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ARTICLE

Risk and prognosis of myocardial infarction in patients with neurofibromatosis type 1: Evidence of compromised survival

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ABSTRACT

Purpose: To analyze the risk and prognosis of myocardial infarction in patients with neurofibromatosis type 1 (NF1) in a Finnish population-based cohort from 1987 to 2021.

Methods: A cohort of 1811 individuals with confirmed NF1 was compared with a control cohort of 18,006 individuals who were matched for sex, date of birth, and municipality. Diagnoses of myocardial infarction and potentially associated risk factors were retrieved from the Finnish Care Register for Health Care and the Causes of Death Register over the years 1987 to 2021.

Results: We observed 42 individuals with NF1 (19 women and 23 men) with myocardial infarction. The hazard ratio (HR) for all was 1.36 (95% CI 0.98-1.88); for women 1.58 (95% CI 0.97-2.57), and for men 1.24 (95% CI 0.81-1.91). The diagnoses preceding myocardial infarction in patients with NF1 did not differ from controls. Disease-specific 5-year survival after hospital admission for myocardial infarction was 69.2% (95% CI 54.8-87.6) in patients with NF1 and 85.0% (95% CI 81.0-89.2) in controls, corresponding to a significantly worse prognosis in the NF1 group (HR 2.22, 95% CI 1.16-4.24). NF1-related cancers and sleep apnea often occurred in association with deaths caused by myocardial infarction.

Conclusion: NF1 appears to be frequently associated with myocardial infarction and a subsequent significantly poor survival.

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Introduction

Neurofibromatosis type 1 (NF1; OMIM #162200) is an autosomal dominant condition whose characteristic manifestations affect the skin, nervous system, and bones. This neurocutaneous syndrome predisposes patients also to benign and malignant tumors of the nervous system as well as other cancers. Its clinical diagnostic features include café-au-lait macules, axillary and inguinal freckling, dermal and plexiform neurofibromas, skeletal dysplasia, iris Lisch nodules, and optic gliomas.[1,2] We have previously reported a birth incidence of approximately 1:2000 for NF1 in Finland.[3] NF1 causes excess mortality at all ages and, consequently, its prevalence decreases in older age groups. The estimates of the average prevalence of NF1 have ranged from 1:4500 to 1:2000.[4-6]

Our previous work documented increased mortality due to circulatory system diseases in patients with NF1, although a detailed analysis was not performed.[3] More recently, we demonstrated that diseases of the circulatory system also contribute significantly to incapacity for work among adults with NF1.[7] Although case reports have described myocardial infarctions related to coronary artery aneurysms[8] and pheochromocytomas[9] in NF1, epidemiologic data on the incidence of myocardial infarction in this group are scarce.[10] Vascular complications in NF1 include renal artery stenosis and cerebral Moya-Moya vascular malformation.[11] Furthermore, vasculopathy involving tunica intima has been described in certain NF1-related lesions.[12] This is plausible given that neurofibromin—the protein encoded by the *NF1* gene—is expressed in vascular endothelial and smooth muscle cells.[12,13] Neurofibromin normally accelerates the conversion of active Ras-GTP to inactive Ras-GDP; pathogenic *NF1* variants lead to upregulation of Ras signaling pathway.[14] However, these vascular complications, which mostly affect younger patients, are unlikely to account for the excess cardiovascular morbidity and mortality observed in NF1.

Atherosclerosis is the primary mechanism underlying ischemic coronary heart disease. Traditional risk factors include dyslipidemia, a family history of heart disease, smoking, hypertension, diabetes mellitus, and physical inactivity.[15] Additionally, low socioeconomic status,[16] chronic kidney disease,[17] and obstructive sleep apnea[18] are linked to increased risk for coronary heart disease. Notably, obstructive sleep apnea affects as many as 38% to 65% of patients with coronary heart disease[19] and has been associated with the onset of myocardial infarction during the night or early morning.[18] Cardiovascular diseases (ICD-10 I00-I99) are the leading cause of death in Finland, accounting for 31.0% of deaths in 2022. Specifically, myocardial infarction (ICD-10 I21-I22) was the underlying cause in 10.3% of these deaths.[20]

In this study, we hypothesized that individuals with NF1 have an increased risk of coronary heart disease and myocardial infarction and that NF1 is associated with poor survival after myocardial infarction. To investigate these hypotheses, we conducted a retrospective cohort study using health register data from 1811 Finnish patients with NF1 and a 10-fold matched control cohort.

