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A rare disease and education: Neurofibromatosis type 1 decreases educational attainment

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Abstract

Rare heritable syndromes may affect educational attainment. Here, we study education in neurofibromatosis 1 (NF1) that is associated with multifaceted medical, social and cognitive consequences. Educational attainment in the Finnish population-based cohort of 1408 individuals with verified NF1 was compared with matched controls using Cox proportional hazards model with delayed entry and competing risk for death. Moreover, models accounting for the effects of cancer at age 15–30 years, parental NF1 and developmental disorders were constructed. Overall, the attainment of secondary education was reduced in individuals with NF1 compared to controls (hazard ratio 0.83, 95%CI 0.74–0.92). History of cancer and developmental disorders were major predictors of lack of secondary education. Individuals with NF1 obtained vocational secondary education more often than general upper secondary education. Consequently, NF1 decreased the attainment of Bachelor's and Master's degrees by 46%–49% and 64%–74%, respectively. Surprisingly, the non-NF1 siblings of individuals with NF1 also had lower educational attainment than controls, irrespective of parental NF1. In conclusion, NF1 is associated with reduced educational attainment and tendency for affected individuals to obtain vocational instead of academic education. Individuals living with NF1, especially those with cancer, developmental disorders or familial NF1, need effective student counseling and learning assistance.

KEYWORDS
educational attainment, multiorgan syndrome, neurofibromatosis 1, rare disease, school performance

1 | INTRODUCTION

Educational achievement in neurofibromatosis type 1 (NF1; OMIM 162200) is compromised[1,2] but the processes affecting the schooling

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of individuals with NF1 are incompletely known. Specifically, the choice of educational field has not been studied and the contribution of cognitive impairment is not fully understood. Also in general, little is known about how rare heritable syndromes affect educational attainment. These syndromes may be associated with cognitive deficits affecting academic skills, yet also the morbidity associated with syndromes, especially those with multi-organ involvement, can cause disruption of studies. Education is known to be associated with better health, and the relationship may be causal because higher educational attainment leads to better health literacy, healthier lifestyle and higher income level.[3,4] Therefore, it is important to better understand the consequences of rare syndromes on educational attainment in order to provide affected individuals with effective support. Most research on rare diseases has focused on medical aspects of the diseases, however these syndromes affect multiple domains of life and understanding their impact is advantageous for optimal care.

NF1 is one of the most common inherited syndromes with an incidence as high as 1/2000 and prevalence of 1/3000.[5,6] NF1 provides sufficient number of individuals to explore how a rare disorder affects the individual's education. NF1 is caused by pathogenic variants of the *NF1* gene which is located in chromosome 17q11.2. NF1 has an autosomal dominant inheritance, but about 50% of the affected individuals have a sporadic disease which causes challenges for early diagnosis. NF1 is a multisystem disorder with very variable presentation between individuals even within the same family. In addition to benign skin manifestations, NF1 typically causes neurofibromas of larger nerves, called plexiform neurofibromas, which occur in 20–50% of individuals.[7]

NF1 is a tumor predisposition syndrome with an increased risk of cancers, especially those originating from central and peripheral nervous systems. The incidence of brain tumors such as gliomas of the optic pathway and other parts of the brain in children with NF1 is over 100 times higher compared to the general population.[8] Complicated plexiform neurofibromas can cause substantial morbidity in childhood and adolescence. Although benign, plexiform neurofibromas are most often inoperable and may cause chronic pain which interferes with daily functions and the quality of life.[9] Pain is also associated with symptoms of depression and anxiety. Plexiform neurofibromas may progress to malignant peripheral nerve sheath tumors (MPNSTs) that are associated with high mortality. MPNSTs start to occur in puberty and cause a marked increase in the cancer risk of individuals aged 20–30 years.[10]

Increasing attention has recently been paid to neurodevelopmental problems in NF1, which have been suggested to affect education and employment of individuals with NF1.[11] Cognitive and behavioral disorders may affect as many as 80% of children, and they are among the most important NF1 manifestations during school age.[12,13] These manifestations include impairments in general cognition, reduced intellectual abilities, impaired visuospatial processing and motor delays.[12,14] Deficits in executive functioning seem to be a core feature of NF1.[15] Various problems in speech are common in children with NF1,[16] which can create obstacles in communication at school. Learning disabilities in reading, writing and mathematics have been reported in about 50% of children.[1] Furthermore, academic achievements may be undermined by attention-deficit–hyperactivity disorder (ADHD), difficulties in social functioning associated with autism spectrum disorder (ASD), and elevated rates of mood and anxiety disorders. Symptoms of ADHD can persist in adolescence and adulthood.[17] Also in adulthood, the IQ of individuals with NF1 remains lower than in the general population.[18,19] In addition to the impact of the lower mean IQ, adults with NF1 experience problems in visual–spatial skills and auditory long-term memory.[19] Challenges at school are therefore caused by a mixture of deficits in academic and executive functioning and problems in social behavior. In addition to cognitive abilities, there are factors that can affect the school performance and final educational attainment, such as morbidity, tumor-related symptoms and their treatment, as well as educational level and socioeconomic status of the parents and urban or rural area of residence.[20]

Educational performance and academic achievements of individuals with NF1 have previously been studied in single centers.[1,13] The results showed that only 10% of the children with NF1 had no school-functioning problems.[13] Thus, NF1 has profound impact on school performance. A recent Danish population-based register study showed that individuals with NF1 had shorter education than the control cohort and graduated from the 9 years of basic education later than the control group without NF1.[2] However, the NF1 diagnoses of the individuals included in the Danish study were not verified, and educational attainment was only studied at the age of 30 years.

