American Journal of Medical Genetics Part A

WILEY

AMERICAN JOURNAL OF medical genetics PART A

ORIGINAL ARTICLE OPEN ACCESS

Hospital Visits Associated With Oral Infections in Patients With Neurofibromatosis Type 1: A Register-Based Analysis

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Received: 19 June 2024 | **Revised:** 12 August 2024 | **Accepted:** 12 September 2024

Funding: The study has been funded with grants from the Turku University Hospital and the Cancer Foundation Finland. R.A.K. is funded by the Children's Tumor Foundation Young Investigator Award (Award ID: 2023-01-006; doi: https://doi.org/10.48105/CTF.CTF-2023-01-006.pc.gr.172004).

Keywords: dental caries | infections | morbidity | neurofibromatosis 1 | oral health

ABSTRACT

Various forms of oral involvement have been reported in patients with neurofibromatosis 1 (NF1). Here, we analyze register-based associations between NF1 and hospital visits related to oral infections. The Finnish NF1 cohort encompasses all individuals with verified NF1 who have visited the Finnish central and university hospitals in 1987–2011. The Finnish Care Register for Health Care allowed the follow-up of 1349 individuals with NF1, their 1894 siblings without NF1, and 13,870 matched controls for diagnoses related to oral infections in 1998–2014. We observed clearly increased hazards for hospital visits associated with dental caries (ICD-10 K02; NF1 vs. controls, hazard ratio [HR] 4.42, 95% CI 3.23–6.04), diseases of pulp and periapical tissues (K04; HR 3.85, 95% CI 2.68–5.54), and gingivitis and periodontal diseases (K05; HR 3.63, 95% CI 2.37–5.56). In contrast, hospital visits related to diseases of salivary glands (K11), and stomatitis and related lesions (K12) did not show significantly increased hazard in NF1 compared with the controls or the non-NF1 siblings. In conclusion, the findings suggest that hospital visits related to oral infections are relatively common among individuals with NF1. The results highlight the need for early detection, proactive prevention, and timely treatment of oral infections in individuals with NF1.

1 | Introduction

Neurofibromatosis type 1 (NF1) is a neurocutaneous-skeletal syndrome caused by pathogenic variants of the *NF1* tumor suppressor gene located at 17q11.2 (Wallace et al. 1990). NF1 is one of the most common rare diseases with a birth incidence of 1/3000–1/2000, and a prevalence of 1/4000–1/2000 (Evans et al. 2010; Uusitalo et al. 2015; Kallionpää et al. 2018; Lee et al. 2023). The inheritance of NF1 follows an autosomal dominant trait with highly variable phenotypic expression (Huson et al. 1989; Gutmann et al. 2017; Wu-Chou et al. 2018). The diagnosis of NF1 is based on criteria outlined by the National Institutes of Health Consensus Development Conference in 1987 and recently revised (National Institutes of Health Consensus

Development Conference 1988; Legius et al. 2021). Cutaneous neurofibromas and café au lait spots are the hallmarks of NF1 in skin (Huson et al. 1989; Gutmann et al. 2017; Ferner 2007). Plexiform neurofibromas grow along peripheral nerves and may form large and disfiguring tumor masses in the craniofacial region, trunk, and extremities (Gutmann et al. 2017). Plexiform neurofibromas may undergo malignant degeneration, and NF1 is also associated with a marked predisposition to cancer overall (Uusitalo et al. 2016). Individuals with NF1 also have, on average, decreased educational attainment and lower income than the general population (Doser et al. 2019; Johansson et al. 2021, 2022). Deficits of motor skills are common in NF1 (Johnson et al. 2010; Rietman et al. 2017), and it can be hypothesized that children with NF1, or their parents with NF1, may have trouble in brushing the child's teeth properly.

Oral infections can be caused by bacteria, viruses, and fungi, and lesions can be localized in teeth, oral mucosa, and tooth supporting tissues such as periodontal and periapical tissues. Diseases such as caries, gingivitis, stomatitis, periodontitis and apical periodontitis, as well as mucosal candidiasis are manifestations of oral infections. Of these infections, apical periodontitis is a prevalent condition around the apex of a root, primarily as a sequel to bacterial infection of dental caries, but can also occur due to response to trauma, attrition and abrasion of the tooth caused by mastication (Segura-Egea, Martín-González, and Castellanos-Cosano 2015). We have previously reported that women with NF1 are frequently present with periapical cemental dysplasia that may be misinterpreted as an inflammatory lesion based on radiographic findings (Visnapuu et al. 2007).

The previously reported estimates of oral involvement in patients with NF1 have ranged from rare to extremely frequent (3.4%–92%) (D'Ambrosio, Langlais, and Young 1988; Hall 2002; Freedus and Doyle 1975; Shapiro et al. 1984; Visnapuu et al. 2011, 2018) and various oral manifestations of patients with NF1 have been described earlier in several studies (Kobayashi, Matsune, and Ohashi 2012; Wotjiuk et al. 2019; Tucker et al. 2007; Javed et al. 2014; Tsang et al. 2010; Bardellini et al. 2011; Friedrich and Reul 2018). Most of these studies have focused on the frequency of dental caries among NF1 patients and the results indicate an increase in the prevalence of caries. However, we have earlier reported that individuals with NF1 who were younger than 35 years had less caries than the Finnish population in general as estimated by the dmft/DMFT index (Visnapuu et al. 2011). Since these results are somewhat conflicting with those of the other publications (D'Ambrosio, Langlais, and Young 1988; Hall 2002; Tucker et al. 2007), we have now chosen a different approach to study the prevalence of caries and certain other oral infections in individuals with NF1.