Materials and Methods

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. 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, Statistics Finland, and all participating hospitals.

The Finnish NF1 cohort was initially collected by searching all NF1-related hospital visits in Finnish central and university hospitals[3] and recently updated to cover an ascertainment period of 1987 to 2020 (unpublished data). The medical records of the patients were reviewed to confirm NF1 diagnoses according to the National Institutes of Health diagnostic criteria.[1,2] For each of the 1811 individuals with NF1, 10 control persons matched for age, sex, and municipality of residence at the time of cohort entry were retrieved from the Finnish Population Register, yielding a control cohort of 18,006 individuals.

We tracked the occurrence of myocardial infarctions and prior morbidity using data from the Finnish Care Register for Health Care, which is overseen by the Finnish Institute for Health and Welfare, and the Causes of Death Register maintained by Statistics Finland. The Finnish Care Register for Health Care compiles detailed records of inpatient care and hospital-based outpatient visits. Dates of birth, emigration and death were obtained from the Finnish Population Register. Data on reimbursed drug purchases were from the Finnish Social Insurance Institution, and information on cancers was from the Finnish Cancer Registry. The highest educational level observed after age 30 was retrieved from Statistics Finland. Hospital visits and deaths related to myocardial infarctions were identified using the International Classification of Diseases 10th revision (ICD-10) diagnosis codes I21 (acute myocardial infarction) and I22 (subsequent myocardial infarction) along with the corresponding ICD-9 code 410. The ICD-9 was used for the years 1987 to 1995 and ICD-10 for the years 1996 to 2021.

Two primary endpoints were studied: (1) a death or hospital visit related to a myocardial infarction and (2) a death with myocardial infarction recorded as the primary or underlying cause of death. The first endpoint aimed to catch all myocardial infarctions in the cohorts, whereas the second endpoint focused on mortality due to myocardial infarctions. Individuals with NF1 were followed up for myocardial infarctions starting at their cohort entry, ie, the first NF1-related hospital visit in 1987 to 2020. The follow-up of the matched controls started at the cohort entry of the respective individual with NF1. The follow-up ended at an event of interest, emigration, death due to other causes, or the end of the study period on December 31st, 2021, whichever occurred first. Age was used as the time scale when the cumulative risk for myocardial infarction was computed using the Nelson-Aalen method. Noninfarction death was included as a competing risk. Age was the time scale also in the estimation of hazard ratios (HRs) comparing NF1 with controls. The HRs were estimated using Cox proportional hazards models. Because of the potential heterogeneity across the matching groups, the Cox models included a frailty term for each stratum of an individual with NF1 and the respective controls.

Disease-specific survival after hospital admission for myocardial infarction was also estimated. The follow-up began at the first hospital record related to myocardial infarction during the study period, and only deaths with myocardial infarction as the primary or underlying cause of death were considered as events. Time since the first hospital admission related to myocardial infarction was used as the time scale in Kaplan-Meier estimation and Cox proportional hazards models related to the survival analyses.

Among those who had an event of interest, the prevalence of potentially related diagnoses and pharmacotherapies were compared between the NF1 and control groups using Fisher's exact test. As a sensitivity analysis, we stratified individuals with NF1 and controls by their age (<50 and ≥50 years), history of cancer and highest educational level after age 30. All analyses were carried out using the R software, version 3.6.2, and package survival, version 3.2-7.