In the present study, we have used the Finnish population-based NF1 cohort and nationwide registers to analyze the educational attainment of 1408 individuals with verified NF1 as compared to their siblings without NF1 and control population. The effects of cancer and cognitive impairment were specifically elucidated, and the choice between academic and vocational educational paths was examined.

2 | METHODS

The study material consisted of three groups: individuals with NF1 (group 1) were compared with matched controls (group 2) and with siblings without NF1 (group 3). The individuals included in the study had to be alive at the end of at least one calendar year during the study period 1987–2016. Individuals who had emigrated from Finland before the start of patient ascertainment in 1987 were excluded.

1. Individuals with NF1 were identified by searching the five University Hospitals and 15 Central Hospitals of mainland Finland for NF1-associated hospital visits 1987–2011 as previously described.[5] The medical records of each individual were retrieved and reviewed to identify individuals who fulfilled the National Institutes of Health (NIH) diagnostic criteria for NF1 for inclusion in the study, which yielded a total of 1408 individuals with NF1. The group included 83 sibling pairs, 19 trios and three families with more than three siblings affected by NF1.
2. For each individual with NF1, ten control individuals were retrieved from the Finnish Population Register Centre. The

controls were matched by age, sex and municipality on the cohort entry date of the respective individual with NF1. First-degree relatives of individuals with NF1 were excluded from the control cohort. Because of the small size of some municipalities, the final number of individuals in the control cohort was 14 012. This control cohort was designed to reduce biases related to calendar time, age and sex.

3. The siblings of individuals with NF1 were retrieved using information from the Finnish Population Register Centre. Siblings were required to have at least one shared parent with an individual with NF1 (group 1). Siblings with confirmed or suspected NF1 (symptoms suggestive of NF1 without fulfilling the NIH diagnostic criteria) were excluded. The final number of siblings without NF1 was 2042 from 904 families. Fifty-seven percent of the non-NF1 siblings were older than their NF1 probands. Although undiagnosed NF1 is possible in this group, to the best of our knowledge these people are not affected by NF1. The sibling cohort allows for the exclusion of the effects of genes other than *NF1* as well as biases related to the socioeconomic status of the family.

Educational attainment, that is, the highest level of education completed, was examined as the primary outcome. In Finland, all children undergo compulsory basic education that typically lasts 9 years during ages 7–16 years (International Standard Classification of Education, ISCED 1–2). The basic education is followed by 3–4 years of voluntary secondary education (ISCED 3). The secondary education may either be general upper secondary education leading to matriculation examination which is typically for preparing the students for further academic studies, or alternatively vocational education. Secondary education is a prerequisite for higher education consisting of bachelor's (3–4 years, ISCED 6) and master's (1–2 years, ISCED 7) degrees. These main components of the Finnish education system have remained essentially the same throughout the study period 1987–2016. Using the Finnish personal identity code as a key, the information on educational attainment was retrieved from Statistics Finland, which collects the information from schools, universities and other organizers of education.

All analyses were adjusted for sex (*model 1*). Moreover, analyses adjusted for history of cancer at ages 15–30 years, parental NF1 and urban or rural area of residence were conducted (*model 2*). History of cancer was retrieved from the Finnish Cancer Registry that features high coverage of malignant tumors and intracranial benign tumors diagnosed in Finland since 1953. Only cancers occurring at ages 15–30 years were considered because this age range corresponded with the period of secondary and higher education. We did not include cancers from younger children, since the register-based data does not allow reliably determining whether optic pathway gliomas have been symptomatic or coincidental findings. All tumors registered in the Finnish Cancer Registry, that is, also benign intracranial neoplasms, were included, yet we use the term 'cancer' to differentiate the tumors from neurofibromas occurring outside the central nervous system. Information on the history of cancer was available for all individuals with NF1 and control persons, and for 1893 siblings without NF1. Parental NF1 was considered positive if one of the parents was known to have NF1 according to the NIH criteria or mosaic NF1, the individual with NF1 had a sibling with NF1, or familial origin of the disorder had been documented in medical records. The rural or urban area of residence was included to account for the local availability of educational resources. The urban–rural classification has been produced by the Finnish Environment Institute and is based on the number of residents in each population center. Furthermore, sensitivity analyses were completed, stratifying by year of birth (<1987 or ≥ 1987), and area of residence (Urban or Rural). To further dissect the role of familial NF1, the non-NF1 siblings of individuals with NF1 were compared to controls.

The Care Register for Health Care maintained by the National Institute for Health and Welfare was used to identify individuals with history of International Classification of Diseases 10th revision (ICD-10) diagnosis codes F70–F98 representing mental retardation (F70–F79), disorders of psychological development (F80–F89), and behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F90–F98). These data were available for all individuals with NF1 and controls, and 1891 siblings without NF1. The history of a diagnosis F70–F98 in 1998–2014 was used as a covariate in an analysis of educational attainment among those born during the ascertainment period 1987–2011 (*model 3*). The time range of the analysis was restricted because specialized outpatient care has only been registered since 1998. As a sensitivity analysis, mental retardation was not considered and only diagnoses F80–F98 were used.

The follow-up of individuals with NF1 started at the date of their cohort entry, that is, the first NF1-related hospital visit during the ascertainment period 1987–2011, since deaths could not be observed before cohort entry. The follow-up of the controls started at the cohort entry of the respective individual with NF1. The follow-up of the siblings without NF1 started at birth or the cohort entry of the first individual with NF1 in the family, whichever occurred last. For all individuals, the follow-up ended at death, emigration or the end of data availability on December 31, 2016. The use of registry data covering the total Finnish population allows practically complete follow-up.

