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ORIGINAL ARTICLE

Hypertension in NF1: A closer look at the primacy of essential hypertension versus secondary causes

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Abstract

Background: We aimed to analyze hypertension in neurofibromatosis type 1 (NF1) in a Finnish population-based cohort in 1996–2014.

Methods: A cohort of 1365 individuals with confirmed NF1 was compared with a control cohort of 13,923 individuals matched for age, sex, and area of residence. Diagnoses of hypertension were retrieved from the Finnish Care Register for Health Care. These registered data were separately analyzed for secondary and essential hypertension. Purchases of antihypertensive drugs were queried from the Finnish Register of Reimbursed Drug Purchases.

Results: We identified 115 NF1 patients with hospital diagnosis of hypertension. Our findings revealed a hazard ratio (HR) of 1.64 (95% CI 1.34–2.00, $p < 0.001$) in NF1 versus controls. NF1 patients presented with a significantly increased hazard for both secondary hypertension ($n = 9$, HR 3.76, 95% CI 1.77–7.95, $p < 0.001$) and essential hypertension ($n = 98$, HR 1.73, 95% CI 1.39–2.14, $p < 0.001$). No difference in the HR of hypertension was observed between men and women, while NF1 patients with essential hypertension were, on average, younger than the controls. The proportions of individuals with antihypertensive medication did not differ between NF1 patients and controls (OR 0.85).

Conclusion: NF1 is a risk factor for hypertension. Despite the recognized risk for secondary hypertension, essential hypertension is the predominant type in NF1.

KEYWORDS

antihypertensive medication, essential hypertension, neurofibromatosis 1, NF1, secondary hypertension

1 | INTRODUCTION

Neurofibromatosis type 1 (NF1, OMIM 162200) is an autosomal and dominantly inherited cancer predisposition syndrome caused by mutations in the *NF1* gene on the long arm of chromosome 17 (Gutmann et al., 2017; Jouhilahti et al., 2011). The disorder is characterized by café-au-lait macules, axillary and inguinal freckling, dermal and plexiform neurofibromas, skeletal dysplasia, iris Lisch nodules and optic gliomas (Legius et al., 2021; National Institutes of Health Consensus Development Conference, 1988). The birth incidence of NF1 is around 1:2000 (Uusitalo et al., 2015). The prevalence of NF1 varies between age groups because of the shortened life expectancy and excess mortality throughout the lifetime of the affected individuals (Kallionpää et al., 2018). The increased mortality in NF1 is due to, for example, cancer and cardiovascular diseases (Uusitalo et al., 2015, 2016). Children with NF1 have an increased risk for congenital anomalies of the circulatory system (Leppävirta et al., 2018), and diseases of the circulatory system also contribute to the excess rate of incapacity to work among adults with NF1 (Kallionpää et al., 2023). However, the frequency and natural history of cardiovascular abnormalities in NF1 have not been analyzed in detail.

Hypertension is a common finding in adults with NF1. 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 versus control population (Kenborg et al., 2020). Hypertension may also develop during childhood (Bergqvist et al., 2020). Up to 16% of children and adolescents with NF1 have been reported to show blood pressure values suggestive of hypertension (Dubov et al., 2016; Lama et al., 2004), and annual monitoring of blood pressure is recommended for individuals with NF1 (Bergqvist et al., 2020; Carton et al., 2023; Merker et al., 2022). Although essential hypertension is the most common type of hypertension in the general population, epidemiological studies on the association of essential hypertension and NF1 are sparse (Kenborg et al., 2020) and our knowledge is mainly based on case reports. For example, a recent report emphasizes the consequences of essential hypertension in NF1 by describing a patient whose essential hypertension led to hemorrhagic stroke at the age of 23 years (Faris et al., 2021).