Results

A total of 1811 individuals with confirmed NF1 and 18,006 matched controls were analyzed (Figure 1). We identified 42 patients with NF1 and 415 control patients with myocardial infarction, yielding a HR of 1.36 (95% CI 0.98-1.88; $P = .062$) for individuals with NF1 compared with controls (Table 1). Those with myocardial infarction included 19 NF1 women and 175 control women (HR 1.58, 95% CI 0.97-2.57; $P = .068$) and 23 NF1 men and 240 control men (HR 1.24, 95% CI 0.81-1.91; $P = .319$). There was no statistically significant difference in the HRs for myocardial infarction between men and women ($P = .635$). The mean age at the first myocardial infarction was 66.2 years (SD 12.8) in patients with NF1 and 69.7 years (SD 12.5) in controls. The cumulative risk for myocardial infarction by age 50 was 0.8% (95% CI 0.3%-2.1%) in the NF1 cohort and 0.6% (95% CI 0.4%-0.9%) in controls when accounting for the competing risk of noninfarction death, increasing to 10.4% (95% CI 7.6%-14.3%) and 11.7% (95% CI 10.5%-13.0%), respectively, by age 80. Notably, a 50-year-old individual with NF1 had a 2.5% (95% CI 1.3%-4.7%) 10-year risk for myocardial infarction, whereas the corresponding risk was 1.5% (95% CI 1.1%-1.9%) in controls.

The prevalence of major risk factors—such as hypertension and disorders of lipoprotein metabolism—did not differ significantly between patients with NF1 and controls before hospital admission or death related to myocardial infarction (Table 2). To understand the lipoprotein disorders in NF1 overall, we analyzed their hazard in the full NF1 cohort. Interestingly, despite the lack of difference in those with myocardial infarction, the full NF1 cohort displayed increased hazards for purchases of lipid-modifying agents (300 individuals with NF1 and 2902 controls; HR 1.33, 95% CI 1.18-1.51, $P < .001$) and for diagnoses of lipoprotein metabolism disorder (74 individuals with NF1 and 696 controls; HR 1.34, 95% CI 1.05–1.71, $P = .017$)

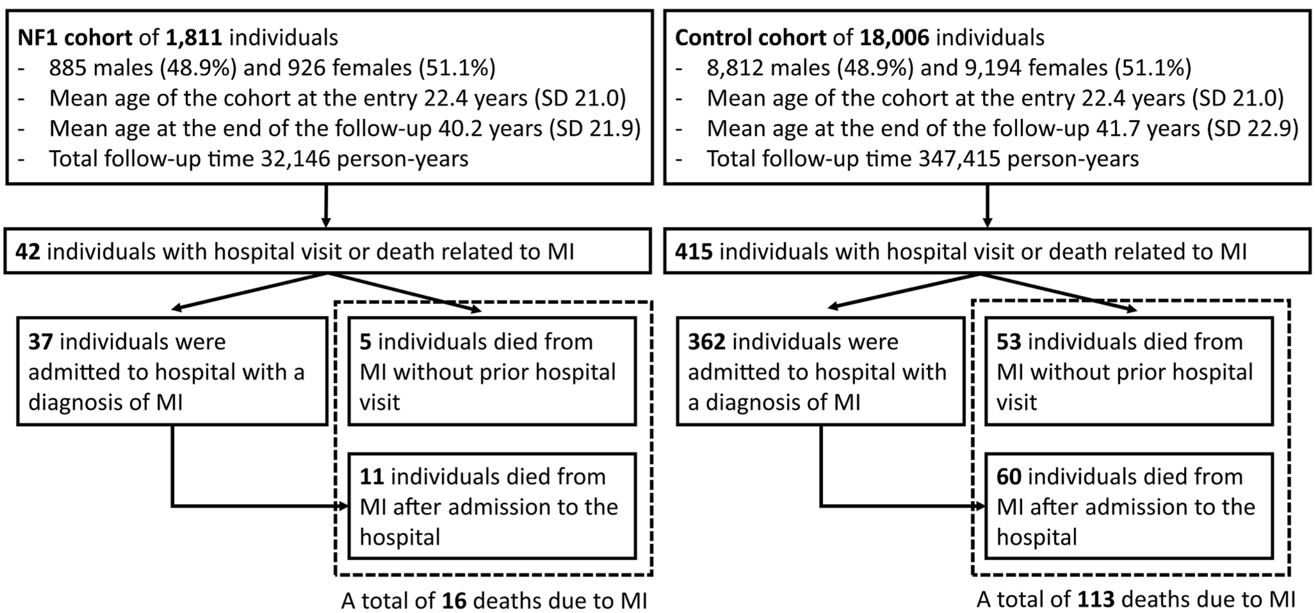

Figure 1 **Frequencies of myocardial infarction (MI) in the NF1 cohort and the matched control cohort.**