In the present register study, we have further investigated oral infections associated with NF1. We used the total population-based Finnish NF1 cohort with verified diagnoses of NF1 (Uusitalo et al. 2015) and the data from the Finnish Care Register for Health Care, which records all inpatient care and outpatient visits in secondary and tertiary referral centers in Finland. Health care visits related to oral infections as classified in the International Classification of Diseases, 10th revision (ICD-10) in individuals with NF1 were compared with their non-NF1 siblings and a 10-fold matched control cohort.

2 | Methods

2.1 | Cohorts

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (66/180/2012), and it adhered to the principles of the Declaration of Helsinki. Research permissions were obtained from the Finnish Institute for Health and Welfare, Finnish Population Register Centre, Statistics Finland, and all participating hospitals. As the study was register-based, no informed consent from the participants was required.

First, all 5 University and 15 Central Hospitals of mainland Finland were searched for NF1-related hospital visits in 1987–2011 (Uusitalo et al. 2015). Medical records of all identified individuals were reviewed to confirm NF1 diagnosis according to the NIH diagnostic criteria (National Institutes of Health Consensus Development Conference 1988), which yielded 1410 individuals with verified NF1.

A matched control cohort of 14,017 individuals was obtained from the Finnish Population Register Centre for comparison with the NF1 cohort. A maximum of 10 controls were retrieved for each individual with NF1. The controls were matched for the year of birth, sex, and municipality of residence on the cohort entry date of the respective individual with NF1. The use of the matched control cohort allows controlling biases related to age, sex, and geographical region. First-degree relatives of individuals with NF1 were excluded from the control cohort.

Individuals with NF1 were also compared with their 1949 non-NF1 siblings. The comparison with non-NF1 siblings of individuals with NF1 accounts for family-related factors such as socioeconomic background and genes other than *NF1*.

2.2 | Data Sources

The Care Register for Health Care is maintained by the Finnish Institute for Health and Welfare, and it covers inpatient care and specialized outpatient care. Specialized outpatient care has been registered since 1998. Up to six diagnosis codes can be associated with each hospital visit in the Care Register for Health Care, all of which were considered in the present analyses. The register was searched for hospital visits with ICD-10 diagnoses for Dental caries (K02), Other diseases of hard tissues of teeth (K03), Diseases of pulp and periapical tissues (K04), Gingivitis and periodontal diseases (K05), Diseases of salivary glands (K11), and Stomatitis and related lesions (K12), including the subcategories. We only considered diagnoses that were observed in at least five individuals with NF1 in order to comply with the current privacy regulations of Finnish register data.

The Care Register for Health Care was also used to identify individuals with tumors that may have affected the oral cavity, such as plexiform neurofibromas. Individuals with ICD-10 codes C00–C14, C30.0, C47.0, C49.0, C72.5, D00.0, D10, D11, D21.0, D33.3, D37.0, or D43.3 were considered to have relevant tumors. In addition, individuals with a diagnosis of dentofacial anomalies, including malocclusion, were identified with the ICD-10 code K07.

TABLE 1 | Characteristics of the study cohorts followed up over 1998–2014.

	NF1	Controls	Siblings
n	1349	13,870	1894
Males, *n* (%)	655 (48.6)	6681 (48.2)	986 (52.1)
Females, *n* (%)	694 (51.4)	7189 (51.8)	908 (47.9)
Year of birth, mean (SD)	1975.2 (21.6)	1974.4 (22.0)	1976.2 (18.5)
Age at the start of follow-up (years), mean (SD)	25.7 (20.7)	26.3 (21.0)	24.6 (17.5)
Age at the end of follow-up (years), mean (SD)	38.3 (20.8)	39.7 (21.5)	38.0 (18.4)
Follow-up time (person-years), mean (SD)	12.7 (4.9)	13.4 (4.5)	13.4 (4.4)
Follow-up time (person-years), sum	17,069.3	185,892.8	25,387.5

Dates of death and emigration were obtained from the Finnish Population Register Centre. The highest educational level of the parents of each individual with NF1 was retrieved from Statistics Finland. Statistics Finland collects information on degrees issued by Finnish institutions directly from the organizers of education. The information is presented using the International Standard Classification of Education (ISCED). We categorized education as short (ISCED 0–2, ~9 years of education), medium (ISCED 3–4, ~12 years), or long (ISCED ≥ 5, ≥ 15 years). Information on parental education was available for 1037 individuals with NF1.