The comparisons of educational attainment between the groups were performed using the Cox proportional hazards model with delayed entry and competing risk for death.[21] All models satisfied the assumption of the proportionality of the hazards. In the comparisons between individuals with NF1 and control individuals, standard errors were clustered within the strata of the 1 individual with NF1 and the maximum of 10 matched control individuals. In the comparisons between individuals with NF1 and their siblings without NF1, standard errors were clustered at the family level. The results are presented with model 95% confidence intervals (CI). The results were not corrected for multiple testing since the aim of this study is to describe the relative contributions of the different variables on educational attainment. The statistical analysis was conducted using Stata software version 15.

3 | ETHICS STATEMENT

The study was approved by the Ethical committee of Southwestern Finland Hospital District and research permission was secured from

the National Institute for Health and Welfare, Statistics Finland and all participating hospitals. The study adhered to the principles set out in the Declaration of Helsinki. The study is register-based and exempt from obtaining informed consent.

4 | RESULTS

4.1 | Cohort characteristics

Totals of 1408 individuals with NF1, 14 012 controls and 2042 siblings without NF1 were included in the analyses. The three cohorts were similar in terms of sex ratio, average year of birth, follow-up time and areas of residence (Table 1). As expected, NF1 was associated with increased mortality and higher prevalence of history of cancer at ages 15–30 years.[5,10] Interestingly, history of psychological, behavioral or emotional disorder or mental retardation (ICD-10 codes F70–F98) was much more common among individuals with NF1 (45%) than among controls (10%) or the siblings without NF1 (15%). On the descriptive level, the highest level of education achieved at the end of the study period was below upper secondary education in 40% of individuals with NF1, whereas this was the case in one third of the control individuals and siblings (Table 1). These descriptive numbers do not account for the follow-up time and are therefore artificially high for all three

TABLE 1 Characteristics of the cohorts

	Individuals with NF1	Control persons	Siblings without NF1
N	1408	14 012	2042
Sex			
Males, n (%)	677 (48.1)	6758 (48.2)	1059 (51.9)
Females, n (%)	731 (51.9)	7254 (51.8)	983 (48.1)
Year of birth, mean (SD)	1974 (22.4)	1974 (22.4)	1976 (19.1)
Start of follow-up (cohort entry)			
Age, mean (SD)	23.6 (20.7)	23.6 (20.7)	22.0 (17.1)
Year, mean (SD)	1991 (6.1)	1991 (6.1)	1991 (6.7)
End of follow-up			
Age, mean (SD)	39.7 (20.7)	41.3 (21.4)	38.9 (18.7)
Year, mean (SD)	2014 (5.7)	2015 (3.3)	2015 (3.2)
Follow-up time, mean (SD)	23.0 (7.4)	24.6 (6.5)	24.5 (7.1)
Deaths during the follow-up			
n (%)	276 (19.6)	1071 (7.6)	108 (5.3)
Age, mean (SD)	54.3 (21.6)	66.9 (17.4)	51.5 (14.3)
Persons with history of cancer			
At ages 15–30 years, n (%)	65 (4.6)	55 (0.4)	7 (0.4)[a]
History of ICD-10 diagnosis F70–F98, n (%)[b]	230 (44.6)	525 (10.2)	99 (14.8)
F70–F79, n (%)[b]	30 (5.8)	25 (0.5)	12 (1.8)
F80–F98, n (%)[b]	224 (43.4)	521 (10.2)	92 (13.7)
Parental NF1, n (%)	579 (41.1)	-	511 (25.0)
Area of residence			
Urban, n (%)	1218 (86.5)	11 924 (85.1)	1667 (81.7)
Rural, n (%)	190 (13.5)	2088 (14.9)	373 (18.3)
Highest level of education obtained by the end of follow-up			
Basic (ISCED 1–2), n (%)	565 (40.1)	4719 (33.7)	674 (33.0)
General upper secondary (ISCED 3), n (%)	83 (5.9)	1681 (12.0)	217 (10.6)
Vocational secondary (ISCED 3), n (%)	572 (40.6)	3810 (27.2)	644 (31.6)
Bachelor's degree (ISCED 6), n (%)	150 (10.7)	2562 (18.3)	361 (17.7)
Master's degree or more (ISCED 7–8), n (%)	38 (2.7)	1240 (8.8)	144 (7.1)

Abbreviations: ICD-10, international classification of diseases, 10th revision; ISCED, international standard classification of education; NF1, neurofibromatosis type 1; SD, standard deviation.

[a]Information available for 1893 siblings without NF1.

[b]Among persons born in 1987 or later: 516 individuals with NF1, 5124 control persons and 671 siblings without NF1.

TABLE 2 The effect of neurofibromatosis type 1 (NF1) on graduation from secondary education

