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Dentofacial Malocclusion in Neurofibromatosis 1 in Finland

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ABSTRACT

Neurofibromatosis 1 (NF1) is an inherited disease that can be accompanied by oral health problems such as caries, periodontitis, and tumors affecting the oral cavity. Also, different maxillary and mandibular malformations are associated with NF1. In this retrospective register-based study, we evaluated hospital visits related to dentofacial malocclusion in 1349 individuals with NF1, 13,870 matched controls and 1894 non-NF1 siblings followed up over 1998–2014 using the Finnish Care Register for Health Care that covers information on inpatient care and specialist outpatient care. Hazard ratios (HRs) and their 95% confidence intervals (CI) were estimated with the Cox proportional hazards model. Individuals with NF1 had a higher hazard for hospital visits related to embedded and impacted teeth (HR 2.1, 95% CI 1.2–3.5), disorders of tooth development and eruption (HR 3.7, 95% CI 1.9–7.1), and dentofacial anomalies (HR 2.7, 95% CI 1.9–3.8) such as anomalies in dental arch relationship (HR 4.8, 95% CI 2.9–7.9) and anomalies of jaw-cranial base relationship (HR 2.2, 95% CI 1.1–4.3) compared with controls. Plexiform neurofibromas did not markedly affect the estimates. Early detection of jaw and dental alterations, which may be linked to previously identified cephalometric features of NF1, is important for preventing occlusal defects, maintaining oral hygiene, and preserving quality of life.

1 | Introduction

Individuals with the heritable multiorgan syndrome neurofibromatosis type 1 (NF1) may display a variety of craniofacial manifestations (Friedrich et al. 2003; Visnapuu et al. 2018). NF1 is caused by pathogenic variants in the *NF1* tumor suppressor gene, located at 17q11.2 (Wallace et al. 1990; Gutmann et al. 2017). NF1 has a birth incidence of 1:3000–1:2000 and a

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prevalence of 1:4000–1:2000 (Uusitalo et al. 2015; Kallionpää et al. 2018; Evans et al. 2010; Lee et al. 2023). 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 typical skin findings related to NF1 (Gutmann et al. 2017; Huson et al. 1989). NF1 is associated with a predisposition to both malignant and benign tumors (Uusitalo et al. 2016; Seminog and Goldacre 2013; Landry et al. 2021). Tumors pathognomonic to NF1, plexiform neurofibromas, may also occur in the craniofacial region, and they may undergo malignant transformation.

Oral soft and hard tissue manifestations have been reported to occur in a significant proportion of children and adults with NF1 (Friedrich et al. 2003; Visnapuu et al. 2018, 2011; Freedus and Doyle 1975; Shapiro et al. 1984; D'Ambrosio et al. 1988; Hall 2002). Dentofacial malocclusion is a dental condition characterized by a misalignment or incorrect relation between the teeth of the upper and lower dental arches, or between the jaws and the face, affecting the overall appearance and function of the teeth, jaw, and facial structures. Few data exist on the frequency of health care visits related to dentofacial malocclusion in patients with NF1. Bardellini et al. suggested that occlusal traits in children with NF1 highlight a significantly higher percentage of class III molar relationship and reverse overjet compared with healthy children (Bardellini et al. 2011, 2016). Class III dental malocclusion represents a growth-related dentofacial deformity with mandibular prognathism in relation to the maxilla and/or cranial base. Several conditions such as environmental or genetic factors may cause the development of class III malocclusion. Others and we have previously reported that adult patients with NF1 have a short mandible, maxilla, and cranial base compared with controls, which often causes mesial occlusion (Heervä et al. 2011; Luna et al. 2018; Cung et al. 2015). The length of the mandible, the maxilla, and the cranial base correlate with the height of NF1 patients among adolescents but not in adults (Heervä et al. 2011).