Table 1 Hospital visit or death related to myocardial infarction in individuals with NF1 and controls

		NF1			Control			
Event of interest	Subgroup	*n* at Risk	*n*, Events	Age, Mean (SD)	*n* at Risk	*n*, Events	Age, Mean (SD)	HR (95% CI), *P*
Hospital visit or death related to myocardial infarction	All patients	1811	42	66.2 (12.8)	18,006	415	69.6 (12.4)	1.36 (0.98 to 1.88), 0.062
	Sex							
	Women	926	19	70.6 (8.1)	9194	175	73.2 (12.4)	1.58 (0.97 to 2.57), 0.068
	Men	885	23	62.5 (14.9)	8812	240	67.0 (11.8)	1.24 (0.81 to 1.91), 0.319
	Age							
	<50 years	1561	4	41.2 (7.4)	15,519	29	43.6 (4.6)	1.51 (0.53 to 4.28), 0.443
	≥50 years	631	38	68.8 (10.2)	6577	390	71.4 (10.6)	1.33 (0.95 to 1.86), 0.100
	History of cancer[a]							
	No history of cancer	1685	32	65.1 (13.9)	17,801	372	68.9 (12.5)	1.35 (0.94 to 1.94), 0.108
	History of cancer	398	10	69.8 (8.4)	1170	51	76.4 (8.9)	1.45 (0.71 to 2.98), 0.312
	Educational level[b]							
	ISCED ≤4	848	36	66.6 (12.5)	6858	303	69.1 (12.7)	1.44 (1.01 to 2.04), 0.044
	ISCED ≥5	197	3	56.9 (20.8)	4160	62	67.7 (12.4)	1.10 (0.33 to 3.72), 0.874
Death due to myocardial infarction	All patients	1811	16	68.7 (13.2)	18,006	113	74.1 (12.4)	2.18 (1.29 to 3.70), 0.004
	Sex							
	Women	926	6	76.5 (2.7)	9194	48	77.8 (10.8)	2.20 (0.93 to 5.18), 0.072
	Men	885	10	64.0 (14.8)	8812	65	71.4 (12.8)	2.15 (1.10 to 4.20), 0.024
	History of cancer[a]							
	No history of cancer	1685	10	67.3 (16.2)	17,801	96	73.0 (12.9)	1.83 (0.95 to 3.52), 0.072
	History of cancer	398	6	71.0 (6.0)	1170	17	80.3 (6.2)	3.21 (1.24 to 8.26), 0.016

CI, confidence interval; *HR*, hazard ratio; *ISCED*, International Standard Classification of Education; *SD*, standard deviation.

[a]For the group without history of cancer, the follow-up was censored at the diagnosis of the first cancer. For the group with history of cancer, the follow-up started at the latter of cohort entry or the diagnosis of the first cancer. Therefore, a single individual could contribute follow-up time to both groups.

[b]Educational level defined as the highest education observed after 30 years of age. The follow-up started at the latter of cohort entry or the 30th birthday.

compared with the full control cohort. As expected, patients with NF1 and hospital admission or death related to myocardial infarction more frequently had a history of cancer preceding the infarction than controls with myocardial infarction. Importantly, the point estimate of the HR for myocardial infarction was essentially unaffected by history of cancer (Table 1). After myocardial infarction, pharmacotherapy for coronary heart disease was similar between the 2 groups. Five patients with NF1 and 53 control patients died with myocardial infarction recorded as the underlying or immediate cause of death, although they had no prior hospital visit related to myocardial infarction.