The *NF1* gene protein product, neurofibromin, is normally expressed by vascular endothelial and smooth muscle cells. Loss of neurofibromin expression by these cells is believed to be responsible for the development of NF1-related vasculopathy (Norton et al., 1995). Secondary hypertension in patients with NF1 is frequent since NF1-associated vasculopathy may manifest as a renal artery stenosis leading to renovascular hypertension (Ferner et al., 2007; Friedman et al., 2002). Thus, evaluation for renal artery stenosis should be initiated in hypertensive children and young adults with NF1 (Fossali et al., 2000; Patel & Cahill, 2021). Aortic coarctation and middle aortic syndrome may also be potential causes of renovascular hypertension in children with NF1 (Dubov et al., 2016). Pheochromocytoma is a rare hormonal cause of secondary hypertension in the general population, but should be suspected as a potential cause of NF1-associated hypertension. Pheochromocytomas are catecholamine-producing tumors located in the adrenal medulla, or extra-adrenally, when 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% (Képénékian et al., 2016; Zinnamosca et al., 2011). Currently, the American College of Medical Genetics and Genomics, and the European Reference Network for Genetic Tumor Risk Syndromes recommend screening for pheochromocytomas in NF1 patients with unexplained elevated blood pressure if the patient is over 30 years of age, during pregnancy and/or has paroxysmal hypertension, hypertension-associated headache, palpitations, or sweating (Carton et al., 2023; Stewart et al., 2018).

The current study was designed to elucidate the hazard for hypertension in NF1. Furthermore, the use of antihypertensive drugs in Finnish NF1 patients was analyzed.

2 | 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 Finland's Ministry of Social

Affairs and Health, the Finnish Institute for Health and Welfare, the Social Insurance Institution of Finland, the Population Register Centre of Finland, Statistics Finland, and all participating hospitals.

The Finnish NF1 cohort was collected by searching all NF1-related hospital visits in the 15 Central and 5 University Hospitals in mainland Finland during the ascertainment period 1987–2011, as previously described (Uusitalo et al., 2015). The medical records of the patients were reviewed to confirm NF1 diagnosis according to the NIH diagnostic criteria (National Institutes of Health Consensus Development Conference, 1988). For each of the 1410 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 Centre, yielding a control cohort of 14,017 individuals.

The present study used the Finnish Care Register for Health Care, which covers inpatient care, and outpatient hospital visits in the secondary and tertiary health care. To provide a complementary view of the use of antihypertensive medication in the Finnish population, the Finnish Register of Reimbursed Drug Purchases was also analyzed.

Hospital visits of individuals with NF1 and controls were retrieved from the Finnish Care Register for Health Care by using the International Classification of Diseases 10th revision (ICD-10) diagnosis codes. The ICD-10 has been used in Finland since 1996, and the analysis covered the period 1996–2014. The following ICD-10 categories for hypertension were searched: I10 (essential hypertension), I11 (hypertensive heart disease), I12 (hypertensive renal disease), I13 (hypertensive heart and renal disease), and I15 (secondary hypertension). To validate the diagnosis of essential hypertension, we excluded patients with diagnoses for both essential and secondary hypertension. Among individuals with hypertension, diagnoses associated with factors potentially contributing to hypertension were searched. These included obstructive sleep apnea (G47.3), obesity (E66), use of tobacco (F17), and common respiratory diseases related to smoking (J44). We also searched the diagnoses associated with harmful use of alcohol (E24.4 alcohol-induced pseudo-Cushing syndrome; F10 mental and behavioral disorders due to use of alcohol; G31.2 degeneration of nervous system due to alcohol; G40.5 special epileptic syndromes; G62.1 alcoholic polyneuropathy; G72.1 alcoholic myopathy; I42.6 alcoholic cardiomyopathy; K29.2 alcoholic gastritis; K70 alcoholic liver disease; K85.2 alcohol-induced acute pancreatitis; K86.0 alcohol-induced chronic pancreatitis; T51.0 toxic effect of alcohol; Y90 evidence of alcohol involvement determined by blood alcohol level; Y91 evidence of alcohol involvement determined by level of intoxication; Z50.2 alcohol rehabilitation; Z71.4 alcohol abuse counseling and surveillance; and Z72.1 alcohol use). The typical underlying causes of secondary hypertension were queried: renal artery stenosis (Q27.1), mid-aortic syndrome (Q25.3) and renovascular hypertension (15.0), malignant pheochromocytoma (C74), benign neoplasm of adrenal gland (D44.1) and adrenomedullary hyperfunction (E27.5) as well as primary hyperaldosteronism (E26.0) and primary hyperparathyroidism (E21.0).

Purchases of antihypertensive drugs were searched over the years 1996–2014 using the Anatomical Therapeutic Chemical (ATC) classification. The Finnish Register of Reimbursed Drug Purchases was searched for ATC codes in the categories C02 (antihypertensives), C03 (diuretics), C07 (beta-blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the renin–angiotensin system) as more specifically shown in Table S1. Drugs commonly used primarily for indications other than hypertension were excluded. Thus, furosemide and spironolactone which are primarily used in the treatment of congestive heart failure and edema were not included.