	All secondary education			General upper secondary education			Vocational education		
	Model 1 all persons	Model 2 all persons	Model 3 persons born 1987 or later	Model 1 all persons	Model 2 all persons	Model 3 persons born 1987 or later	Model 1 all persons	Model 2 all persons	Model 3 persons born 1987 or later
Individuals with NF1 vs. control persons									
NF1	**0.83 [0.74,0.92]**	**0.95 [0.83,1.09]**	**1.01 [0.87,1.17]**	**0.33 [0.27,0.39]**	**0.42 [0.33,0.53]**	**0.50 [0.35,0.72]**	**2.04 [1.80,2.31]**	**2.00 [1.69,2.37]**	**1.57 [1.29, 1.92]**
Female	1.12 [1.04,1.21]	1.13 [1.04,1.22]	1.10 [1.02,1.18]	1.55 [1.35,1.77]	1.55 [1.35,1.78]	1.54 [1.36,1.76]	0.63 [0.55,0.71]	0.63 [0.55,0.71]	0.69 [0.61,0.79]
Cancer at age 15–30 years	–	0.59 [0.44,0.80]	0.96 [0.65,1.42]	–	0.70 [0.44,1.10]	0.78 [0.41,1.50]	–	0.60 [0.41,0.89]	0.76 [0.42, 1.35]
Parental NF1	–	0.83 [0.67,1.02]	0.89 [0.72,1.11]	–	0.62 [0.42,0.92]	0.83 [0.50,1.40]	–	1.08 [0.85,1.38]	1.05 [0.79,1.38]
Urban area of residence	–	0.98 [0.92,1.04]	0.97 [0.90,1.05]	–	1.10 [0.98,1.24]	1.07 [0.93,1.24]	–	0.61[0.55,0.68]	0.68 [0.60,0.78]
Diagnosis F70–F98	–	–	0.60 [0.53,0.67]	–	–	0.45 [0.35,0.57]	–	–	1.08 [0.94,1.25]
n, observations (n, NF1)	31 229 (2947)	31 229 (2947)	13 448 (1296)	56 177 (6420)	56 177 (6420)	18 763 (1977)	64 283 (4213)	64 283 (4213)	19 981 (1565)
n, subjects (n, NF1)	6954 (620)	6954 (620)	3788 (337)	6968 (623)	6968 (623)	3788 (377)	6954 (620)	6954 (620)	3788 (337)
n, events (n, NF1)	5581 (464)	5581 (464)	2767 (226)	3054 (129)	3054 (129)	1449 (61)	2573 (337)	2573 (337)	1332 (165)
n, competing (n, NF1)	43 (20)	43 (20)	<17 (<10)[a]	70 (39)	70 (39)	<18 (<10)[a]	60 (26)	60 (26)	<17 (<10)[a]
Individuals with NF1 vs. siblings without NF1									
NF1	**0.91 [0.80,1.05]**	**0.99 [0.87,1.14]**	**1.00 [0.87, 1.16]**	**0.45 [0.36,0.56]**	**0.49 [0.39,0.62]**	**0.67 [0.49,0.91]**	**1.68 [1.41,1.99]**	**1.67 [1.40,1.99]**	**1.41 [1.14,1.74]**
Female	1.19 [1.06,1.35]	1.21 [1.07,1.37]	1.03 [0.90,1.19]	2.03 [1.64,2.53]	2.05 [1.64,2.58]	1.63 [1.21,2.20]	0.66[0.56,0.79]	0.68[0.57,0.81]	0.71 [0.58,0.88]
Cancer at age 15–30 years	–	0.52 [0.34,0.81]	0.82 [0.46,1.45]	–	0.83 [0.44,1.55]	1.85 [0.83,4.15]	–	0.47[0.28,0.79]	0.43 [0.20,0.95]
Parental NF1	–	0.93 [0.80,1.09]	0.95 [0.81,1.12]	–	0.76 [0.57,1.02]	0.64 [0.44,0.92]	–	1.18[0.97,1.45]	1.26 [1.01,1.56]
Urban area of residence	–	0.87 [0.76,1.00]	0.87 [0.75,1.00]	–	1.27 [0.93,1.74]	1.62 [1.05,2.46]	–	0.57[0.47,0.69]	0.55 [0.44,0.67]
Diagnosis F70–F98	–	–	0.63 [0.52, 0.74]	–	–	0.34 [0.21,0.55]	–	–	1.07 [0.85,1.34]
n, observations (n, NF1)	7370 (2947)	7201 (2947)	2971 (1296)	14 847 (6420)	14 545 (6420)	4478 (1977)	12 362 (4213)	11 978 (4213)	3986 (1565)
n, subjects (n, NF1)	1530 (620)	1495 (620)	787 (337)	1535 (623)	1500 (623)	787 (337)	1530 (620)	1495 (620)	787 (337)
n, events (n, NF1)	1191 (464)	1160 (464)	549 (226)	483 (129)	464 (129)	214 (61)	720 (337)	707 (337)	336 (165)
n, competing (n, NF1)	28 (20)	28 (20)	6 (5)	50 (39)	50 (39)	8 (7)	36 (26)	31 (26)	6 (5)

[a]In accordance with the privacy regulations of Statistics Finland, the exact number is not shown where n < 5, or case numbers <5 can be inferred from the data shown in this and other tables.

Note: The results (hazard ratios and 95% confidence intervals) are shown for models adjusted for sex only (model 1) and models adjusted for additional factors (model 2: Adjusted for sex, cancer diagnosis at 15–30 years of age, parental NF1 and area of residence; model 3: Adjusted also for diagnoses F70–F98). In the analyses, event was defined as achieving the educational level of interest, and death was considered as a competing risk. End of follow-up due to other reasons led to censoring.

TABLE 3 Sex-stratified analysis of the effect of neurofibromatosis type 1 (NF1) on graduation from secondary education

