062). Women had a HR of 1.58 (95% CI 0.97–2.57; P=0.068) and men HR of 1.24 (95% CI 0.81–1.91; P=0.319) and there was no significant difference in the HRs between women and men (P=0.635). Mean age at first diagnosis of MI was 66.2 years (SD 12.8) in patients with NF1 and 69.7 years (SD 12.5) in controls. The cumulative risk of MI by age 50 was 0.8% (95% CI 0.3%–2.1%) in NF1 versus 0.6% (95% CI 0.4%–0.9%) in controls and by age 80, the risk was 10.4% (95% CI 7.6%–14.3%) versus 11.7% (95% CI 10.5%–13.0%), respectively. Furthermore, a 50-year-old individual with NF1 had a 10-year MI risk of 2.5% (95% CI 1.3%–4.7%) compared with 1.5% (95% CI 1.1%–1.9%) in controls.

Before MI admission or MI-related death, hypertension and lipoprotein disorder diagnoses did not differ significantly between groups. In the full cohort, however, NF1 was associated with higher hazards for purchases of lipid-modifying agents (HR

1.33, 95% CI 1.18–1.51; P<0.001) and for a diagnosis of lipoprotein metabolism disorders (HR 1.34, 95% CI 1.05–1.71; P=0.017). A prior cancer was more frequent among NF1 patients with MI than among controls with MI, but the HR for MI was essentially unaffected by cancer history. Pharmacotherapy after myocardial infarction was similar in NF1 and controls. Five NF1 and 53 control patients died with MI listed as underlying or immediate cause without a prior hospital visit for MI.

Among the 37 NF1 patients admitted to hospital with MI, disease-specific survival was 69.2% (95% CI 54.8%–87.6%) at 5 years and 62.9% (95% CI 46.6%–85.0%) at 10 years, versus 85.0% (95% CI 81.0%–89.2%) and 80.9% (95% CI 76.0%–86.1%) in controls. Survival after MI admission was significantly worse in NF1 (HR 2.22, 95% CI 1.16–4.24; P=0.016), and remained so after excluding those with prior cancer (HR 2.16, 95% CI 1.02–4.56; P=0.046).

Across the entire NF1 cohort, MI was the primary or underlying cause of death in 16 individuals. The HR for death due to MI was 2.18 (95% CI 1.29–3.70; P=0.004) in NF1 versus control cohort. The mean age at MI death was 68.7 years (SD 13.2) in NF1 and 74.1 years (SD 12.4) in controls, and sex did not modify the hazard. Hypertension and heart failure before death due to MI did not differ significantly, although sleep apnea was more frequent in NF1 (OR 6.14). The excess hazard of MI death appeared greater among those with prior cancer.

6 Discussion

This thesis integrates population-based evidence on three clinically connected aspects of neurofibromatosis type 1 (NF1): 1) intestinal tumors with emphasis on gastrointestinal stromal tumors (GISTs), 2) hypertension, and 3) myocardial infarction (MI) and its prognosis. By combining nationwide Finnish health registers with individually verified NF1 diagnoses, the studies highlight that NF1 is a multisystem disorder with substantial gastrointestinal and cardiovascular burdens. NF1 was associated with markedly elevated hazards for small intestinal tumors including fatal NF1-related GISTs (Study I); a predominance of essential hypertension with potentially earlier onset (Study II); and a worse survival after MI despite broadly similar pharmacotherapy (Study III). These conditions were partly age-dependent in NF1. The findings have implications for surveillance, diagnostic strategies, and risk reduction in everyday care. The actions may include targeted diagnostic pathways for the GI tract, age-aware blood pressure monitoring with special focus on secondary causes, and control of atherosclerotic risk factors including dyslipidemia and sleep apnea.