2.3 | Statistical Methods

The follow-up of individuals with NF1 started on January 1, 1998, or the day of the first NF1-related hospital visit during the ascertainment period, whichever occurred later. The follow-up of controls started at the same time as the follow-up of the respective individual with NF1. The follow-up of the non-NF1 siblings started at birth or at the start of follow-up of the first sibling with NF1, whichever occurred later. In all groups, the follow-up ended at the first hospital visit of interest or censoring due to death, emigration or the end of follow-up on December 31, 2014.

In the primary analysis, the hazard ratio (HR) of each diagnosis of interest was estimated based on the whole study population and also separately for age groups ≤ 18 and > 18 years. As a secondary analysis, individuals with tumors near the oral cavity, or individuals with dentofacial anomalies were excluded to assess whether NF1 affects teeth and salivary glands independent of plexiform neurofibromas, other tumors, and dentofacial anomalies. Also, two other sensitivity analyses were conducted: First, hospital visits in our own institution, Turku University Hospital were excluded to ensure that the previous clinical study (Visnapuu et al. 2011) does not cause artificial excess incidence in the NF1 group. Second, individuals with hospital visits of interest within 30 days of cohort entry were excluded to control for a possible selection bias arising from NF1-related hospital visits made in close association with hospital visits related to oral infections.

Individuals with NF1 were compared with controls and non-NF1 siblings using Cox proportional hazards model with delayed entry and age as the timescale. The proportional hazards assumption was assessed with scaled Schoenfeld residuals and visual inspection. A frailty term was included to account for heterogeneity between the strata of each individual with NF1 and the matched controls, and between families when the sibling cohort was used. The rate of additional hospital visits with each diagnosis code among those with at least one encounter of interest was estimated using negative binomial regression with an offset for follow-up time. The point estimates are reported with 95% confidence intervals (CI). Differences between groups were considered statistically significant if the 95% CI did not contain 1. All analyses were conducted using the R software version 3.6.2 and packages survival, version 3.2-7, and MASS, version 7.3-53.

3 | Results

A total of 1349 individuals with NF1, 1894 siblings without NF1, and 13,870 controls contributed follow-up time during the study period of 1998–2014 (Table 1). Overall, 96 individuals with NF1 had at least one diagnosis of an oral infection, yielding a HR of 2.87 (95% CI 2.30–3.60) as compared with 377 controls, and a HR of 2.47 (95% CI 1.79–3.43) as compared with 60 non-NF1 siblings diagnosed with oral infections (Table 2). We observed significantly higher hazard for visiting a hospital with a diagnosis of dental caries (ICD-10 K02), other diseases of hard tissues of teeth (K03), diseases of pulp and periapical tissues (K04), and gingivitis and periodontal diseases (K05) in the NF1 cohort compared with the control cohort (Table 2). In contrast, there was no significant association between NF1 and hospital visits related to diseases of salivary glands (K11), and stomatitis and related lesions (K12).

3.1 | Dental Caries

The increased hazard for dental caries in NF1 was evident in the subcategories of caries limited to enamel (K02.0) and caries of dentine (K02.1) (Table 2). Dentine caries was the most frequently recorded type of dental caries affecting 48 individuals with NF1, 113 controls, and 17 non-NF1 siblings. Individuals with NF1 showed over 4-fold hazard for dentine caries compared with the control cohort or the siblings without NF1 (Table 2). The

TABLE 2 | Oral infections and diseases of salivary glands among 1349 individuals with neurofibromatosis type 1 (NF1) compared with 13,870 control individuals and 1894 siblings without NF1.

		NF1		Controls		Siblings			
	ICD-10	*n*	Mean age (SD)	*n*	Mean age (SD)	*n*	Mean age (SD)	Individuals with NF1 vs. controls, HR (95% CI)	Individuals with NF1 vs. siblings without NF1, HR (95% CI)
Any oral infection or a disease of salivary glands	K02, K03, K04, K05, K11, K12	96	28.5 (18.9)	377	35.6 (20.6)	60	33.1 (17.9)	2.87 (2.30–3.60)	2.47 (1.79–3.43)
Dental caries	K02	55	23.8 (18.7)	136	29.8 (21.0)	18	28.5 (20.8)	4.42 (3.23–6.04)	4.45 (2.59–7.64)
Caries limited to enamel	K02.0	10	15.2 (6.8)	9	37.8 (24.9)	< 5[a]	—[a]	11.8 (4.78–29.0)	—[a]
Caries of dentine	K02.1	48	24.7 (19.7)	113	30.0 (20.8)	17	29.8 (20.7)	4.65 (3.31–6.52)	4.09 (2.34–7.17)
Other diseases of hard tissues of teeth	K03	6	16.6 (12.2)	20	39.7 (22.1)	< 5[a]	—[a]	3.29 (1.32–8.19)	—[a]
Diseases of pulp and periapical tissues	K04	39	30.9 (19.5)	115	43.4 (18.7)	16	33.3 (18.8)	3.85 (2.68–5.54)	3.70 (2.06–6.65)
Pulpitis	K04.0	7	20.1 (18.3)	7	37.0 (18.0)	< 5[a]	—[a]	10.6 (3.73–30.3)	—[a]
Chronic apical periodontitis	K04.5	16	33.8 (17.4)	48	47.7 (17.9)	5	29.8 (25.8)	3.85 (2.18–6.80)	5.03 (1.83–13.8)
Radicular cyst	K04.8	7	48.0 (15.2)	16	46.4 (16.2)	< 5[a]	—[a]	4.92 (2.02–12.0)	—[a]
Gingivitis and periodontal diseases	K05	28	35.3 (17.5)	89	39.3 (18.0)	11	33.9 (16.7)	3.63 (2.37–5.56)	3.93 (1.94–7.92)
Chronic periodontitis	K05.3	18	41.5 (17.0)	73	40.5 (18.1)	9	32.6 (17.2)	2.83 (1.69–4.74)	3.08 (1.37–6.91)
Diseases of salivary glands	K11	10	35.1 (19.7)	75	37.2 (21.2)	16	36.8 (16.0)	1.47 (0.76–2.84)	1.02 (0.45–2.27)
Mucocele of salivary Gland	K11.6	5	25.4 (17.5)	13	25.3 (13.1)	< 5[a]	—[a]	4.08 (1.45–11.4)	—[a]
Stomatitis and related lesions	K12	5	30.6 (10.1)	23	33.2 (19.6)	8	31.7 (20.2)	2.35 (0.89–6.19)	1.08 (0.35–3.30)