	All secondary education			General upper secondary education			Vocational education		
	Model 1 all persons	Model 2 all persons	Model 3 persons born 1987 or later	Model 1 all persons	Model 2 all persons	Model 3 persons born 1987 or later	Model 1 all persons	Model 2 all persons	Model 3 persons born 1987 or later
Individuals with NF1 vs. control persons, WOMEN									
NF1	**0.80 [0.69,0.93]**	**0.89 [0.73,1.08]**	**0.84 [0.65,1.09]**	**0.38 [0.30,0.48]**	**0.53 [0.39,0.73]**	**0.68 [0.42,1.08]**	**2.09 [1.72,2.53]**	**1.68 [1.27,2.22]**	**1.18 [0.79,1.76]**
Cancer at age 15–30 years	–	0.60 [0.42,0.85]	0.78 [0.46,1.32]	–	0.59 [0.34,1.02]	0.63 [0.29,1.39]	–	0.70 [0.44,1.12]	0.62 [0.26,1.46]
Parental NF1	–	0.91 [0.68,1.22]	1.14 [0.84,1.56]	–	0.51 [0.31,0.85]	0.71 [0.38,1.35]	–	1.65 [1.13,2.41]	1.64 [1.02,2.63]
Urban area of residence	–	0.99 [0.91,1.08]	1.01 [0.91,1.12]	–	0.95 [0.81,1.11]	0.90 [0.75,1.07]	–	0.72 [0.61,0.85]	0.80 [0.65,1.00]
Diagnosis F70–F98	–	–	0.53 [0.43,0.66]	–	–	0.32 [0.20,0.49]	–	–	1.39 [1.08,1.78]
n, observations (n, NF1)	14 461 (1394)	14 461 (1394)	5814 (575)	25 051 (2945)	25 051 (2945)	7803 (838)	33 731 (2251)	33 731 (2251)	9424 (748)
n, subjects (n, NF1)	3322 (294)	3322 (294)	1705 (151)	3336 (297)	3336 (297)	1705 (151)	3322 (294)	3322 (294)	1705 (151)
n, events (n, NF1)	2750 (226)	2750 (226)	1276 (102)	1725 (85)	1725 (85)	775 (39)	1054 (142)	1054 (142)	509 (63)
n, competing (n, NF1)	12 (8)	12 (8)	<5 (<5)[a]	22 (16)	22 (16)	<5 (<5)[a]	22 (11)	22 (11)	<5 (<5)[a]
Individuals with NF1 vs. control persons, MEN									
NF1	**0.85 [0.73,0.99]**	**1.00 [0.83,1.20]**	**1.13 [0.95,1.34]**	**0.26 [0.19,0.36]**	**0.28 [0.19,0.43]**	**0.35 [0.20,0.63]**	**2.02 [1.72,2.38]**	**2.24 [1.81,2.78]**	**1.78 [1.42,2.23]**
Cancer at age 15–30 years	–	0.64 [0.38,1.08]	1.30 [0.78,2.15]	–	0.96 [0.44,2.08]	1.15 [0.40,3.32]	–	0.55 [0.29,1.05]	0.90 [0.40,2.05]
Parental NF1	–	0.76 [0.57,1.01]	0.76 [0.56,1.02]	–	0.85 [0.45,1.61]	0.98 [0.42,2.31]	–	0.81 [0.58,1.12]	0.82 [0.57,1.17]
Urban area of residence	–	0.97 [0.88,1.06]	0.94 [0.85,1.05]	–	1.33 [1.12,1.59]	1.35 [1.08,1.70]	–	0.55 [0.48,0.64]	0.62 [0.53,0.73]
Diagnosis F70–F98	–	–	0.64 [0.56,0.72]	–	–	0.57 [0.43,0.74]	–	–	0.97 [0.82,1.16]
n, observations (n, NF1)	16 768 (1553)	16 768 (1553)	7634 (721)	31 126 (3475)	31 126 (3475)	10 960 (1139)	30 552 (1962)	30 552 (1962)	10 557 (817)
n, subjects (n, NF1)	3632 (326)	3632 (326)	2083 (186)	3632 (326)	3632 (326)	2083 (186)	3632 (326)	3632 (326)	2083 (186)
n, events (n, NF1)	2831 (238)	2831 (238)	1491 (124)	1329 (44)	1329 (44)	674 (22)	1519 (195)	1519 (195)	823 (102)
n, competing (n, NF1)	31 (12)	31 (12)	12 (<5)[a]	48 (23)	48 (23)	13 (<5)[a]	38 (15)	38 (15)	12 (<5)[a]

[a]In accordance with the privacy regulations of Statistics Finland, the exact number is not shown where n < 5, or case numbers <5 can be inferred from the data shown in this and other tables.

Note: The results (hazard ratios and 95% confidence intervals) are shown for unadjusted models (model 1) and models adjusted for additional factors (model 2: Adjusted for cancer diagnosis at 15–30 years of age, parental NF1 and area of residence; model 3: Adjusted also for diagnoses F70–F98). In the analyses, event was defined as achieving the educational level of interest, and death was considered as a competing risk. End of follow-up due to other reasons led to censoring.

TABLE 4 Educational field of the highest degree obtained among individuals with neurofibromatosis type 1 (NF1), their siblings without NF1 and matched controls without NF1. The numbers are n (%)

	Individuals with NF1		Control persons		Siblings without NF1	
	Secondary	At least bachelor	Secondary	At least bachelor	Secondary	At least bachelor
Generic	44 (6.6)	<5 (<2.8)[a]	1147 (20.5)	<5 (<0.1)[a]	140 (16.3)	<5 (<1.0)[a]
Education	<5 (<0.8)[a]	7 (4.0)	7 (0.1)	270 (7.4)	<5 (<0.6)[a]	31 (6.1)
Arts and humanities	30 (4.5)	16 (9.0)	168 (3.0)	349 (9.6)	34 (3.9)	38 (7.5)
Social sciences, journalism and information	<5 (<0.8)[a]	<5 (<2.8)[a]	<5 (<0.1)[a]	193 (5.3)	<5 (<0.6)[a]	22 (4.4)
Business, administration and law	64 (9.6)	56 (31.6)	540 (9.6)	907 (24.9)	73 (8.5)	119 (23.6)
Natural sciences, mathematics and statistics	<5 (<0.8)[a]	8 (4.5)	9 (0.2)	136 (3.7)	<5 (<0.6)[a]	18 (3.6)
Information and communication technology	24 (3.6)	11 (6.2)	100 (1.8)	190 (5.2)	12 (1.4)	40 (7.9)
Engineering, manufacturing and construction	187 (28.1)	25 (14.1)	1697 (30.3)	646 (17.7)	292 (33.9)	100 (19.8)
Agriculture, forestry, fisheries and veterinary	33 (5.0)	<5 (<2.8)[a]	257 (4.6)	100 (2.7)	49 (5.7)	17 (3.4)
Health and welfare	93 (14.0)	37 (20.9)	681 (12.2)	666 (18.3)	102 (11.8)	96 (19.0)
Services	191 (28.7)	9 (5.1)	997 (17.8)	191 (5.2)	158 (18.4)	24 (4.8)
Unknown	<5 (<0.8)[a]	<5 (<2.8)[a]	<5 (<0.1)[a]	<5 (<0.1)[a]	<5 (<0.6)[a]	<5 (<1.0)[a]

[a]In accordance with the privacy regulations of Statistics Finland, the exact number is not shown where n < 5, or case numbers <5 can be inferred from the data shown in this and other tables.

groups because the data included many individuals who were too young to have graduated from upper secondary education.