Using the Finnish NF1 cohort (Uusitalo et al. 2015), we have previously reported increased hazards for various oral infections such as dental caries, gingivitis, and periodontal diseases in NF1 (Reinhold et al. 2025). The aim of the present study was to further expand our understanding of oral health in NF1 by examining dentofacial malocclusion and related diagnoses in the same cohort. We analyzed outpatient and inpatient hospital visits for diagnoses related to the disorders of tooth development and eruption, embedded and impacted teeth, and dentofacial anomalies. Individuals with NF1 were compared with their non-NF1 siblings as well as with matched controls.

2 | Patients and Methods

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland, and it adhered to the principles of the Declaration of Helsinki. Research permissions were secured from the Finnish Institute for Health and Welfare, Finnish Population Register Centre, Statistics Finland, and all participating hospitals. The study was register-based and therefore exempt from obtaining informed consent from the participants.

2.1 | Participants and Data Sources

The NF1 cohort of 1410 individuals was previously established based on the records of NF1-related hospital visits in the five University and 15 Central Hospitals of mainland Finland during 1987–2011 (Uusitalo et al. 2015). The NF1 diagnoses were confirmed by reviewing the medical records of all the individuals in the NF1 cohort. An individually matched control cohort was obtained from the Finnish Population Register Centre by sampling a maximum of 10 controls for each NF1 individual matched for age, sex, and area of residence, resulting in a total of 14,017 controls. The first-degree relatives of the individuals with NF1 were considered ineligible for the control cohort. In addition, a second control cohort consisted of 1949 non-NF1 siblings of the NF1 individuals, aimed to match unobserved family-related factors such as parental socioeconomic status and genetic background. The cohorts have previously been used to analyze oral infections in individuals with NF1 (Reinhold et al. 2025).

Hospital visits for all individuals were searched from the Care Register for Health Care, maintained by the Finnish Institute for Health and Welfare. The register covers specialized outpatient care since 1998. The endpoint events were defined as hospital visits with diagnoses for disorders of tooth development and eruption (K00), embedded and impacted teeth (K01), and dentofacial anomalies including malocclusion (K07), as classified in the International Classification of Diseases, 10th Edition (ICD-10). In addition, hospital visits related to relevant ICD-10 subcodes of these diagnoses were analyzed. The dates of death and emigration were obtained from the Finnish Population Register Centre.

The start of the follow-up (cohort entry) for all individuals within each matched group was set to either the day of the first NF1-related hospital visit of the NF1 individual or January 1st, 1998, whichever was later. For the non-NF1 siblings, the start of follow-up was the latter of birth or the cohort entry date of the first family member with NF1. The follow-up was terminated at the first hospital visit with a diagnosis of interest or death, emigration, or reaching the end date of the study, that is, December 31st, 2014.

2.2 | Statistical Analyses

The incidence of hospital visits of interest was compared between the NF1 and control cohorts using Cox proportional hazards models similar to our previous study on oral infections in NF1 (Reinhold et al. 2025). Age was used as the time scale. The analysis was left-truncated at the age of cohort entry, and the events of death, emigration, or reaching the end of the study were considered as uninformative right censoring. The proportional hazards assumption of the Cox model was assessed by visual inspection and testing for a linear dependency of scaled Schoenfeld residuals on the time scale. A frailty term was included for each stratum containing an NF1 individual and the matched controls, or in the case of the

sibling cohort, containing the members of the same family. The analyses were also performed separately for age groups ≤ 18 years and > 18 years.

Three sensitivity analyses were conducted. First, individuals with hospital visits within 30 days of the cohort entry were excluded to control for the possibility of an association between the probabilities of cohort entry and endpoint diagnoses. In the second sensitivity analysis, diagnoses made at the Turku University Hospital were ignored to eliminate the potential contribution of an earlier clinical study to diagnostic sensitivity (Visnapuu et al. 2011). The third sensitivity analysis excluded individuals with diagnoses related to head and neck tumors such as plexiform neurofibromas that could affect the oral cavity (ICD-10 codes C00–C14, C30.0, C47.0, C49.0, C72.5, D00.0, D10, D11, D21.0, D33.3, D37.0, and D43.3).