Survival after myocardial infarction was evaluated in the 37 patients with NF1 who had been admitted to hospital with a myocardial infarction diagnosis (Figure 1). Disease-specific 5-year survival for patients with NF1 was 69.2% (95% CI 54.8%-87.6%) and 10-year survival was 62.9% (95% CI 46.6%-85.0%). In contrast, the corresponding survival probabilities for controls were 85.0% (95% CI 81.0%-89.2%) at 5 years and 80.9% (95% CI 76.0%-86.1%) at 10 years. Disease-specific survival after hospital admission for myocardial infarction was significantly worse in patients with NF1 compared with controls (HR 2.22, 95% CI 1.16-4.24; $P = .016$) (Figure 2). The exclusion of individuals with a history of cancer had essentially no effect on the survival comparison (HR 2.16, 95% CI 1.02-4.56, $P = .046$).

Within the overall NF1 cohort of 1811 individuals, myocardial infarction was listed as the primary or underlying cause of death in 16 individuals (Figure 1), which is consistent with the observed poor survival after hospital admission for myocardial infarction. The HR for death due to myocardial infarction was 2.18 (95% CI 1.29-3.70; $P = .004$) compared with matched controls over the period 1987 to 2021. The mean age at death due to myocardial infarction was 68.7 years (SD 13.2) among patients with NF1 and 74.1 years (SD 12.4) among controls. Sex did not modify the effect of NF1 on the hazard for death due to myocardial infarction (Table 1). Furthermore, the prevalence of hypertension and heart failure before myocardial infarction did not significantly differ between patients with NF1 and controls, although sleep apnea was significantly more common among patients with NF1 (OR 6.14) (Table 3). The effect of NF1 on the hazard for death due to myocardial infarction was more pronounced in those with a history of cancer compared with those without (Table 1).

Discussion

Our retrospective register-based analysis of hospital visits for myocardial infarction in the Finnish cohort of 1811 patients with NF1 demonstrated a HR of 1.36 for myocardial infarction and 2.18 for death due to myocardial

Table 2 Factors potentially associated with the risk for myocardial infarction among patients with NF1 and myocardial infarction and the controls before the first infarction-related encounter (hospital admission or death related to myocardial infarction)

Associated Factor	Search Criteria	Patients With NF1 (42) *n* (%)	Controls (415) *n* (%)	OR (95% CI), *P*
Hospital-based diagnoses				
Hypertension	ICD-10: I10-I15, ICD-9: 401-405	12 (28.6)	134 (32.3)	0.84 (0.38 to 1.75), 0.729
Angina pectoris	ICD-10: I20, ICD-9: 413	6 (14.3)	85 (20.5)	0.65 (0.22 to 1.62), 0.420
Heart failure	ICD-10: I50, ICD-9: 428	4 (9.5)	45 (10.8)	0.87 (0.21 to 2.57), 1.000
Disorders of lipoprotein metabolism	ICD-10: E78, ICD-9: 272	5 (11.9)	41 (9.9)	1.23 (0.36 to 3.39), 0.597
Sleep apnea	ICD-10: G47.3, ICD-9: 3472A	3 (7.1)	21 (5.1)	1.44 (0.26 to 5.16), 0.475
Cancers				
Cancer	Cancers included in the Finnish cancer statistics[a]	10 (23.8)	43 (10.4)	2.70 (1.10 to 6.12), 0.019
Drug purchases				
Organic nitrates	ATC: C01DA	12 (28.6)	155 (37.3)	0.67 (0.30 to 1.40), 0.314
Beta blocking agents	ATC: C07	20 (47.6)	211 (50.8)	0.88 (0.44 to 1.75), 0.747
Calcium channel blockers and agents acting on the renin-angiotensin system	ATC: C08, C09	20 (47.6)	241 (58.1)	0.66 (0.33 to 1.31), 0.196
Lipid-modifying agents	ATC: C10	15 (35.7)	167 (40.2)	0.83 (0.40 to 1.66), 0.622

ATC, Anatomical Therapeutic Chemical Classification; *CI*, confidence interval; *ICD-9*, International Standard Classification of Diseases, 9th revision; *ICD-10*, International Standard Classification of Diseases, 10th revision; *OR*, Odds Ratio.