Abbreviations: CI: confidence interval; HR: hazard ratio; ICD-10: International classification of diseases, 10th edition.
[a]In accordance with the regulations of Statistics Finland, case numbers < 5 and the associated mean ages and model estimates are not provided to protect patient privacy.

difference was not likely caused by ascertainment bias, since the estimates remained similar after excluding hospital visits at the site of our previous clinical study, Turku University Hospital (HR NF1 vs. controls 3.98, 95% CI 2.69–5.91), or the individuals with hospital visits of interest within 30 days of the cohort entry (HR NF1 vs. controls 4.58, 95% CI 3.26–6.44). Head and neck tumors such as plexiform neurofibromas, and dentofacial anomalies including malocclusion may complicate the maintenance of oral hygiene. The exclusion of those who had a hospital visit related to a tumor of the head or neck yielded a HR of 4.26 (95% CI 2.95–6.15) for individuals with NF1 versus controls, suggesting that the association of dentine caries with NF1 was not due to NF1-related tumors. The exclusion of individuals with dentofacial anomalies slightly attenuated the HR estimate for dentine caries yet the effect of NF1 remained clearly significant (HR 4.03, 95% CI 2.76–5.87).

Despite the relatively high hazard for an initial hospital visit associated with dentine caries among individuals with NF1, the rates of follow-up visits did not differ between individuals with NF1 and controls (Table 3). Of the first hospital visits associated with dentine caries, 46%, 41%, and 35% occurred at ages under 18 years among individuals with NF1, controls, and the siblings without NF1, respectively. The effect of NF1 on the hazard for dentine caries compared with the controls or with the siblings without NF1 did not significantly differ between individuals younger and older than 18 years (Table 4). Effect modification by parental education was assessed by stratifying the analysis of individuals with NF1 compared with their non-NF1 siblings with the parental highest level of education (Table 5). The results demonstrated a U-shaped pattern with the largest effect of NF1 among those with low and high parental education, whereas a medium education was associated with the smallest HR. A combined estimate with adjustment for parental education demonstrated an HR of 5.26 (95% CI 2.61–10.60) for a hospital visit associated with dentine caries, indicating that the increased hazard for dentine caries observed in the NF1 group is not attributable to the differences in the educational background of the parents of individuals with NF1, their non-NF1 siblings, or controls.

3.2 | Diseases of Pulp and Periapical Tissues

Individuals with NF1 showed a higher hazard for hospital visits related to diseases of pulp and periapical tissues compared with the controls and the non-NF1 siblings of individuals with NF1 (Table 2). Diseases of pulp and periapical tissues had been recorded in 39 individuals with NF1, 115 controls, and 16 non-NF1 siblings. The subcategories of pulpitis (K04.0), chronic apical periodontitis (K04.5), and radical cyst (K04.8) showed increased hazards in NF1 (Table 2). In addition, individuals with NF1 had a lower mean age at the first hospital visit related to chronic apical periodontitis compared with the controls ($p = 0.010$; Table 2). Compared with the plain HR of 3.85 for diseases of pulp and periapical tissues between the NF1 and control cohorts (Table 2), the exclusion of individuals with tumors of the head and neck, or individuals with dentofacial anomalies affected the results only slightly (HRs 3.26, 95% CI 2.17–4.88, and 3.67, 95% CI 2.48–5.44, respectively). Similarly, the exclusion of hospital visits in the Turku University Hospital (HR 4.39, 95% CI 2.97–6.49) or the individuals with hospital visits of interest within 30 days of cohort entry (HR 3.85, 95% CI 2.68–5.54) had little to no effect on the comparison between individuals with NF1 and controls.

The rates of follow-up visits related to the diseases of pulp and periapical tissues did not differ between individuals with NF1 and controls (Table 3). Surprisingly, although an increased hazard for chronic apical periodontitis was observed in NF1 compared with controls, the rate of follow-up visits related to this diagnosis was significantly lower among individuals with NF1 than among controls ($p = 0.027$; Table 3).