Since socioeconomic status is associated with the risk for hypertension (Leng et al., 2015), the educational level and annual disposable income were retrieved from Statistics Finland. Statistics Finland obtains information on completed degrees from the providers of education. Educational level was coded using the International Standard Classification of Education (ISCED), and the highest educational level achieved by each individual during the study period was used. Disposable income takes income earned from work, property income, social income transfers, and taxation into account. The highest disposable income observed during the study period was used for each individual.

The follow-up of individuals with NF1 started at the beginning of the study period on January 1, 1996, or cohort entry, whichever occurred later. The cohort entry was the date of the first NF1-related hospital visit during the ascertainment period. For controls, the cohort entry date of the respective individual with NF1 was used. The follow-up ended at the first event of interest (hypertension-related hospital visit or purchase of antihypertensive drug), death, emigration, or the end of the study period on December 31, 2014, whichever occurred first. A total of 1365 individuals with NF1 and 13,923 controls contributed 18,329 and 199,223 person-years of follow-up in 1996–2014, respectively (Table 1). To assess the impact of the increased medical attention potentially associated with the diagnosis of NF1, the 6 months following the cohort entry and all individuals with diagnoses of interest during this period were excluded in a sensitivity analysis. The Cox proportional hazards model with delayed entry and age as the time scale was used to compare the rates of incident diagnoses

TABLE 1 Characteristics of the cohorts followed up over 1996–2014.

	Individuals with NF1	Controls	*p* (NF1 versus controls)
n	1365	13,923	
Sex			
Males, *n* (%)	661 (48.4)	6715 (48.2)	0.996
Females, *n* (%)	704 (51.6)	7208 (51.8)	
Year of birth, mean (SD)	1974.9 (21.8)	1974.3 (22.1)	0.857
Start of follow-up			
Age, mean (SD)	25.0 (20.7)	25.5 (20.9)	0.953
Age 0–19, *n* (%)	690 (50.5)	6926 (49.7)	
Age 20–39, *n* (%)	321 (23.5)	3290 (23.6)	
Age 40–64, *n* (%)	304 (22.3)	3119 (22.4)	
Age ≥ 65, *n* (%)	50 (3.7)	588 (4.2)	
End of follow-up			
Age, mean (SD)	38.4 (20.8)	39.8 (21.5)	<0.001
Age 0–19, *n* (%)	322 (23.6)	3112 (22.4)	
Age 20–39, *n* (%)	454 (33.3)	4476 (32.1)	
Age 40–64, *n* (%)	408 (29.9)	4186 (30.1)	
Age ≥ 65, *n* (%)	181 (13.3)	2149 (15.4)	
Follow-up time (person-years)			
Sum	18,329	199,223	
Mean (SD)	13.4 (5.6)	14.3 (5.3)	<0.001
Deaths during the follow-up, *n* (%)	175 (12.8)	703 (5.0)	<0.001
Highest annual income (euros), mean (SD)[a]	19,208 (12,727)	25,161 (17,953)	<0.001
Highest educational level[b]			
ISCED 0–2 (≤9 years of education), n (%)	535 (39.2)	4648 (33.4)	<0.001
ISCED 3–4 (~12 years of education), n (%)	653 (47.8)	5595 (40.2)	
ISCED ≥5 (≥15 years of education), n (%)	177 (13.0)	3677 (26.4)	

Abbreviations: ISCED, International Standard Classification of Education; NF1, neurofibromatosis type 1; SD, standard deviation.

[a]Information on the highest annual income available for 1307 individuals with NF1 and 12,943 controls.