6.1 Gastrointestinal tract tumors in NF1: anatomical distribution, lethality, and diagnostic gaps

Studying the epidemiology of GIST is difficult. Searching registers for site-based ICD-10 codes cannot differentiate GISTs from other GI tumors, and morphological coding is only available for those registered as cancers. In addition, many GISTs are indolent and may remain undetected (Miettinen et al., 2006). Thus, the incidence and prevalence of GISTs has not been reliably estimated previously and could not be analyzed in this study either. Also, a personal experience of finding benign GISTs in the autopsies of two NF1 patients supports the view that GISTs are frequent in NF1 and may remain undetected if the tumors are asymptomatic. This is in line with previous evidence from autopsies of individuals with NF1 (Andersson et al., 2005).

A site-specific analysis of specialized outpatient and inpatient encounters showed that gastrointestinal tumors were more frequently detected in NF1 than in matched controls (HR 2.6), with the most frequent localization in the small intestine

(HR 15.6). This distribution strongly suggests a predominant contribution from GISTs of the small intestine, which are characteristically multiple and spindle cell type in NF1 (Miettinen et al., 2006).

Among deceased NF1 patients, GIST was identified as the primary cause of death in 7 out of 8 individuals where it was recorded on the death certificate, demonstrating that NF1-associated GISTs are not necessarily indolent. Importantly, standard endoscopies may miss GISTs in the small intestine. Thus, abdominal CT or MRI should be applied particularly in middle-aged or older NF1 patients with unexplained anemia, pain, weight loss, or other GI symptoms (Casali et al., 2022). Furthermore, despite low-risk histopathology of some primary tumors (e.g., duodenal lesions), fatal courses occurred. This questions the applicability of histopathological grading in the context of NF1 and highlights the need for cautious post-excision follow-up. Finally, the resistance to imatinib is typical in NF1 GIST due to the absence of hereditary *KIT/PDGFRA* mutations, with only limited evidence for benefit from multikinase inhibitors. Early diagnosis and multidisciplinary surgical evaluation are therefore essential. It is important to keep in mind that NF1 GISTs can be multiple and careful follow-up is needed for early detection of new tumors.

6.2 Hypertension in NF1: essential hypertension predominates, secondary hypertension is important in differential diagnosis at young age

Hypertension is very common in adults of the general population and in NF1 individuals. Patients with essential hypertension are usually treated in the primary health care without need for specialized health care or hospital admission. The possibility of secondary hypertension must be considered in young hypertensive patients especially if hypertension is resistant to antihypertensive therapies. Furthermore, the risk of secondary hypertension caused by renal artery stenosis and pheochromocytoma is considerably higher in NF1 than in the general population.

Hospital-based data (1996–2014) revealed increased hazards for hypertension (I10, I11, I12, I14, I15) in NF1 (HR 1.64), driven by both secondary (HR 3.76) and essential hypertension (HR 1.73). This is in line with a Danish study by Kenborg et al. (2020), who reported relative risk of 1.5 for hypertensive disorders other than renal vascular hypertension in NF1. Noteworthly, essential hypertension clearly predominates among NF1 adults seen in specialized health care. To cover all patients at every level of health care we used the Finnish Register of Reimbursed Drug Purchases which provides comprehensive data on antihypertensive drug purchases. This complementary analysis of reimbursed drug purchases for antihypertensive medication in the whole Finnish NF1 cohort shows that the hazard for purchasing

calcium channel blockers or agents acting on the renin-angiotensin system does not differ between the NF1 and control cohorts. This suggests that the increased hazard for hypertension-related hospital visits may be partly due to the greater overall probability of visiting a hospital in the NF1 group.

The mean age at the time of the first hospital consultation with a record of essential hypertension was 63 years in NF1 and 69 years among the controls. The relative hazard for essential hypertension was highest in the 17 individuals aged 50 or younger (HR 3.24). These findings support longitudinal blood pressure monitoring also in individuals with NF1. This is most pertinent in cases of secondary hypertension, such as renovascular hypertension and the catecholamine-producing tumors pheochromocytomas and paragangliomas. At the same time, clinicians should not overestimate secondary aetiologies at the expense of timely recognition and treatment of essential hypertension which is the most common possibility.