[a]Leinonen et al, 2017.[39]

infarction in individuals with NF1 compared with matched controls. Patients with NF1 had significantly worse disease-specific survival after hospital admission for myocardial infarction compared with the controls. The results are concordant with our previous report of increased cardiovascular mortality in NF1.[3] Thus, NF1 seems to be associated with an increased risk of death due to myocardial infarction.

The average age at the first myocardial infarction-related encounter was slightly younger in patients with NF1 than in controls. The pharmacotherapy for coronary heart disease initiated after myocardial infarction was similar between the 2 groups. These results indicate that the age and pharmacotherapy do not explain the poor prognosis of patients with NF1. Although hypertension, angina pectoris, and heart failure are associated with myocardial infarction, these diagnoses were less prevalent in patients with NF1 than in controls before myocardial infarction, even if not statistically significantly (Table 2). This disparity may reflect either the true absence or the underdiagnosis of predisposing diseases and warning signs, such as chest pain. Notably, also purchases of lipid-modifying agents were nonsignificantly less prevalent among individuals with NF1 and myocardial infarction, although NF1 was associated with increased hazards for purchases of these drugs and for diagnoses of disorders of lipoprotein metabolism in the overall cohort. This suggests that individuals with NF1 and myocardial infarction may have had undiagnosed hypercholesterolemia, and individuals with NF1 could benefit from improved surveillance for disorders of lipoprotein metabolism. Future studies should investigate the

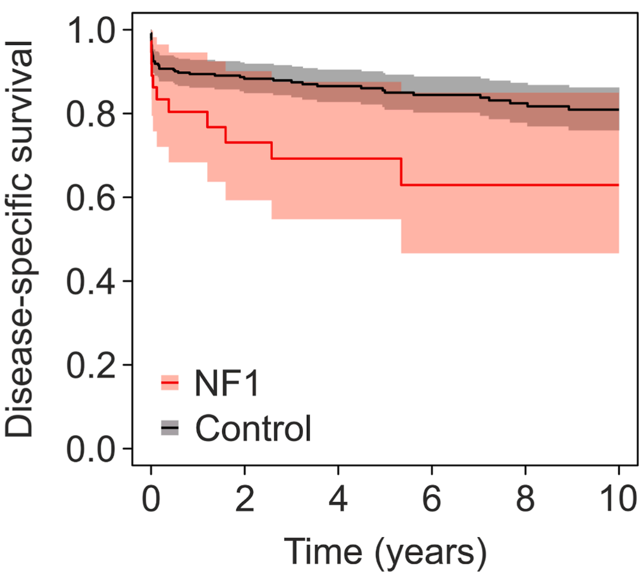

Figure 2 Disease-specific survival of patients with NF1 and control patients after hospital admission for myocardial infarction. The shaded areas show the 95% confidence intervals of the Kaplan-Meier estimates.

Table 3 Profile of patients with NF1 and the controls who had a record of myocardial infarction (I21, I22, and 410) as the primary or underlying cause of death