[b]Information on the highest educational level available for 1365 individuals with NF1 and 13,920 controls.

of hypertension or purchases of antihypertensive drugs between individuals with NF1 and controls. The matching of individuals with NF1 and controls was accounted for using a frailty term. The proportionality of the hazards was assessed visually and using scaled Schoenfeld residuals. Effect modification by sex and age group (≤50 or >50 years) was assessed by including an interaction term with NF1 status. In addition, estimates adjusted for educational level or parental NF1 were computed. Educational level was classified as ISCED 0–2 (≤9 years of education), ISCED 3–4 (~12 years of education), and ISCED ≥5 (≥15 years of education). Parental NF1 was deduced as previously described and was included to account for the socioeconomic consequences of having familial NF1 (Johansson et al., 2021). Among individuals with hypertension, the prevalence of co-occurring diagnoses and drug purchases was compared between individuals with NF1 and controls using odds ratio (OR) and the Fisher's exact test. Statistical significance was defined at the two-sided 5% level. All the analyses were performed using the R software for statistical computing (version 3.6.2) and package survival (version 3.2-7).

3 | RESULTS

A total of 1365 individuals with confirmed NF1 and 13,923 controls 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 (Table 1). Hospital visits were searched in the Care Register for Health Care for essential hypertension (I10), hypertensive heart disease (I11), hypertensive renal disease (I12), hypertensive heart and renal disease (I13), or secondary hypertension (I15) over the years 1996–2014. We found a total of 115 individuals with NF1 and 914 controls with a diagnosis for a hypertensive disease, yielding a hazard ratio (HR) of 1.64 (95% CI 1.34–2.00) for individuals with NF1 compared with controls (Table 2).

Nine out of the 115 NF1 patients had a diagnosis of secondary hypertension (I15) yielding a markedly high HR of 3.76 (95% CI 1.77–7.95, $p < 0.001$) when compared to the control group (Table 2). The mean age at the time of the first hospital record of secondary hypertension was 35 years (SD 30) in NF1 individuals, and 56 years (SD 19) among the controls. Renovascular hypertension (I15.0) was reported in five individuals with NF1. Pheochromocytoma (C74), neoplasm of the adrenal gland (D44.1) and/or adrenomedullary hyperfunction (E27.5) were recorded for two individuals with NF1. In two patients, the cause of secondary hypertension was not specified in the register data. None of the patients had a diagnosis of primary hyperaldosteronism (E26.0) or primary hyperparathyroidism (E21.0).

In order to study essential hypertension, we limited the analysis to the ICD-10 category I10, and the individuals with an additional diagnosis of secondary hypertension (I15) at any time during the follow-up were excluded. As a result, we found 98 individuals with NF1 and essential hypertension. The hazard for essential hypertension in NF1 was elevated with a HR of 1.73 (95% CI 1.39–2.14, $p < 0.001$) compared to the controls (Table 2). The HR remained essentially unchanged when the 6 months following cohort entry were excluded as a sensitivity analysis. The mean age at the time of the first hospital consultation with a record of essential hypertension was 63 years (SD 15) in NF1 individuals, and 69 years (SD 13) among the controls. The hazard for essential hypertension was higher among individuals with NF1 compared to the controls at ages ≤50 years with a HR of 3.24 ($p < 0.001$) and remained high in the NF1 patients >50 years with a HR of 1.59 ($p < 0.001$; Table 3). There was no statistically significant difference in the HRs for essential hypertension between men and women (Table 3). The HR for essential hypertension remained essentially unchanged after adjustment for educational level (HR 1.71, 95% CI 1.38–2.13). Adjustment for having a parent with NF1 slightly attenuated the estimate, yet the effect of NF1 remained significant (HR 1.53, 95% CI 1.18–1.98, $p = 0.001$). Among

TABLE 2 Comparison of hypertension diagnoses in NF1 individuals and controls based on hospital register data.

	ICD-10 category	Number of individuals with NF1	Number of controls	HR (95% CI)	*p* value
Any type of hypertension	I10, I11, I12, I13, I15	115	914	1.64 (1.34–2.00)	<0.001
Essential hypertension (excluding patients with also I15)	I10	98	862	1.73 (1.39–2.14)	<0.001
Secondary hypertension	I15	9	31	3.76 (1.77–7.95)	<0.001

Note: The table in based on the Finnish NF1 cohort of 1365 individuals, and a control cohort of 13,923 individuals followed up over the years 1996–2014.
Abbreviations: CI, confidence interval; HR, hazard ratio; ICD-10, International Standard Classification of Diseases, 10th revision.

TABLE 3 Essential hypertension in NF1 individuals compared to the controls and stratified by age and sex.