6.3 Myocardial infarction in NF1: higher risk and worse survival after MI

In the expanded cohort (1987–2021), NF1 showed a trend toward higher hazard for myocardial infarction (HR 1.36) and a clearly higher hazard of death due to MI (HR 2.18) compared to controls. This is consistent with the results of Kenborg et al. (2020), who reported relative risk of 1.4 for diseases of circulatory system. After hospital admission for MI, disease-specific survival was worse in patients with NF1. Specifically, the results showed that disease-specific survival was 69% at 5 years in NF1 versus 85% in controls, even though the age at MI and post-MI pharmacotherapy did not suggest that the survival in NF1 would be worse. Thus, equal treatment did not close the survival gap.

Health conditions recorded in specialized health care before MI were broadly similar between groups, but two points can guide care. First, in the overall NF1 cohort (not restricted to MI), hazards were higher for both diagnoses of lipoprotein disorders and for purchases of lipid-modifying therapy—suggesting dyslipidemia is common and merits systematic detection and management. Second, obstructive sleep apnea was overrepresented among NF1 individuals who died due to MI, indicating a practical target for risk reduction. Notably, the NF1 cohort was relatively young, with a mean age of 40.2 years at the end of follow-up. With longer follow-up, coronary artery disease is likely to become more evident as additional cases occur. Together, these data argue for regular health checks and proactive management of lipids and sleep apnea in NF1, alongside standard coronary artery disease risk management.

6.4 Molecular context

The observations of this thesis are consistent with known NF1 pathobiology (Ras hyperactivation). At the molecular level, pathogenic variants of the *NF1* gene over-activate the Ras pathway in the endothelium of blood vessels and in vascular smooth muscle cells (Xu et al., 2007). NF1-associated vasculopathy affects arteries and contributes to different vascular complications. Based on murine models of NF1, hyperplasia of intima media can lead to the occlusion of an artery (Lasater et al., 2008), and structural changes in aorta predispose to formation of aneurysms (Li et al., 2014). These mechanisms likely contribute to, but are unlikely to fully explain, the higher rates of hypertension and the worse outcomes after MI seen at the population level.

6.5 Register-based analyses

The potential shortcomings of all registers relate to which degree they are complete, and accurate. Potential pitfalls include missing or incorrect entries. The cause for missing or incorrect data may be as simple as misspelling, or selection of a wrong ICD code. Thus, careful validation of the data is needed before it can be used for proper analyses. With respect to NF1, the question is, how covering the cohort of patients is, and, are the diagnoses correct.

A population-based health register tries to find all individuals with a specific condition. In an ideal case, all true diagnoses are included, and no false diagnoses are present. In the ideal case, HR, RR, and OR are unbiased and as precise as the number of patients allows. Missing cases mean fewer events, leading to wider CIs and less power, but the HR and RR stay about right on average, or unbiased. False positives in the register would lead to overestimation of disease frequency, reduce statistical power, and weaken or lead to spurious associations.

A register or cohort of patients based on the records of specialized NF1 clinics or centers have the benefit that the diagnoses are correct. However, these cohorts do not cover the whole population which can lead e.g., to selection bias and potentially to overestimation of severe complications.

6.6 Strengths and limitations across studies (I-III)

The shared strengths include 1) validated NF1 diagnoses based on NIH criteria; 2) large, matched reference population cohorts, and 3) long follow-up with linkage across Finnish national registers (specialized care, causes of death, drug reimbursements). Limitations are typical of register-based research: lack of primary care blood pressure values and risk biomarkers, incomplete morphologic data for intestinal tumors in administrative coding, and potential surveillance biases tied to

hospital-based cohort entry, thus potentially leaving out patients with a very mild form of NF1. The limitations of this study also include small numbers of patients with myocardial infarction and specific comorbidities, such as sleep apnea or previous cancer. Furthermore, the incidence of silent MI cannot be estimated. Autopsy-based research of patients with sudden cardiac death (< 50 years) found that 34% had previously undetected infarction scars, showing silent infarction can occur even at a young age (Vähätalo et al., 2021). However, sensitivity analyses and consistent findings across endpoints (e.g., mortality, drug purchases) mitigate major concerns and support the accuracy of main conclusions.