To assess differences in disease severity and diagnostic pathways between the NF1 cohort and the matched control cohort, the rates of follow-up visits after the first hospital visit with each diagnosis of interest were compared using a negative-binomial regression model. This analysis included only those individuals for whom a first visit was observed. The time from the first visit to death, emigration, or the end of study was included as an offset term.

All analyses were conducted using the R software version 3.6.2. The Cox models and subsequent tests for proportionality of hazards were conducted using the package survival, version 3.2-7, and the negative-binomial models using the package MASS, version 7.3-53.

3 | Results

Over a study period of 17 years, 1349 individuals with NF1, 13,870 matched controls, and 1894 non-NF1 siblings of the affected individuals contributed follow-up time (Table 1). We estimated higher hazards in the NF1 cohort compared with controls for diagnoses related to disorders of tooth development and eruption (ICD-10 K00), embedded and impacted teeth (K01), and dentofacial anomalies (K07). In the analyses by age group, a clear pattern was observed: the effect of NF1 was more pronounced in individuals younger than 18 years, which was also reflected as violations of the proportional hazards assumption of the Cox model. During the initial 30 days of follow-up, we observed no instances of the diagnoses of interest, rendering the sensitivity analysis that excludes these cases unnecessary.

3.1 | Increased Hazard for Dentofacial Anomalies Including Malocclusion in Young Individuals With NF1

Individuals with NF1 were more prone to have a diagnosis of dentofacial anomalies (ICD-10 K07) than those without NF1. Individuals with NF1 had an overall HR of 2.7 (95% CI 1.9–3.8) compared with the controls (Table 2). However, the proportional hazards assumption was violated. In particular, when looking at specific age groups, the effect of NF1 was significantly greater in individuals younger than 18 years than in older individuals (Table 3). In the age group of 0–18 years, the hazard was 5.0-fold (95% CI 3.0–8.2) in the NF1 cohort compared with the control group. In contrast, for those older than 18 years, the HR was only 1.7 (95% CI 1.0–2.8). The Schoenfeld residuals implied that the HR varied with age even within the younger age group. Individuals with NF1 had a higher hazard for dentofacial anomalies, including malocclusion, also when compared with their non-NF1 siblings, with a HR of 2.9 (95% CI 1.7–5.0; Table 2). In the comparison with the non-NF1 siblings, the effect of NF1 did not statistically significantly differ between age groups, yet the estimates did show a similar pattern of an over 5-fold hazard for the NF1 cohort in individuals younger than 18 years and a 2-fold hazard in individuals older than 18 years (Table 3). The mean age at the first hospital-based diagnosis of dentofacial anomalies was 20.9 years in individuals with NF1, 30.5 years in controls, and 28.4 years in siblings (NF1 vs. controls, $p < 0.001$; NF1 vs. siblings, $p = 0.046$; Table 2). When comparing the rates of follow-up visits for the diagnosis of dentofacial anomalies or for its major subcategories, there were no significant differences between the NF1 group and the control group (Table 4).

The estimates only slightly changed when individuals with head and neck tumors such as plexiform neurofibromas were excluded, or when diagnoses made at the Turku University Hospital were ignored. Ignoring diagnoses of dentofacial anomalies made at the Turku University Hospital resulted in roughly 20% fewer cases and a non-significant effect estimate for

TABLE 1 | Characteristics of the NF1, control, and sibling 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)
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
Age at the end of follow-up (years), mean (SD)	38.3 (20.8)	39.7 (21.5)	38.0 (18.4)

TABLE 2 | Disorders of tooth development and eruption, embedded and impacted teeth, and dentofacial anomalies among 1349 individuals with NF1 compared with 13,870 control individuals and 1894 siblings without NF1.