	Number of individuals with NF1	Number of controls	NF1 versus controls, HR (95% CI), *p*	Test between the subgroups[a] *p*
Age				
≤50	17	57	3.24 (1.88–5.59), <0.001	0.017
>50	81	805	1.59 (1.25–2.01), <0.001	
Sex				
Women	48	486	1.51 (1.11–2.05), 0.007	0.207
Men	50	376	2.01 (1.47–2.75), <0.001	

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Interaction between NF1 status and stratifying factor (age or sex).

individuals with a diagnosis of essential hypertension, the prevalence of factors potentially contributing to hypertension such as sleep apnea, obesity, smoking, or alcohol consumption did not differ between individuals with NF1 and the controls (Table 4).

Almost all patients with essential hypertension had purchased antihypertensive medication at least once (98.0% of individuals with NF1 and 98.3% of the controls). However, a smaller proportion of individuals with NF1 compared to the controls had purchased calcium channel blockers or agents acting on the renin-angiotensin system (Table 5). A total of 24.5% of individuals with NF1 had purchased drugs from only single ATC group during the follow-up, while the corresponding proportion was 12.4% among the controls ($p = 0.003$).

3.1 | The purchases of antihypertensive drugs by all individuals of the Finnish NF1 cohort

Since the essential hypertension is usually treated in the primary health care, which is not covered by The Finnish Care Register for Health Care, we performed a complementary analysis of all purchases of antihypertensive drugs. These purchases do not necessarily imply diagnosis of hypertension, yet they cover all levels of health care.

Analysis of the Finnish Register for Reimbursed Drug Purchases identified 388 individuals with NF1 and 3563 controls who had purchased antihypertensive medication at least once during the study period. No significant differences were observed in purchases of calcium channel blockers, or agents acting on the renin–angiotensin system (Table 6). Only diuretics and beta-blocking agents were associated with increased hazards in NF1.

4 | DISCUSSION

In this retrospective register-based study, we analyzed hospital visits for hypertension in a cohort of 1365 individuals with NF1 and 13,923 matched controls. We found a total of 115 individuals with NF1 and 914 controls with a diagnosis for a hypertensive disease. Not unexpectedly, secondary hypertension was relatively frequent (7.8%) in

TABLE 4 Comparison of factors potentially contributing to hypertension among NF1 individuals and the controls with essential hypertension.

Diagnosis of contributing factor	ICD-10	NF1 patients (98 individuals), *n* (%)	Controls (862 individuals), *n* (%)	OR (95% CI), *p*
Obstructive sleep apnea	G47.3	6 (6.1)	56 (6.5)	0.94 (0.32–2.26), 1.000
Obesity	E66	5 (5.1)	70 (8.1)	0.61 (0.19–1.54), 0.425
Use of tobacco and common respiratory diseases related to tobacco use	F17, J44	9 (9.2)	54 (6.3)	1.51 (0.63–3.23), 0.279
Harmful use of alcohol; behavioral, mental dependence, and diseases related to excessive alcohol consumption	ICD-10 codes[a]	6 (6.1)	66 (7.7)	0.79 (0.27–1.88), 0.690

Abbreviations: ICD-10, International Standard Classification of Diseases, 10th revision; OR, odds ratio.

[a]E24.4, F10, G31.2, G40.51, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, T51.0, Y90, Y91, Z50.2, Z71.4, Z72.1.

TABLE 5 Comparison of drug purchases between NF1 individuals and the controls with essential hypertension.

Purchases of antihypertensive treatment	ATC category[a]	NF1 patients (98 individuals), *n* (%)	Controls (862 individuals), *n* (%)	OR (95% CI), *p*
All types combined	C02, C03, C07, C08, C09	96 (98.0)	847 (98.3)	0.85 (0.19–7.78), 0.689
Antihypertensives	C02	NA	51 (5.92)	NA
Diuretics	C03	33 (33.7)	282 (32.7)	1.04 (0.65–1.65), 0.910
Beta-blocking agents	C07	67 (68.4)	615 (71.3)	0.87 (0.54–1.41), 0.557
Calcium channel blockers	C08	39 (39.8)	501 (58.1)	0.48 (0.30–0.74), 0.001
Agents acting on the renin–angiotensin system	C09	72 (73.5)	725 (84.1)	0.52 (0.32–0.89), 0.011

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification; CI, confidence interval; NA, number of patients <3; OR, odds ratio.

[a]The drugs considered in each category are listed in Table S1.