Associated Factor	Search Criteria	Patients With NF1 (16) *n* (%)	Controls (113) *n* (%)	OR (95% CI), *P*
Hospital-based diagnoses				
Hypertension	ICD-10: I10-I15, ICD-9: 401-405	6 (37.5)	48 (42.5)	0.81 (0.23 to 2.67), 0.791
Ischemic heart disease	ICD-10: I20-I25 ICD-9: 410-414,4292A, 4295A, 4296A	12 (75.0)	83 (73.5)	1.08 (0.30 to 4.97), 1.000
Heart failure	ICD-10: I50, ICD-9: 428	4 (25.0)	40 (35.4)	0.61 (0.13 to 2.19), 0.575
Sleep apnea	ICD-10: G47.3, ICD-9: 3472A	3 (18.8)	4 (3.5)	6.14 (0.81 to 40.94), 0.041
Cancers				
Cancer	Cancers included in the Finnish cancer statistics[a]	6 (37.5)	17 (15.0)	3.35 (0.88 to 11.86), 0.039
Drug purchases				
Organic nitrates	ATC: C01DA	8 (50.0)	62 (54.9)	0.82 (0.25 to 2.71), 0.792
Beta blocking agents	ATC: C07	10 (62.5)	79 (69.9)	0.72 (0.22 to 2.61), 0.571
Calcium channel blockers and agents acting on the renin-angiotensin system	ATC: C08, C09	10 (62.5)	78 (69.0)	0.75 (0.23 to 2.72), 0.580
Lipid-modifying agents	ATC: C10	6 (37.5)	51 (45.1)	0.73 (0.20 to 2.40), 0.603

The table in based on the Finnish NF1 cohort of 1811 individuals, and a control cohort of 18,006 individuals followed up over the years 1987 to 2021. *ATC*, Anatomical Therapeutic Chemical Classification; *CI*, confidence interval; *ICD-9*, International Standard Classification of Diseases, 9th revision; *ICD-10*, International Standard Classification of Diseases, 10th revision; *OR*, odds ratio.

[a]Leinonen et al, 2017.[39]

underlying factors contributing to the poor prognosis in patients with NF1 and myocardial infarction.

Individuals with NF1 had a history of a prior cancer before experiencing myocardial infarction more often compared with the control group. Cancer itself and cancer treatments may increase the risk for cardiovascular events via several mechanisms.[21] Cancer and myocardial infarction have shared underlying risk factors and pathophysiological pathways such as chronic inflammation. Cancer therapies may be prothrombotic and cause thrombosis of coronary arteries.[21] The exclusion of individuals with a history of cancer had little effect on the point estimates for new myocardial infarctions. However, the comparison between patients with NF1 and controls yielded a particularly elevated HR point estimate for death due to myocardial infarction among those with a prior history of cancer. The disease-specific survival after hospital admission for myocardial infarction was worse in the patients with NF1 than in the controls also after the exclusion of those with a prior cancer. Therefore, the HRs for myocardial infarctions are not explained by the high rate of cancer in the NF1 cohort; yet, a history of cancer may further increase the NF1-related hazard for death due to myocardial infarction. However, the stratified analysis only included a rather small number of individuals who died of myocardial infarction, and the result needs confirmation in future studies.

Individuals with NF1 display lower average educational attainment and income,[22,23] which may contribute to lifestyle factors associated with the risk and poor prognosis of myocardial infarction. Studies from the United States, Finland, and Italy have shown that low income and low education contribute to the risk of myocardial infarction.[24,25] Educational level may affect access and utilization of health resources because those with lower education may not be aware of potentially severe disease symptoms or available health care services.[26,27] Unemployment likely decreases the access to preventive cardiovascular care, such as the regular health controls and screenings accessible through occupational health care or insurance coverage. Furthermore, lower income may limit the use of private health care services. Although the number of individuals with NF1 and high educational attainment was very limited in this study, the estimates suggested that higher education may be protective against myocardial infarction also in the context of NF1 (Table 1). Nevertheless, in our recent analysis of hypertension in patients with NF1, educational level did not significantly modify the risk for hypertension.[28]

Sleep apnea was diagnosed in 3 out of 42 individuals with NF1 before their first infarction-related hospital encounter. Notably, all these 3 individuals with sleep apnea preceding myocardial infarction died during the follow-up, and the prevalence of sleep apnea in 3 of 16 patients with

NF1 who died from myocardial infarction was significantly higher than in the control group. This observation highlights the need to monitor the risk for myocardial death in patients with NF1 and sleep apnea and promote a healthy lifestyle. Sleep apnea may be related to the craniofacial characteristics typical of NF1, which include short maxilla, mandible, and cranial base,[29] and which are reflected in the increased hazard for dentofacial anomalies, such as retrognathism in individuals with NF1.[30] In addition, muscle weakness and hypotonia associated with NF1[31,32] may also contribute to sleep apnea by compromising the tonus in the muscles of the upper airways.