	NF1		Controls		Siblings without NF1		Individuals with NF1 vs. controls, HR (95% CI)	Individuals with NF1 vs. siblings without NF1, HR (95% CI)
ICD-10 diagnosis	***n***	**Mean age (SD)**	***n***	**Mean age (SD)**	***n***	**Mean age (SD)**		
K00 Disorders of tooth development and eruption	12	12.2 (3.4)	34	20.0 (15.0)	8	27.3 (15.7)	3.66 (1.89–7.06)	1.99 (0.79–4.97)
K01 Embedded and impacted teeth	17	18.1 (7.8)	87	23.9 (10.9)	12	25.9 (11.7)	2.08 (1.23–3.49)	2.01 (0.96–4.22)
K07 Dentofacial anomalies (including malocclusion)	40	20.9 (14.4)	160	30.5 (17.5)	20	28.4 (12.9)	2.71 (1.92–3.84)	2.91 (1.69–4.99)
K07.1 Anomalies of jaw-cranial base relationship	10	15.8 (9.1)	49	29.5 (14.8)	6	36.1 (14.5)	2.17 (1.10–4.29)	2.35 (0.85–6.50)
K07.10 Asymmetry of jaw	6	14.5 (5.2)	7	25.3 (16.7)	—[a]	—[a]	9.23 (3.10–27.50)	—[a]
K07.13 Retrognathism (mandibular)	4	16.2 (7.5)	30	30.4 (13.6)	6	36.2 (14.6)	1.42 (0.50–4.05)	1.01 (0.28–3.59)
K07.2 Anomalies of dental arch relationship	23	18.1 (13.3)	51	25.4 (14.1)	5	22.0 (10.0)	4.82 (2.94–7.88)	6.21 (2.35–16.40)
K07.23 Anomalies of dental arch relationship (deep overbite)	7	22.5 (20.3)	22	30.0 (14.1)	4	24.1 (10.6)	3.38 (1.44–7.91)	2.45 (0.71–8.42)
K07.24 Anomalies of dental arch relationship (openbite)	6	27.8 (13.1)	21	23.0 (13.5)	—[a]	—[a]	3.02 (1.22–7.49)	—[a]
K07.25 Anomalies of dental arch relationship (crossbite)	9	11.1 (4.3)	6	31.8 (16.1)	—[a]	—[a]	16.20 (5.76–45.60)	—[a]
K07.3 Anomalies of tooth position	13	14.4 (7.1)	35	23.4 (17.2)	—[a]	—[a]	3.91 (2.07–7.40)	—[a]
K07.30 Anomalies of tooth position (crowding)	12	13.9 (7.2)	24	22.1 (14.9)	—[a]	—[a]	5.25 (2.62–10.50)	—[a]

Abbreviations: CI: confidence interval; HR: hazard ratio; ICD-10: International Classification of Diseases, 10th Edition; SD: standard deviation.
[a]In accordance with the Finnish privacy regulations, patient numbers < 3 and the associated model estimates are not provided to protect patient privacy.

TABLE 3 | 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 diagnosis	***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***
K01 Embedded and impacted teeth	8	22	—[a]	3.74 (1.66–8.39)	—[a]	9	65	—[a]	1.49 (0.74–2.99)	—[a]	0.092	—[a]
K07 Dentofacial anomalies (including malocclusion)	23	48	5	4.98 (3.03–8.18)	5.31 (2.02–14.00)	17	112	15	1.68 (1.01–2.80)	1.99 (0.99–3.98)	0.003	0.780
K07.1 Anomalies of jaw-cranial base relationship	7	13	—[a]	5.48 (2.19–13.70)	—[a]	3	36	—[a]	0.91 (0.28–2.95)	—[a]	0.018	—[a]
K07.2 Anomalies of dental arch relationship	16	21	—[a]	7.89 (4.11–15.10)	—[a]	7	30	—[a]	2.56 (1.12–5.82)	—[a]	0.036	—[a]

Abbreviations: CI: confidence interval; HR: hazard ratio; ICD-10: International Classification of Diseases, 10th Edition.
[a]Data not shown for analyses involving subgroups with < 3 individuals.

TABLE 4 | The numbers of follow-up visits per year of follow-up after an initial hospital visit with each diagnosis.