4.2 | The effect of NF1 on educational attainment

NF1 was associated with a negative effect on the attainment of upper secondary education in comparison with control subjects but not with the non-NF1 siblings (Table 2, all secondary education, model 1). Controlling for cancer between age 15–30 years, parental NF1 and urban residence revealed that the effect of NF1 was explained by the history of cancer (Table 2, all secondary education, model 2). As a sensitivity analysis, model 2 was restricted to those born in 1987 or later, and the hazard ratio of obtaining secondary education was 0.83 (95% CI 0.72 to 0.96) among individuals with NF1 compared to controls. However, when the history of a diagnosis of psychological, behavioral or emotional disorder or mental retardation (F70–F98) was included as a covariate, NF1 as such was not significantly associated with the attainment of upper secondary education (Table 2, all secondary education, model 3). The lower rate of secondary education in NF1 was more strongly predicted by a diagnosis of psychological, behavioral or emotional disorder or mental retardation (F70–F98) than the history of cancer (Table 2, all secondary education, model 3). A sensitivity analysis where mental retardation was not taken into account and only diagnoses F80–F98 were considered produced essentially unchanged results, that is, the estimate of the effect of NF1 was 1.00 (95% CI 0.86 to 1.16) and the estimate of the effect of diagnoses F80-F98 was 0.60 (95% CI 0.53 to 0.67). When the history of cancer was replaced with the total number of hospital visits and stays during the ages of 15–30 years in the models 2 and 3, the results remained robust, in accordance with the expected high correlation between cancer diagnoses and the number of hospital encounters. Limiting the analysis to those born before 1987, that is, the beginning of the ascertainment period of the present study, had little effect on the estimates. Moreover, the estimates remained essentially the same after stratification by urban or rural area of residence. When the competing risk of death was not accounted for in models 1–3, the negative effect of NF1 was smaller, but still significant in the unadjusted model.

Individuals with NF1 obtained vocational upper secondary education more often than general upper secondary education. These two types of education are mostly alternative, with general upper secondary education preparing the students for further studies and vocational secondary education for a specific trade. NF1 lowered the probability of the individual attaining general upper secondary education by 55%–67% (Table 2, general upper secondary education, model 1) while the probability of the individual attaining vocational secondary education was increased by 68%–104% in NF1 (Table 2, vocational education, model 1). These effects largely persisted after controlling for cancer at ages 15–30, parental NF1 and urban residence: In comparison to controls, NF1 was associated with a hazard ratio of 0.42 for general upper secondary education and 2.00 for vocational secondary education (Table 2, model 2). History of a diagnosis of psychological, behavioral or emotional disorder or mental retardation (F70–F98) lowered the probability of the individual

TABLE 5 The effect of neurofibromatosis type 1 (NF1) on graduation from higher education

	Bachelor's degree			Master's degree		
	Model 1 all persons	Model 2 all persons	Model 3 persons born 1987 or later	Model 1 all persons	Model 2 all persons	Model 3 persons born 1987 or later
Individuals with NF1 vs. control persons						
NF1	**0.51 [0.40,0.64]**	**0.63 [0.47,0.84]**	**0.94 [0.55,1.59]**	**0.26 [0.16,0.41]**	**0.32 [0.18,0.57]**	**0.26 [0.039,1.76]**
Female	1.79 [1.59,2.01]	1.78 [1.58,2.00]	2.04 [1.57,2.63]	1.56 [1.30,1.88]	1.55 [1.29,1.86]	1.66 [1.04,2.64]
Cancer at age 15–30 years	–	1.01 [0.65,1.56]	2.16 [1.11,4.21]	–	1.02 [0.51,2.05]	4.2×10^{-9} [2.2×10^{-9}, 8.2×10^{-9}]
Parental NF1	–	0.59 [0.37,0.95]	0.49 [0.22,1.12]	–	0.58 [0.22,1.53]	1.64 [0.15,17.4]
Urban area of residence	–	1.54 [1.29,1.83]	1.85 [1.29,2.66]	–	2.72 [2.01,3.67]	3.48 [1.50,8.08]
Diagnosis F70–F98	–	–	0.11 [0.05,0.23]	–	–	0.13 [0.035,0.50]
n, observations (n, NF1)	77 147 (7058)	77 147 (7058)	24 290 (2197)	84 771 (7577)	84 771 (7577)	25 173 (2245)
n, subjects (n, NF1)	6968 (623)	6968 (623)	3788 (337)	6968 (623)	6968 (623)	3788 (337)
n, events (n, NF1)	1513 (77)	1513 (77)	462 (22)	705 (18)	705 (18)	128 (<5)[a]
n, competing (n, NF1)	69 (38)	69 (38)	16 (7)	85 (43)	85 (43)	16 (7)
Individuals with NF1 vs. siblings without NF1						
NF1	**0.54 [0.41,0.71]**	**0.57[0.43,0.76]**	**0.63 [0.38,1.06]**	**0.36 [0.22,0.59]**	**0.38 [0.22,0.66]**	**0.98 [0.32,2.979**
Female	2.10 [1.58, 2.56]	1.97 [1.54,2.52]	2.14 [1.34,3.40]	1.83 [1.20,2.80]	1.71 [1.09,2.70]	3.58 [0.84, 15.3]
Cancer at age 15–30 years	–	1.07 [0.56,2.07]	3.77 [1.65,8.61]	–	1.99 [0.64,6.16]	0.7×10^{-6} [0.2×10^{-6}, 0.3×10^{-5}]
Parental NF1	–	0.73 [0.55,0.98]	0.53 [0.31,0.98]	–	0.50 [0.27,0.93]	0.46 [0.12, 1.74]
Urban area of residence	–	1.47 [1.01,2.15]	2.29 [0.98,5.33]	–	1.78 [0.84,3.77]	1.9×10^{6} [8.8×10^{5}, 4.2×10^{6}]
Diagnosis F70–F98	–	–	0.25 [0.11,0.55]	–	–	0.42 [0.07,2.62]
n, observations (n, NF1)	17 742 (7058)	17 290 (7058)	5318 (2197)	19 295 (7577)	18 793 (7577)	5841 (2245)
n, subjects (n, NF1)	1535 (623)	1500 (623)	787 (337)	1535 (623)	1500 (623)	787 (337)
n, events (n, NF1)	280 (77)	272 (77)	85 (22)	92 (18)	87 (18)	9 (<5)[a]
n, competing (n, NF1)	53 (42)	55 (42)	8 (7)	56 (43)	53 (43)	8 (7)