In the comparison between the NF1 and control cohorts, a significantly higher HR for diseases of pulp and periapical tissues was observed among individuals younger than 18 years

TABLE 3 | The numbers of follow-up visits per years of follow-up after an initial hospital visit with each diagnosis of interest.

	ICD-10	NF1, mean (10% percentile–90% percentile)	Controls, mean (10% percentile–90% percentile)	Individuals with NF1 vs. controls, RR (95% CI)
Dental caries	K02	0.50 (0.00–1.30)	0.33 (0.00–1.00)	1.39 (0.78–2.47)
Caries of dentine	K02.1	0.52 (0.00–1.10)	0.33 (0.00–0.86)	1.34 (0.75–2.38)
Diseases of pulp and periapical tissues	K04	0.56 (0.00–1.40)	0.49 (0.00–1.10)	0.90 (0.46–1.76)
Chronic apical periodontitis	K04.5	0.18 (0.00–0.33)	0.47 (0.00–1.10)	0.30 (0.10–0.87)
Gingivitis and periodontal diseases	K05	0.46 (0.00–1.70)	1.10 (0.00–2.30)	0.52 (0.19–1.46)
Chronic periodontitis	K05.3	0.45 (0.00–1.70)	1.00 (0.00–1.90)	0.60 (0.17–2.17)
Diseases of salivary glands	K11	0.68 (0.00–1.60)	0.20 (0.00–0.60)	2.65 (1.03–6.78)

Note: The number of individuals with NF1 and controls with an initial hospital visit related to each diagnosis are shown in Table 2. The results were only computed for diagnosis codes observed in at least 10 individuals with NF1 and 10 control individuals.
Abbreviations: CI: confidence interval; ICD-10: International classification of diseases, 10th edition; RR: rate ratio.

TABLE 4 | Age-stratified comparison of the hazards for certain diagnoses among individuals with NF1, controls, and siblings without NF1.

		Age ≤ 18 years					Age > 18 years					
	ICD-10	*n* (NF1)	*n* (Controls)	*n* (Siblings)	Individuals with NF1 vs. controls, HR (95% CI)	Individuals with NF1 vs. siblings without NF1, HR (95% CI)	*n* (NF1)	*n* (Controls)	*n* (Siblings)	Individuals with NF1 vs. controls, HR (95% CI)	Individuals with NF1 vs. siblings without NF1, HR (95% CI)	Difference between age groups, NF1 vs. controls, *p*	Difference between age groups, NF1 vs. siblings, *p*
Dental caries	K02	26	56	7	4.82 (3.03–7.68)	4.37 (1.88–10.2)	29	80	11	4.11 (2.68–6.28)	4.43 (2.20–8.93)	0.620	0.490
Caries of dentine	K02.1	22	46	6	4.99 (3.00–8.30)	4.28 (1.72–10.6)	26	67	11	4.39 (2.79–6.91)	4.00 (1.96–8.16)	0.720	0.470
Diseases of pulp and periapical tissues	K04	12	12	—	10.3 (4.64–23.0)	—	27	103	—	3.02 (1.98–4.62)	—	0.008	—

Note: Diagnoses with < 5 individuals in either age category are not shown.
Abbreviations: CI: confidence interval; HR: hazard ratio.

compared with older individuals ($p = 0.008$; Table 4). When the comparison between individuals with NF1 and their siblings without NF1 was stratified with the highest parental level of education, an adjusted HR of 5.33 (95% CI 2.53–11.20) was observed (Table 5). Similar to dental caries, the parental education modified the effect of NF1 in a bimodal pattern with the smallest effect of NF1 observed among those with medium parental education.

3.3 | Gingivitis and Periodontal Diseases

A total of 28 individuals with NF1 had a diagnosis for gingivitis and periodontal diseases (K05) during the follow-up, while the respective number was 89 in controls and 11 in the non-NF1 siblings of individuals with NF1. Gingivitis and periodontal diseases were associated with an increased hazard in individuals with NF1 as compared with controls or with the non-NF1 siblings of individuals with NF1 (HR point estimates 3.63 and 3.93, respectively; Table 2). Hospital visits related to the subcategory of chronic periodontitis also showed an increased hazard among individuals with NF1 compared with controls and the non-NF1 siblings of individuals with NF1. The increased hazard for gingivitis and periodontal diseases in the NF1 cohort compared with the controls remained essentially unchanged in the sensitivity analyses excluding individuals with head and neck tumors (HR 3.43, 95% CI 2.13–5.52), visits to Turku University Hospital (HR 3.54, 95% CI 2.23–5.60), or visits within 30 days of cohort entry (HR 3.63, 95% CI 2.37–5.56). The exclusion of individuals with dentofacial anomalies slightly attenuated the estimate (HR 2.88, 95% CI 1.74–4.76). The rate of follow-up visits related to gingivitis and periodontal diseases, or to the subcategory of chronic periodontitis was slightly although not statistically significantly lower in individuals with NF1 compared with the controls (Table 3). Gingivitis and periodontal diseases demonstrated an interaction between NF1 and parental education similar to the above analyses, that is, the HR was lowest among those with medium parental education (Table 5).