6.7 Clinical recommendations

Extensive efforts have been made to develop follow-up guidelines for individuals with NF1 (Stewart et al., 2018; Miller et al., 2019; Bergqvist et al., 2020; Carton et al., 2023; Peltonen et al., 2025). However, many of these guidelines are primarily focused on tumors, pediatric populations, or they lack clear age-specific recommendations. In contrast, there is a notable scarcity of guidance regarding the management of aging patients with NF1. When monitoring aging patients with NF1, it is important to consider the increased risk of dementia (Kallionpää et al., 2021), which may manifest as cognitive decline and challenges in adhering to pharmacological treatment. The findings of this thesis propose specific care models that could be considered in the clinical follow-up of individuals with NF1.

Gastrointestinal care. For NF1 patients from middle aged onwards with GI symptoms 1) imaging modality that can detect the tumors of small intestine early (CT or MRI) should be used, 2) structured follow-up after surgery is essential, even for low-risk primary tumors. Furthermore, it is important to keep in mind that standard targeted drugs like tyrosine kinase inhibitors often work less well in NF1-associated GISTs, so complete surgical removal and early detection are especially crucial.

Blood pressure management. Blood pressure management should include the following: 1) Blood pressure check at every visit; 2) In children, teens, and young adults, the possibility of renal artery stenosis and pheochromocytoma or paraganglioma should be considered when elevated blood pressure has been found; 3) In adults, essential hypertension should be treated following national guidelines, noting that it may develop earlier in NF1.

Atherosclerotic risk and MI. 1) Excess risk of MI posed by NF1 should be acknowledged in addition to the traditional risk factors such as smoking, hypertension and dyslipidemia, as well as the potentially worse survival after MI in NF1; 2) Blood lipids should be screened for routinely and treated according national guidelines; 3) Monitoring for sleep apnea is needed when symptoms or risk factors

are present, including consultation of respiratory physician if sleep apnea is suspected. Importantly, fast assessment is needed if chest pain or other warning signs of coronary artery disease appear.

6.8 Future directions

Three areas require attention: 1) prospective NF1-specific GI pathways that prioritize small intestine imaging and careful follow-up after resection; 2) age-tailored hypertension algorithms that couple essential hypertension management with streamlined screening for renovascular disease and pheochromocytoma in younger patients with NF1; and 3) cardiovascular risk programs that integrate lipid management and sleep apnea assessment, and evaluate whether intensified secondary prevention can close the survival gap after MI. Mechanistic work on neurofibromin regulated vascular biology may help identify new therapies.

To conclude, NF1 is associated with distinctive, clinically consequential risks across the gastrointestinal and cardiovascular systems. GISTs in small intestine are common and sometimes lethal; essential hypertension is the dominant type of hypertension despite a meaningful burden of secondary hypertension in the young; and MI outcomes may be worse compared to general population. These findings highlight the need for proactive care that takes NF1 into account, involving different medical specialties to detect comorbidities early, provide personalized follow-up, and help prevent avoidable deaths.

7 Conclusions

Based on the results of the present study the following conclusions were made:

1. Careful evaluation and monitoring of gastrointestinal (GI) symptoms in patients with NF1 are essential for early diagnosis and treatment. Diagnosing NF1-associated GIST is challenging because the tumors typically arise intramurally in small intestine, which is not reliably accessible with conventional endoscopy. NF1-related GISTs may behave unpredictably and can be fatal.
2. NF1 may be associated with an increased risk of hypertension, encompassing both essential and secondary forms.
3. NF1 is associated with an increased hazard of myocardial infarction. Furthermore, survival after myocardial infarction may be poorer in individuals with NF1 than in controls. The results also showed that these findings were not explained by prior cancers.
4. Clinical recommendations for NF1 monitoring: application of early small-intestine–capable imaging for GI alarm symptoms; routine blood pressure measurements with selective evaluation for renovascular disease and pheochromocytoma, and systematic lipid management and sleep apnea assessment to narrow the post-MI survival gap.

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