[a]In accordance with the privacy regulations of Statistics Finland, the exact number is not shown where n < 5, or case numbers <5 can be inferred from the data shown in this and other tables.
Note: The results (hazard ratios and 95% confidence intervals) are shown for models adjusted for sex only (model 1) and models adjusted for additional factors (model 2: Adjusted for sex, cancer diagnosis at 15–30 years of age, parental NF1 and area of residence; model 3: Adjusted also for diagnoses F70–F98). In the analyses, event was defined as achieving the educational level of interest, and death was considered as a competing risk. End of follow-up due to other reasons led to censoring.

attaining general upper secondary education by 55%–66% and slightly attenuated the effect of NF1 (Table 2, general upper secondary education, model 3) whereas it had only little effect on the attainment of vocational upper secondary education (Table 2, vocational education, model 3). The effect of the other, uncontrolled features of NF1 remained very large after adjusting for diagnoses F70-F98.

Whereas the unadjusted effect of NF1 on the ratio of general and vocational upper secondary education did not differ between males and females (Table 3, model 1), females showed more pronounced effects of history of cancer, parental NF1 and history of diagnoses F70-F98 (Table 3, models 2 and 3). Therefore, after the adjustments, the effect of NF1 was smaller among females than among males. The educational field of vocational upper secondary degree was "services" more often among individuals with NF1 (31%) than among controls or siblings without NF1 (22%; Table 4). In contrast, individuals with NF1 were educated to "engineering, manufacturing and construction" less often than controls or siblings (30% vs. 38–41%).

In accordance with the results on the general upper secondary education, NF1 decreased the attainment of Bachelor's (ISCED 6) or Master's (ISCED 7) degree with reductions of 46%–49% and 64%–74%, respectively (Table 5, model 1). The effect of NF1 was generally larger in the case of the Master's level. History of cancer did not explain the effect of NF1 on either Bachelor's or Master's degrees (Table 5, model 2). Diagnoses F70–F98 seemed to be associated with lower rates of obtaining Bachelor's and Master's degrees yet the low numbers of cases hamper our ability to draw conclusions on their role in explaining the effects of NF1 (Table 5, model 3). The educational fields of the Bachelor's and Master's degrees obtained by individuals with NF1 did not markedly differ from those of the controls (Table 4).

4.3 | The effect of having a family member with NF1 on educational attainment

In the cohort of non-NF1 siblings, all individuals have a sibling with NF1, yet some also have a parent with NF1. The non-NF1 siblings were compared with controls to elucidate the contributions of having family members with NF1. The hazard ratio of obtaining secondary education was 0.90 (95% CI 0.83 to 0.99) among the non-NF1 siblings of individuals with NF1 compared to controls. When the analysis was adjusted for parental NF1, the effect of having a sibling with NF1 was 0.89 (95% CI 0.80 to 0.99) and the effect of also having a parent with NF1 was 1.06 (95% CI 0.89 to 1.27). When the attainment of general upper secondary education was studied, the hazard ratio was 0.72 (95% CI 0.63 to 0.82). After adjusting the analysis for parental NF1, the effect of having a sibling with NF1 was 0.76 (95% CI 0.65 to 0.88) and the effect of having a parent with NF1 was 0.82 (95% CI 0.62 to 1.09). The hazard ratio of obtaining Master's education was 0.71 (95% CI 0.56 to 0.90) in the unadjusted analysis. In the analysis adjusted for parental NF1, the effect of parental NF1 was more pronounced (hazard ratio 0.46, 95% CI 0.24 to 0.88) than the effect of having a sibling with NF1 (0.82, 95% CI 0.64 to 1.06).