ICD-10 diagnosis	NF1, mean (10% percentile–90% percentile)	Controls, mean (10% percentile–90% percentile)	Individuals with NF1 vs. controls, RR (95% CI)
K00 Disorders of tooth development and eruption	0.19 (0.00–0.66)	0.88 (0.00–1.60)	0.23 (0.06–0.95)
K01 Embedded and impacted teeth	0.48 (0.00–1.20)	0.34 (0.00–0.33)	1.71 (0.56–5.21)
K07 Dentofacial anomalies (including malocclusion)	1.20 (0.00–2.40)	1.40 (0.00–4.10)	0.89 (0.50–1.58)
K07.1 Anomalies of jaw-cranial base relationship	1.70 (0.20–2.80)	1.40 (0.00–4.00)	1.26 (0.39–4.11)
K07.2 Anomalies of dental arch relationship	1.10 (0.00–2.60)	1.30 (0.00–3.20)	0.79 (0.36–1.76)
K07.3 Anomalies of tooth position	0.64 (0.00–1.90)	1.60 (0.00–6.40)	0.42 (0.10–1.78)

Note: The corresponding numbers of individuals with at least one hospital visit with each diagnosis of interest are shown in Table 2.
Abbreviations: CI: confidence interval; ICD-10: International Classification of Diseases, 10th Edition; RR: rate ratio.

individuals > 18 years of age (HR 1.6, 95% CI 0.87–2.8); yet otherwise, the conclusions did not change in the sensitivity analyses.

3.1.1 | Anomalies of the Jaw-Cranial Base Relationship

For the subcategory of anomalies in the jaw-cranial base relationship (K07.1), the hazard was higher for the NF1 individuals with a HR of 2.2 (95% CI 1.1–4.3) compared with controls. A similar estimate was obtained when comparing the NF1 individuals with their non-NF1 siblings, yet the confidence interval was much wider (HR 2.4, 95% CI 0.85–6.5; Table 2). In the age-stratified analysis (Table 3), the effect of NF1 on the hazard for anomalies in the jaw-cranial base relationship was high for individuals under 18 years of age (HR 5.5, 95% CI 2.2–14) but the difference seemed to vanish among the older individuals (HR 0.91, 95% CI 0.28–3.0). Individuals with NF1 were clearly younger at the first hospital diagnosis of anomalies in the jaw-cranial base relationship than the controls ($p = 0.001$) or the siblings ($p = 0.017$; Table 2). Considering the subcategories of the diagnoses related to the anomalies of the jaw-cranial base relationship, the hazard for visits related to asymmetry of jaw (K07.10) was significantly higher in NF1 compared with the controls (HR 9.2, 95% CI 3.1–28), whereas there was no significant difference between the groups in the hazard for visits related to mandibular retrognathism (Table 2).

3.1.2 | Anomalies of the Dental Arch Relationship

The most frequently observed subcategory of dentofacial anomalies was anomalies of dental arch relationship (K07.2), for which the overall HR for individuals with NF1 compared with controls was 4.8 (95% CI 2.9–7.9; Table 2). The effect varied significantly across age groups, with a HR of 7.9 (95% CI 4.1–15) for individuals younger than 18 years and 2.6 (95% CI 1.1–5.8) for individuals older than 18 years (Table 3). However, the exclusion of diagnoses from the Turku University Hospital resulted in a non-significant estimate for the older age group (HR 1.9, 95% CI 0.66–5.5). There were too few individuals with the diagnosis K07.2 in the sibling cohort for age-group-specific analyses, yet the overall effect estimate showing a 6.2-fold (95% CI 2.4–16) hazard for the NF1 individuals compared with their non-NF1 siblings was consistent with the analysis comparing NF1 to controls (Table 2). The mean age at the first hospital-based diagnosis of anomalies of the dental arch relationship was 18.1 years in the NF1 group (Table 2), which was younger than that among the controls (mean age 25.4 years; $p = 0.038$) but did not significantly differ from the siblings (mean age 22.0 years, $p = 0.489$).