3.4 | Diseases of Salivary Glands

The hazard of initial hospital visits associated with diseases of salivary glands (K11) was not significantly higher among individuals with NF1 compared with controls or the non-NF1 siblings (Table 2). Hospital visits related to diseases of salivary glands were observed in 10 individuals with NF1, 75 controls, and 16 non-NF1 siblings. We also searched for hospital visits related to dry mouth (ICD-10 R68.2), yet the number of diagnoses was insufficient to allow analysis. However, follow-up visits related to diseases of salivary glands were more frequent among individuals with NF1 than among controls ($p = 0.043$; Table 3). Interestingly, the subcategory of mucocele of salivary gland (K11.6) was associated with an increased hazard in individuals with NF1 compared with controls (HR 4.08, 95% CI 1.45–11.4; Table 2). The increased hazard for mucocele of salivary gland persisted in the sensitivity analyses excluding individuals with head and neck tumors (HR 3.44, 95% CI 1.12–10.5), individuals with dentofacial anomalies (HR 4.18, 95% CI 1.49–11.7), visits to Turku University Hospital (HR 5.29, 95% CI 1.81–15.5), or visits within 30 days of cohort entry (HR 4.08, 95% CI 1.45–11.4).

TABLE 5 | The hazard ratios for certain diagnoses among individuals with NF1 versus siblings without NF1 stratified by the parental highest level of education.

	ICD-10	ISCED 0–2, HR (95% CI)	ISCED 3–4, HR (95% CI)	ISCED 5–8, HR (95% CI)	Combined estimate with adjustment for parental education, HR (95% CI)
Dental caries	K02	9.32 (1.96–44.3)	3.63 (1.31–10.0)	6.18 (2.10–18.2)	5.41 (2.77–10.5)
Caries of dentine	K02.1	9.32 (1.96–44.3)	3.14 (1.13–8.71)	6.48 (1.88–22.4)	5.26 (2.61–10.6)
Diseases of pulp and periapical tissues	K04	7.50 (2.46–22.9)	1.82 (0.54–6.08)	13.30 (1.69–105.0)	5.33 (2.53–11.2)
Gingivitis and periodontal diseases	K05	4.94 (1.25–19.6)	2.65 (0.81–8.63)	10.40 (1.28–85.0)	4.50 (2.00–10.2)
Chronic periodontitis	K05.3	5.53 (1.04–29.4)	1.51 (0.40–5.62)	8.06 (0.94–69.1)	3.49 (1.41–8.65)
Disease of Salivary glands	K11	0.67 (0.13–3.39)	5.67 (0.63–51.3)	2.27 (0.37–13.8)	1.61 (0.63–4.11)

Abbreviations: CI: confidence interval; HR: hazard ratio; ISCED: international standard classification of education.

3.5 | Stomatitis and Related Lesions

The hazard of initial hospital visits for stomatitis and related lesions was not significantly higher among individuals with NF1 compared with the controls or the siblings without NF1 (Table 2), although the point estimate for the comparison of the NF1 cohort versus the control cohort suggested a potentially increased hazard (HR 2.35, 95% CI 0.89–6.19). The result was unaffected by the exclusion of visits to Turku University Hospital (HR 2.29, 95% CI 0.78–6.73), or the 30 days following the cohort entry (HR 2.35, 95% CI 0.89–6.19). The number of individuals with NF1 and stomatitis and related lesions was only five, and many of them had tumors of the head and neck. Therefore, the HR could not be evaluated after exclusion of those with head and neck tumors.

4 | Discussion

The present results provide an overview of oral infections among individuals with NF1. We observed increased hazards for hospital visits related to a variety of different manifestations of oral infections including dental caries, diseases of pulp and periapical tissues, gingivitis and periodontal diseases. The results highlight that oral health needs to be specifically considered in the clinical care of individuals with NF1. This is particularly important since individuals with NF1 often undergo major surgeries due to, for example, plexiform neurofibromas, cancer or skeletal problems (Uusitalo et al. 2016; Elefteriou et al. 2009), and oral infections may increase the risks associated with surgeries. Individuals with NF1 also show increased propensity for diseases of the circulatory system (Uusitalo et al. 2015; Kenborg et al. 2020; Kallionpää et al. 2024; Loponen et al. 2024), the risk of which is also increased by poor oral health (Bui et al. 2019; Mesa et al. 2019; Priyamvara et al. 2020; Pietiäinen et al. 2018). Individuals with NF1 showed increased hazard for dental caries, and for diseases of pulp and periapical tissues at ages both below and above 18 years (Table 4). This suggests that the NF1-related predisposition to these manifestations is not limited to either children or adults.