5 | DISCUSSION

The present register-based analysis of a cohort of patients with confirmed NF1 diagnosis shows that NF1 has multifaceted effects on the educational attainment of the affected persons. It seems that cancers cause dropping out from the education system while the other features of NF1 may be particularly hampering in the case of more theoretical and abstract education, and the individuals with NF1 often end up to a non-academic educational pathway. The present study is the first to show the contributions of familial NF1 and learning, developmental and behavioral problems to educational pathways and educational attainment in NF1. The lower educational attainment among individuals with NF1 is corroborated by previous literature.[1,2,13]

The rate of obtaining secondary education was 17% lower among individuals with NF1 than in the control cohort. This was apparently explained by the morbidity associated with NF1 during the school years, such as cancers and developmental disorders. Cancers frequently occur already at a young age among individuals with NF1,[8,10] and may cause disruption of studies and lead to dropping out from the education system due to both psychological and physical stress. Central nervous system tumors represented approximately one third of the cancers in the NF1 group. These also included the benign intracranial tumors registered in the Finnish Cancer Registry. Even histologically benign brain tumors and their treatment can plausibly interfere with the ability to pursue education. As expected, also the diagnosis of psychological, behavioral or emotional disorder or mental retardation (ICD-10 codes F70–F98) seems to play an important role in graduating from secondary education. Importantly, this effect was not due to mental retardation (F70–F79) but persisted in a sensitivity analysis only considering psychological, behavioral or emotional disorders (F80–F98).

Interestingly, individuals with NF1 also had an increased likelihood of obtaining vocational education instead of the general upper secondary education. The effects of NF1 on these two types of secondary education were largely mirror images, since most school-aged Finns pursue at least one type of upper secondary education. For instance, the proportion of 30–34 year-old individuals who have not obtained secondary education in Finland during the last 10 years has been around 13%–16%.[22] Consistent with the increased rate of obtaining vocational secondary education, the Bachelor's and Master's degrees were significantly less frequent among individuals with NF1. The cancer morbidity associated with NF1 did not completely explain the increased rate of obtaining vocational education nor the lower rates of Bachelor's and Master's degrees.

Previous studies on the academic skills and cognitive abilities of individuals with NF1 have identified common cognitive deficits[12-16,18,19] that likely contribute to the lower educational attainment, and the preferential choice of vocational rather than academic education, observed in the present study. When we adjusted our analyses with the diagnoses of psychological, behavioral or emotional disorders or mental retardation (ICD-10 F70–F98), this covariate was observed to have major contribution on the educational attainment but the effect of NF1 could not be completely attributed to these diagnoses. Despite the potential under-diagnosis of the conditions

F70–F98, the results confirm that in addition to these clearly pathological conditions known to be associated with NF1, NF1 is also associated with milder impairment of academic skills. In contrast to our findings, psychiatric disorders did not modify the effect of NF1 on educational attainment in the recent Danish study by Doser et al.[2] However, Doser and co-workers observed a markedly lower prevalence of psychiatric diagnoses despite using a wider selection of diagnosis codes, which suggests that these diagnoses were incompletely represented in their data.

Among the diagnoses of psychological, behavioral or emotional disorders or mental retardation (ICD-10 F70–F98), especially the developmental disorders of speech and language, scholastic skills, and motor function, and mixed developmental disorders were frequently observed among individuals with NF1. Interestingly, the history of a diagnosis of psychological, behavioral or emotional disorder or mental retardation affected females more severely than males since such a diagnosis had larger effect on the choice between general or vocational secondary education among females.

Parents' education and socioeconomic status are known to affect the educational attainment of their children.[23] We had no access to information on the educational attainment of the parents of the study persons and we thus decided to use parental NF1 status as a surrogate that may represent both parental education as well as the other effects of NF1. The results clearly show that parental NF1 reduced the likelihood of obtaining general upper secondary education or Bachelor's or Master's degree even though this covariate was not statistically significant in all of the models. The non-NF1 siblings of individuals with NF1 also had lower educational attainment, irrespective of parental NF1. However, when general upper secondary education and especially when Master's education were studied, parental NF1 had a negative effect on educational attainment. This suggests that the effect of parental NF1 may be particularly important for more academic forms of education. Having a family member with NF1 may affect the resources of the whole family, and the effect may be larger when both a sibling and a parent are affected. The findings highlight that children with a familial NF1 might benefit from additional support and student counseling to ensure finding a suitable education.

The major strengths of our study include the verification of NF1 diagnoses by individually reviewing medical records,[5] and the use of register data to retrieve the information on education and virtually complete follow-up of the patients, their siblings and controls. The register-based information on educational attainment is free from the biases associated with self-reported measures of educational level, and the data have full coverage of degrees issued by Finnish institutions. Practically all education in Finland is public and tuition free, which reduces the biases associated with the financial status of the family and allows dissecting the effects of NF1 and its co-morbidities. The results naturally represent the Finnish society and may not be generalizable to other countries. It is possible that the impact of NF1 on educational attainment is even greater in countries where public health care and education are not as extensively provided as in Finland. The limitations of the study include hospital-based ascertainment of the individuals with NF1 which may bias the cohort towards more severe phenotypes, as not all Finnish individuals with NF1 are known to us.[6] Awareness of the cognitive problems associated with NF1 has grown in the recent years and the support received by individuals with NF1 may have increased during the study period. However, the results were robust with regard to limiting the analysis to those born 1987–2011, who have reached the educational levels studied here after the year 2000. It is possible that there are undiagnosed persons with NF1 in the control and especially in the sibling cohort.

Individuals with rare diseases may have a major role in their own treatment, as they convey information on the syndrome to non-specialist care providers. In the case of tumor predisposition syndromes, affected individuals are also required to stay alert for signs of malignancy and to seek medical attention at the rise of new symptoms. Education may play a role in these functions. For example, a study on skin self-examination pre- and post-melanoma diagnosis found a positive association with education.[24] Moreover, higher level of education is associated with better health literacy.[25] The reduced educational attainment observed among individuals with NF1 may need to be accounted for in the health education provided for this patient group. NF1 affects academic skills, yet also other factors such as cancer morbidity and parental disease contribute to the final educational attainment and may also play a role in other rare diseases. The effects on educational attainment observed here likely translate to labor market performance and the use of social assistance among individuals with NF1, yet these are topics for future research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Data are available for researchers with appropriate research permissions from Finnish Institute for Health and Welfare, Statistics Finland and Finnish Population Register Centre.

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