3.2 | Increased Hazard for Embedded and Impacted Teeth Among NF1 Individuals

Individuals with NF1 were more prone to have a diagnosis of embedded and impacted teeth (K01) compared with control individuals (HR 2.1, 95% CI 1.2–3.5; Table 2). The exclusion of patients with head and neck tumors resulted in the attenuation of the effect estimate (HR 1.6, 95% CI 0.87–2.9). The pattern of age group specific effect was again present for the diagnoses of embedded and impacted teeth, with a HR of 3.7 (95% CI 1.7–8.4) for individuals ≤ 18 years and 1.5 (95% CI 0.74–3.0) for individuals > 18 years, yet the difference between age groups was not statistically significant (Table 3). The HR estimate for the younger age group remained similar after the exclusion of patients with head and neck tumors, yet the estimate in the older age group diminished to 0.91 (95% CI 0.37–2.3). Individuals with NF1 were slightly younger at the first diagnosis of embedded and impacted teeth compared with the controls ($p = 0.014$) or the non-NF1 siblings ($p = 0.059$; Table 2).

3.3 | Increased Hazard Yet Lower Rate of Follow-Up Visits for Disorders of Tooth Development and Eruption in Individuals With NF1

Individuals with NF1 showed a higher hazard for disorders of tooth development and eruption (K00) compared with control individuals (HR 3.7, 95% CI 1.9–7.1). However, the comparison

with the non-NF1 siblings showed a smaller and non-significant HR (Table 2). An age group-specific analysis was not possible for disorders of tooth development due to an insufficient number of events. The average age at the first diagnosis of disorders of tooth development and eruption was 12.2 years among the NF1 patients, while the mean age was 20.0 years among the controls ($p = 0.007$) and 27.3 years among the non-NF1 siblings ($p = 0.030$; Table 2). Interestingly, despite a higher hazard, individuals with NF1 appeared to have a lower rate of follow-up visits regarding disorders of tooth development and eruption compared with controls (rate ratio 0.23, 95% CI 0.057–0.95; Table 4).

4 | Discussion

Our register-based analysis suggests that hospital diagnoses for disorders of tooth development and eruption, embedded and impacted teeth, and dentofacial anomalies may be more common in individuals with NF1 than in the general population. Comparing individuals with NF1 to their non-NF1 siblings further supports the increased hazard for these disorders due to NF1. For several of the disorders, the hazards did not differ statistically significantly between individuals with NF1 and their siblings. However, this was likely due to the low number of siblings with the diagnoses of interest rather than a lack of difference, since the estimates were largely similar to those obtained in the comparisons of NF1 individuals versus controls. The effect of NF1 was consistently more pronounced in the younger age group (≤ 18 years) than in the older individuals.

Adults and possibly also adolescents with NF1 have been reported to exhibit a short mandible, maxilla, and skull base, which contribute to the characteristic facial features of individuals with NF1 (Heervä et al. 2011; Luna et al. 2018; Cung et al. 2015). In addition, Bardellini and co-workers suggested that children with NF1 display an increased rate of class III molar relationship and reverse overjet compared with healthy children (Bardellini et al. 2011, 2016). Thus, the present findings describing increased hazards for dentofacial malocclusion and embedded and impacted teeth in NF1 are concordant with the previous literature, and they likely represent consequences of the previously described cephalometric alterations associated with NF1. Previous studies have also described that anomalies in the jaw-cranial base relationship and dental arch abnormalities are particularly common in individuals with NF1 under 18 years of age (Bardellini et al. 2011, 2016; Heervä et al. 2011), in agreement with the present results. An analysis of a large registry with data from multiple clinics reported facial asymmetry in 3.3%–8.0% of individuals with NF1 (Friedman and Birch 1997), and our results showed a HR of 9.2 for a diagnosis of asymmetry of the jaw (Table 2).