The results and study settings of previous studies on oral infections including caries among individuals with NF1 have varied from survey studies and clinical case series to register studies (D'Ambrosio, Langlais, and Young 1988; Hall 2002; Visnapuu et al. 2011, 2018; Kobayashi, Matsune, and Ohashi 2012; Wotjiuk et al. 2019; Tucker et al. 2007; Javed et al. 2014; Freedus and Doyle 1975; Shapiro et al. 1984; Tsang et al. 2010; Bardellini et al. 2011). The present study on hospital registry data showed a 4-fold increase in the hazard for hospital visits associated with dentine caries compared with the control cohort or the siblings without NF1, and the HR was similar in both children and adults. Caries was also suggested to be common among individuals with NF1 in a questionnaire study by Tucker et al. (2007). A study of 11 patients reported NF1-related excess caries only in older age groups (Thota et al. 2022). Tsang et al. (2010) found similar prevalence of caries in 18 children with NF1 and their non-NF1 siblings. Our previous study on 110 NF1 patients included both dental and radiological examinations, and no increase in the prevalence of caries was observed as compared with the Finnish population in general (Visnapuu et al. 2011). It is possible that there was a selection bias, that is, the healthy volunteer bias, and the patients enrolled in the study may have taken better care of their dental health than average patients with NF1. Kobayashi, Matsune, and Ohashi (2012) suggested that individuals with NF1 have more oral infections compared with controls. Concordant with the present results, a Danish register-based study reported a relative risk of 4.3 (95% CI 3.0–6.0) for hospitalizations related to diseases of the teeth and supporting structures among individuals with NF1 (Kenborg et al. 2020).

As expected, the initial hospital visits associated with each diagnosis were often followed by additional hospital visits. Despite the generally high HRs for initial hospital visits related to oral infections in the comparisons of individuals with

NF1 versus their non-NF1 siblings and matched controls, the rates of follow-up visits were mostly similar between the NF1 and control cohorts. It thus seems that individuals with NF1 are diagnosed with oral infections more frequently and sometimes also earlier than the controls or the non-NF1 siblings, yet the management of the infections mostly does not differ from the controls. The follow-up visits related to chronic apical periodontitis were even significantly fewer among individuals with NF1 compared with the controls (rate ratio 0.30) although the initial visits associated with chronic apical periodontitis displayed a HR of 3.85. Such a difference between the first and subsequent contacts could be caused by a milder disease, mandating fewer follow-up visits, which could be caused by a higher sensitivity of making the initial diagnosis due to the co-morbidities of NF1, such as oral health examinations preceding major surgeries. In addition, many radiolucent lesions of non-endodontic origin mimic endodontic pathoses such as inflammation of the pulp in individuals with NF1 (Visnapuu et al. 2007), and the relatively modest rate of follow-up visits could be caused by false initial diagnoses. Another hypothetical possibility is that individuals with NF1 do not adhere to the treatment, which could be due to, for example, their cognitive difficulties (Descheemaeker et al. 2013; Plasschaert et al. 2016) or lower income (Johansson et al. 2022). The role of factors associated with socioeconomic status is supported by the association of parental education with the HR for initial hospital visits related to oral infections.

When we stratified the HRs for initial hospital visits by the parental highest level of education, most diagnoses displayed a bimodal pattern: the highest HR estimates were observed among those with the lowest and highest parental education, whereas medium parental education resulted in the lowest HR for hospital visits related to the oral infections of interest. This is probably due to the interference of two different mechanisms. Low parental education may indeed lead to a greater risk for oral infections, and this could increase the NF1-related predisposition to oral infections. The result highlights the need to support and provide sufficient oral health care follow-up for families with low parental education and children with NF1. In contrast, the high HR among those with the highest parental education is likely due to greater interest in health and better possibilities to seek medical attention. Individuals with NF1 from families with medium parental education may therefore represent a population who do not suffer from problems serious enough to mandate health care contacts, but they could benefit from increased follow-up to match the level of health care contacts observed in the group with the highest parental education.

Saliva has a crucial role in protecting the oral cavity. Accordingly, individuals with low unstimulated salivary flow rate have a higher risk for dental caries due to lowered buffering capacity of their saliva and the low clearance rate of food debris. Dental plaque due to hyposalivation or poor oral hygiene initiates not only caries but also gingivitis, which might progress toward periodontal disease (Dawes and Wong 2019). Unfortunately, there are only few studies which have analyzed salivary flow rate or its composition in association with NF1. Thota et al. reported in their case–control study in 2022 that NF1 was associated with gingivitis and periodontitis, decreased salivary flow rates, compromised salivary amylase activities, and high prevalence of caries, all in an age-dependent manner (significant changes in individuals with NF1 older than 20 years vs. those under 20 years) (Thota et al. 2022). Recently, it was shown that neurofibromin is expressed in the cytoplasm of serous and mucous acinar cells, and ductal cells of salivary glands, suggesting that this protein may be involved in the regulation of salivary gland function (Luna et al. 2021).

In the present register study, the salivary glands could only be assessed using hospital-based diagnosis codes for the diseases of salivary glands. Neither salivary gland diseases nor stomatitis and related lesions showed a significantly higher hazard in NF1 versus controls or the non-NF1 siblings. However, the subcategory of mucocele of salivary gland was associated with an increased hazard among patients with NF1 compared with controls, and the category of diseases of salivary glands showed a higher rate of follow-up visits among individuals with NF1 than among controls. We have earlier shown that oral mucosal neurofibromas are common among individuals with NF1 (Jouhilahti et al. 2012). Differential diagnosis between mucocele and mucosal neurofibroma may be difficult for a clinician, and the increased hazard for mucocele may in fact represent oral neurofibromas in the NF1 group. This hypothesis is also supported by the slight increase in the relative hazard for mucocele when visits to Turku University Hospital were excluded. The Turku University Hospital represents a major center for specialist care of individuals with NF1 in Finland, and the rate of misdiagnosed mucosal neurofibromas may therefore be lower.