TABLE 6 Purchases of antihypertensive drugs in the Finnish NF1 cohort of 1365 individuals and the control cohort of 13,923 individuals in 1996–2014.

ATC category[a]	Number of individuals with NF1	Number of controls	HR (95% CI)	*p* value
C02, C03, C07, C08, C09	388	3563	1.35 (1.21–1.50)	<0.001
C02 antihypertensives	6	83	0.87 (0.38–2.00)	0.749
C03 diuretics	74	687	1.33 (1.04–1.69)	0.021
C07 beta-blocking agents	276	2430	1.41 (1.24–1.60)	<0.001
C08 calcium channel blockers	93	1223	0.90 (0.73–1.11)	0.319
C09 agents acting on the renin–angiotensin system	202	2188	1.09 (0.94–1.26)	0.248

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification; CI, confidence interval; HR, hazard ratio.

[a]The drugs considered in each category are listed in Table S1.

NF1. The underlying causes for secondary hypertension were in line with those previously identified in the literature (Carton et al., 2023). Renovascular hypertension was found in five out of nine individuals with secondary hypertension and NF1. None of the patients had a diagnosis of primary hyperaldosteronism or primary hyperparathyroidism. The possibility of secondary hypertension has to be kept in mind especially in younger NF1 individuals with hypertension, and in these cases, the evaluation of renovascular causes or pheochromocytoma should be initiated.

Despite the recognized association between NF1 and secondary hypertension, essential hypertension was the most common type of hypertension in patients with NF1. A total of 98 individuals with NF1 were observed to have essential hypertension, which corresponds to at least 85% of hypertensive NF1 individuals visiting hospital. The number of all NF1 individuals within the Finnish NF1 cohort with purchases of antihypertensive medication was 388. This suggests that the number of NF1 patients with hypertension is much higher than that observed in the specialized health care, and most individuals without need for specialized health care for hypertension likely had essential hypertension. This further highlights the predominance of essential hypertension in NF1.

The HR of 1.73 for essential hypertension observed in the present study is concordant with a Danish analysis that reported a relative risk of 1.5 (95% CI 1.1–2.0) for hospitalizations related to hypertensive disorders other than renal vascular hypertension in NF1 versus control population (Kenborg et al., 2020). In our study, the hazard for essential hypertension was increased among NF1 individuals visiting hospital compared to the controls in all age groups, yet the HR of 3.24 for essential hypertension in the age group ≤50 years was significantly higher than the HR of 1.59 in the age group >50 years. The hospital visits of NF1 individuals could have been due to any clinical reason and hypertension may have been diagnosed previously. The age difference suggests the possibility of earlier onset of hypertension in NF1 individuals compared to controls. However, one can speculate that this phenomenon is biased by the need of NF1 individuals to visit specialized health care for other health-related reasons or routine controls for NF1. In addition, the knowledge of the increased risk for hypertension in NF1 could lead to screening for blood pressure and thus patients with NF1 might have an increased probability to become diagnosed with hypertension. Nevertheless, it should be noted that there are no official government-supported NF expert centers in Finland and only a very small minority of adult patients with NF1 have regular health controls for their syndrome.

Sex was not associated with the relative hazard for secondary or essential hypertension in NF1 patients. Neither did the prevalence of potentially contributing conditions, such as sleep apnea, obesity, or tobacco/alcohol consumption differ between the NF1 and control groups with essential hypertension. The register-based data on diagnoses likely underestimate the prevalence of lifestyle factors, yet the threshold for recording these conditions can be assumed similar in the NF1 and control groups. NF1 is familial in 50% of the affected individuals and this may have a slight effect on the risk for hypertension, possibly mediated by lifestyle factors associated with the lower average educational attainment and income of individuals with NF1 (Colhoun et al., 1998; Doser et al., 2019; Johansson et al., 2021, 2022; Leng et al., 2015). However, the adjustment of the analyses for educational level had little impact on the estimates.

Almost all patients with essential hypertension had purchased antihypertensive medication at least once (98.0% of individuals with NF1 and 98.3% of the controls). However, a smaller proportion of individuals with NF1 than those of the controls had purchased drugs specific for the treatment of hypertension, that is, calcium channel blockers or agents acting on the renin–angiotensin system. In addition, individuals with NF1 had purchased, on the average, antihypertensive medication from fewer

ATC groups than the controls. The reasons for using fewer antihypertensive medicines in the NF1 group remain unresolved. This could be due to the earlier detection of hypertension as a result of the known association of hypertension with NF1. However, the proportions of the most severe essential hypertension entitled for a special drug reimbursement did not significantly differ between the NF1 and control groups (51% and 53%, respectively; $p = 0.749$), which suggests that the groups are not fundamentally different.