Sailer and colleagues were among the first to identify unique NF1-related maxillofacial and especially mandibular malformations, including deepening of the semilunar incisura, lengthening and narrowing of the coronoid and articular processes, shortening of the ramus, retained teeth, and irregularities of the inferior mandibular margin (Sailer et al. 1988). These malformations, seen also in children, were not observed to be directly linked to adjacent neoplasms; yet, the authors suggested that the detection of adjacent fatty tissue may represent manifestations of mesodermal dysplasia. Many others have described marked contributions of NF1-related tumors to oral findings. For example, Friedrich et al. (2021) described an 8-year-old boy with NF1 who had a dysplastic supernumerary tooth embedded in a nerve sheath tumor. A study of 43 NF1 patients with and 76 NF1 patients without facial plexiform neurofibromas found that plexiform neurofibromas were associated with deformations and misalignments of midfacial bones (Friedrich et al. 2022). In addition, aplasia of second inferior molars is a dental finding only associated with NF1 and plexiform neurofibromas, and malformations of the facial skeleton are often linked to plexiform neurofibromas affecting the trigeminal nerve (Friedrich et al. 2003). We previously reported that radiologic abnormalities in the head and neck region were found in 28% of NF1 patients, and the most severe deformities of the mandible and maxilla are associated with plexiform neurofibromas (Visnapuu et al. 2012).

Taken together, current evidence suggests that NF1-associated deformities of the jaws and teeth and malocclusion are more common and severe in patients with plexiform neurofibromas in the oral and maxillofacial region. It is therefore surprising that in only three individuals with NF1, a diagnosis of dentofacial anomalies and a relevant tumor were identified in the present register-based analysis, and their exclusion had practically no effect on the HR for dentofacial anomalies (HR 2.76 vs. HR 2.71). Overall, the exclusion of individuals with head and neck tumors slightly attenuated some of the HR estimates, suggesting that the NF1-related tumors can contribute but do not solely explain the increased hazard for these diagnoses. Our hospital-based register data may lack records of very small, undiagnosed plexiform neurofibromas, leading to under-reporting of tumors that could be detected in detailed imaging, yet we are confident that clinically detectable plexiform neurofibromas have been recorded in the register used for the present study. Even though the prior literature shows that plexiform neurofibromas may underlie dentofacial anomalies in the context of NF1, the present results suggest that the disorders of tooth development and eruption and dentofacial anomalies are associated with NF1 also independently of plexiform neurofibromas. Interestingly, the mandible is a neural crest derivative (Hinrichs 1986), and NF1 is known to particularly affect cells derived from the neural crest (Cichowski and Jacks 2001).

Disorders of tooth development and eruption can lead to tooth malocclusion (Lammert et al. 2007; Chaillet et al. 2004). Our results suggest that individuals with NF1 are more prone to disorders of tooth development and eruption, as well as embedded and impacted teeth compared with the general population. The effect of NF1 on embedded and impacted teeth may be greater in individuals under 18 years old, though the difference between the age groups was not statistically significant in our analysis. However, individuals with NF1 were diagnosed with these conditions at a significantly younger age than the controls: the mean age at the diagnosis of disorders of tooth development and eruption was only 12.2 years, and the age at the diagnosis of embedded and impacted teeth was 18.1 years among individuals with NF1 (Table 2). At these ages, tooth development is still ongoing. The deciduous teeth start to exfoliate and the permanent teeth begin to emerge between the ages of 6 and 7 years.

By the age of about 21 years, the average person has 32 permanent teeth, including the third molar (wisdom) teeth. However, the dental roots of the 2nd and 3rd molars are completed only at the ages of 12–16 years and 18–25 years, respectively (Ash and Nelson 2003). In our previous study, we showed that the timing of dental maturation is unaffected in patients with NF1 up to the age of 17 years (Jääsaari et al. 2012). Correspondingly, no differences in the development of dentition could be demonstrated in a recent study (Friedrich and Schön 2024). It therefore remains unclear whether the young mean ages observed in the NF1 group reflect increased sensitivity for recording diagnoses related to tooth development in individuals with NF1.