Tumors such as plexiform neurofibromas are a frequent cause of craniofacial manifestations in NF1 (Kobayashi, Matsune, and Ohashi 2012). Tumors may cause compression and complicate the maintenance of oral hygiene. However, the treatment of head and neck tumors may also lead to increased attention to oral health and thereby rather affect the diagnostic sensitivity than the true incidence of oral diseases. This is also the case with dentofacial anomalies, which may affect oral hygiene, or increase the number of dentist's appointments and thereby affect the diagnostic sensitivity. In the present study, we performed sensitivity analyses where individuals diagnosed with head and neck tumors or dentofacial anomalies were excluded. This led to the exclusion of 0%–32% of individuals with a diagnosis of interest depending on the analysis and had little effect on the HRs for oral infections, and therefore indicates that the results were not because of tumor compression or increased diagnostic sensitivity related to the treatment of head and neck tumors or dentofacial anomalies. However, since the present retrospective epidemiological study was based on information on hospital visits, it is possible that the overall higher rates of NF1-related morbidity and hospital visits among individuals with NF1 (Kenborg et al. 2020; Johansson et al. 2022) could also induce artificially high numbers of hospital visits related to oral infections. In addition to the lack of effect of the exclusion of individuals with head and neck tumors, the exclusion of those with hospital visits related to oral infections within 30 days following the cohort entry had no effect on the results, leading to the exclusion of 0%–2% of individuals with a diagnosis of interest, which speaks against a bias caused by the increased medical attention for NF1. Moreover, the exclusion of visits to Turku University Hospital, the site of our previous clinical study, led to

no marked changes in the estimates with 0%–29% reductions in the numbers of individuals with diagnoses of interest.

The Finnish Care Register for Health Care has registered visits in specialized outpatient care since 1998, and it also covers inpatient care. However, most dentist's appointments occur in primary health care and are therefore not covered by the present material. This leads to relatively low numbers of individuals with visits related to the diagnoses of interest (Table 2). Nevertheless, the ratio of hospital visits of individuals with and without NF1 is likely reflective of the true relative risk in the NF1 cohort, unless there is a systematic difference in the severity or subtypes of oral infections between the NF1 cohort, and the cohorts without NF1, as discussed above. Since the data are register-based, we had to adhere to the diagnostic categories included in the ICD-10 classification. Due to the limited number of patients with the diagnoses of interest, we are not able to provide fully detailed description of the conditions associated with NF1 or to detect subtle differences in the subtypes of oral infections.

We aimed to provide an overview of oral infections in NF1. Therefore, multiple relevant diagnosis codes were analyzed and, since the analysis was explorative in nature, no correction for multiple testing was applied. This increases the risk for false positive findings. The concordant results from the comparisons of NF1 versus controls and NF1 versus the non-NF1 siblings, as well as the similar estimates for the different types of oral infections with shared etiological factors suggest that the observed associations are reliable. One individual could have multiple different oral infections and may therefore have been included in multiple analyses. On the other hand, when an individual has had multiple simultaneous oral infections, the diagnosis code for the most severe one may have been more likely to be recorded than the codes for other diseases. To mitigate this issue, all the diagnosis codes associated with each visit were considered, yet some degree of underreporting even within the hospital-based visits has likely occurred. The use of controls matched with age, sex, and area of residence, and the non-NF1 siblings of individuals with NF1 as points of comparison allows us to exclude confounders related to, for example, geographic differences, genes other than *NF1*, or calendar time. The analyses were not adjusted for calendar time, since the current practices of promoting oral health had already been well established at the beginning of the study period in 1998.

In conclusion, hospital visits related to oral infections are relatively frequently recorded among individuals with NF1. The present data does not provide conclusive evidence of the mechanism linking NF1 with hospital visits related to oral infections, and future studies should address this question. While there is no evidence of greater severity of these diagnoses among individuals with NF1, the results highlight the need for early observation, prevention, and treatment of oral infections in patients with NF1.

Author Contributions

Conceptualization: V.R., R.A.K., S.P., and J.P. Formal analysis: R.A.K., M.V., and K.A. Investigation: All authors. Writing – original draft: V.R., R.A.K., S.S., S.P., and J.P. Writing – revising: All authors. All authors read and approved the final manuscript.

Acknowledgments

The study has been carried out in Turku University Hospital which is a member of the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS). ERN GENTURIS is funded by the European Union.

Ethics Statement

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (66/180/2012), and it adhered to the principles of the Declaration of Helsinki. Research permissions were obtained from the Finnish Institute for Health and Welfare, Finnish Population Register Centre, Statistics Finland and all participating hospitals.

Consent

The study is retrospective and register-based and therefore exempt from obtaining informed consent from the participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from Finnish Social and Health Data Permit Authority Findata. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of Finnish Social and Health Data Permit Authority Findata.

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