Even though the hospital data suggest that essential hypertension is more common in NF1, the analysis of purchases of antihypertensive medication does not necessarily support this concept. To gain an overview of the total number of NF1 patients treated for hypertension, we performed a complementary analysis of data from the Finnish Register for Reimbursed Drug Purchases, which covers all purchases of antihypertensive medicines irrespective of hospital care. Purchases of any type of antihypertensive medication showed a HR of 1.35 (95% CI 1.21–1.50) in the comparison between the NF1 and control groups. However, the hazards for the purchases of calcium channel blockers or agents acting on the renin–angiotensin system did not significantly differ between the groups. The analysis based on drug purchases only is less specific for hypertension than the hospital-based analysis, and the drugs may also have been prescribed for indications other than hypertension, such as prevention of migraine or cardiac arrhythmias. Nevertheless, the similar rates of entitlement for special drug reimbursement among NF1 and control individuals with antihypertensive medication suggest that the underlying distribution of indications for drug treatment does not differ between these two groups.

A major strength of this study is that the diagnoses of the Finnish NF1 cohort have been verified by individually reviewing medical records to meet the NIH criteria (National Institutes of Health Development Conference, 1988). Furthermore, the diagnoses recorded in the Care Register for Health Care allow distinguishing essential and secondary hypertension, which increases the specificity of the analysis. The hospital-based data cover specialized outpatient care in addition to inpatient hospitalizations, and the analysis of drug purchases unrelated to hospital visits further broadens the catchment of individuals with hypertension. The limitations of this study include lack of blood pressure values in the register data and hospital-based ascertainment of individuals with NF1, which may bias the cohort toward those with more severe disease manifestations. It is also likely that some patients with a record of essential hypertension have not been diagnosed with secondary hypertension yet. In addition, there is no unitary diagnosis method for the etiology of hypertension in NF1. Furthermore, the NF1 patients may receive more medical attention than controls, leading to higher diagnostic sensitivity.

The present results provide an overview of NF1-associated hypertension and confirm that NF1 is a risk factor for hypertension. While we cannot exclude the role of selection bias in the estimation of the hazard for essential hypertension, it is evident that essential hypertension is the predominant type in NF1.

AUTHOR CONTRIBUTIONS

Niina Loponen, Heli Ylä-Outinen, Roope A. Kallionpää, Mikko Valtanen, Kari Auranen, Hannu Järveläinen, Sirkku Peltonen, and Juha Peltonen: Conceptualization. Niina Loponen, Heli Ylä-Outinen, Roope A. Kallionpää, Mikko Valtanen, Sirkku Peltonen, and Juha Peltonen: Data curation. Roope A. Kallionpää, Mikko Valtanen, and Kari Auranen: Formal analysis. Niina Loponen, Heli Ylä-Outinen, Roope A. Kallionpää, Mikko Valtanen, Kari Auranen, Hannu Järveläinen, Sirkku Peltonen, and Juha Peltonen: Investigation. Juha Peltonen and Sirkku Peltonen: Resources. Niina Loponen, Heli Ylä-Outinen, and Roope A. Kallionpää: Writing—original draft. Niina Loponen, Heli Ylä-Outinen, Roope A. Kallionpää, Mikko Valtanen, Kari Auranen, Hannu Järveläinen, Sirkku Peltonen, and Juha Peltonen: Writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request for researchers though data access is restricted. Please contact the Finnish Institute for Health and Welfare, The Social Insurance Institution of Finland and Statistics Finland for permission. Data can be requested from the corresponding author Juha Peltonen: Institute of Biomedicine, University of Turku, Kiinamyllynkatu 10, FI-20520 Turku, Finland; juhpel@utu.fi.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (66/180/2012) and had research permissions from Finland's Ministry

of Social Affairs and Health, the Finnish Institute for Health and Welfare, the Social Insurance Institution of Finland, and the Population Register Centre of Finland. The study is register-based and retrospective and therefore exempt from obtaining informed consent from the participants.

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SUPPORTING INFORMATION

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