In the age-stratified comparisons, the hazards for embedded and impacted teeth as well as the anomalies of jaw-cranial base relationship were significantly increased in NF1 only in the younger age group of ≤18 years. In addition, the HR for anomalies of dental arch relationship was significantly greater at ages ≤18 years than among older individuals. Individuals under 18 typically receive more detailed orthodontic screening compared to older age groups. In Finland, patients under 18 receive free public orthodontic treatment, which may partly explain the observed greater effect size related to dentofacial malocclusion in children with NF1 at ages under 18. In adults, only serious bite defects are covered by public health care.

The present study setting is designed to detect associations between NF1 and the diagnoses of interest, yet the verification of the results and identification of causal mechanisms need to be addressed in future studies. Multiple diagnosis codes and their subcodes were analyzed, and no correction for multiple comparisons was applied due to the exploratory nature of the study, the analysis of nested diagnosis codes, and the expected correlations between the different diagnoses. While we consider this analysis approach optimal for obtaining clinically applicable estimates, the future replication of the results is particularly important. The study is exclusively based on hospital data from national registers, which limits our ability to study the detailed clinical presentation of the patients with dentofacial anomalies. However, the present approach allowed a nationwide study of a cohort including a substantial number of individuals with verified NF1. Most dentist's appointments occur in the primary health care, which explains the relatively low numbers of patients with the diagnoses of interest in the present hospital-based dataset. For example, a diagnosis of dentofacial anomalies had been recorded for only 3.0% of individuals with NF1 and 1.2% of controls, indicating that the register data only identifies a subset of all individuals with dentofacial malocclusion. Moreover, often only the most acute or the most severe diagnosis related to the condition treated during the visit may be recorded, and potentially associated subsidiary diagnoses may be omitted even though recording multiple codes for a single hospital visit is technically possible. This further affects the coverage of the dataset. The relatively low numbers of individuals with the specific diagnoses of interest obviously introduce some uncertainty in the estimates. However, the present study is focused on the relative hazard in NF1 compared with the controls and the patients' siblings, and the incomplete coverage of the dental diagnoses in the register data does not compromise our findings as long as the coverage is similar between the different cohorts.

The pediatric patients who are followed up by specialists for their NF1 may have a higher likelihood to be referred to the secondary oral health care, while the controls without NF1 may be treated in primary health care, which may exaggerate the effect of NF1 observed in hospital-based registries. However, the rate of follow-up visits related to dentofacial anomalies did not differ between NF1 patients and controls, suggesting that the severity of these conditions was similar in both groups. Irrespective of NF1, many adult patients are devoid of contact with oral health specialists, which may cause underdiagnosis of dental problems. In the case of dentofacial anomalies, the exclusion of visits made at the Turku University Hospital resulted in a marked reduction in the number of patients with NF1 and a non-significant HR at ages >18 years, which suggests that our previous clinical study (Visnapuu et al. 2011) increased the probability of diagnosing dentofacial anomalies in adult patients with NF1.

Anomalies in dental arch relationship and embedded or impacted teeth can cause pain conditions in the temporomandibular joint, headaches, and accordingly, a decrease in the quality of life (Gauer and Semidey 2015). Malocclusion can cause sleep bruxism, which causes pain in the masticatory muscles, tooth wear, and headaches (Kataoka et al. 2015). The narrowing of the dentition complicates oral hygiene, predisposing individuals to tooth decay and connective tissue diseases. The consequences of dental malocclusion have not been studied in NF1; yet, we have reported that NF1 is associated with increased hazards for dental caries, pulpitis, and periodontitis (Reinhold et al. 2025). All professionals treating individuals with NF1 should therefore be well-informed of the effect of NF1 on oral health and dentofacial abnormalities. Early diagnosis of NF1 and its head and neck manifestations is extremely important for young patients. Orthodontic treatment at an early age can be utilized to prevent the development of severe malocclusion. The present study setting focused on identifying associations between NF1 and dentofacial malocclusion, and further research exploring the underlying mechanisms of dental anomalies in individuals with NF1 is needed.

Author Contributions

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

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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. 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

Data are available upon reasonable request for researchers though data access is restricted. Please contact the Finnish Institute for Health and Welfare for permission.

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