Studies in murine models have shown that neurofibromin deficiency can lead to both cardiovascular and muscular dysfunction: cardiomyocyte-specific loss of neurofibromin promotes cardiac hypertrophy and dysfunction,[33] whereas the absence of neurofibromin in vascular smooth muscle and myeloid cells contributes to abnormal proliferative responses.[34,35] These findings highlight the critical role of neurofibromin in maintaining cardiac structure and vascular integrity through Ras-dependent pathways.[33-35] These biological mechanisms may contribute to the pathogenesis and prognosis of myocardial infarction in NF1. Given that NF1 is characterized by hyperactivation of the Ras pathway, future studies should evaluate whether cardiovascular therapies that downregulate Ras signaling, such as statins, may help mitigate cardiovascular risks in individuals with NF1.

The limitations of this study include small numbers of patients with myocardial infarction and specific comorbidities, such as sleep apnea or previous cancer. Moreover, we had no information on smoking or biomarkers of cardiovascular risk factors, such as cholesterol profiles or high-sensitivity CRP.[36,37] Furthermore, the register data used in this study only cover inpatient care and specialized outpatient care. Because diagnoses from primary health care were not accessible to us, diagnoses preceding myocardial infarction may actually be more common than observed. Moreover, the Finnish NF1 cohort is hospital-based and patients with NF1 may therefore show increased likelihood of hospital-based diagnoses for diseases that can be treated in either primary or specialized health care compared with the controls. There may thus be a bias toward an apparently higher rate of diagnoses for risk factors of infarction in the patients with NF1 than in the control patients, which may partly conceal the underdiagnosis of infarction-predisposing diseases in NF1. However, such bias is unlikely to affect our main results because patients with myocardial infarction are always treated in hospital.

A major strength of this study is the verification of the diagnoses in the Finnish NF1 cohort by individually reviewing medical records to meet the National Institutes of Health diagnostic criteria for NF1. The recently updated Finnish NF1 cohort of 1811 individuals has been followed up over the years 1987 to 2021 and provides a long observation period that is particularly suitable for studying diseases prevalent in older populations. Furthermore, the diagnosis of myocardial infarction is highly reliable and well documented in hospitals, and treatment practices for myocardial infarction are consistent throughout Finland.

Several models have been developed to estimate the risk for coronary heart disease and stroke. For the Finnish population, the FINRISK calculator predicts the 10-year risk for coronary heart disease, stroke, or both and is widely used in clinical practice.[38] For instance, tobacco smoking as a sole risk factor confers a 2.04% 10-year risk for coronary heart disease in 50-year-old males in the Finnish population.[38] In our study, NF1 was associated with a 2.5% 10-year risk for myocardial infarction at age 50, suggesting that NF1 is a major risk factor for myocardial infarction. These findings emphasize that clinicians should be aware of the poor prognosis in patients with NF1 and myocardial infarction. The NF1-related tumors and other characteristic manifestations may understandably occupy much of the follow-up appointment of an individual with NF1, yet the issues discussed in general population health surveillance also need to be considered. Although there are no international follow-up recommendations for atherosclerosis in individuals with NF1, physicians should actively inform patients about NF1-associated comorbidities and their symptoms, encourage healthy lifestyle and pay attention to the early detection and treatment of coronary heart disease symptoms and risk factors in this population.

Data Availability

The sensitive personal data used in this study are controlled by third parties and cannot be shared by the authors. Please contact the Finnish Social and Health Data Permit Authority Findata and Statistics Finland for more information and permissions.

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Author Contributions

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Ethics Declaration

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (66/180/2012) and had research permissions from Finnish Social and Health Data Permit Authority Findata, Ministry of Social Affairs and Health, the Finnish Institute for Health and Welfare, Statistics Finland, and all participating hospitals. The study is register-based and retrospective and therefore exempt from obtaining informed consent from the participants.

Conflict of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT for grammatical proofreading. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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