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Neurofibromatosis Type 1 and Chronic Neurological Conditions in the United States: An Administrative Claims Analysis

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Abstract

Purpose—Neurofibromatosis Type 1 (NF1) has been linked to several neurological conditions including: epilepsy, Parkinson's disease, headache, multiple sclerosis, and sleep disturbances, predominantly through case reports and series that lack comparison groups. Our objective was to assess whether specific neurological conditions occur more frequently in individuals with NF1 vs. those without NF1.

Methods—We used the 2006-2010 MarketScan *Commercial Claims and Encounters* database to examine associations between neurological conditions and NF1. The NF1 group was identified through ≥2 ICD-9-CM NF codes (237.70, 237.71) occurring ≥30 days apart or one inpatient NF code. A non-NF1 comparison group was frequency-matched to the NF1 group on age and enrollment length at a 10:1 ratio. Unconditional logistic regression was employed to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for associations between NF and neurological conditions.

Results—Compared to the non-NF1 group (n=85,790), the NF1 group (n=8,579) had a significantly higher odds of health insurance claims for epilepsy (OR=7.3; 95% CI 6.4-8.3), Parkinson's disease (OR=3.1; 95% CI 1.3-7.5), headache (OR=2.9, 95% CI 2.6-3.1), multiple sclerosis (OR=1.9, 95% CI 1.2-2.9), and sleep disturbances/disorder (OR=1.4, 95% CI 1.2-3.6).

Conclusion—This large study provides strong evidence for positive associations between several neurological conditions and NF1.

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Keywords

Neurofibromatosis Type 1; multiple sclerosis; Parkinson's disease; epilepsy; headache; migraine; sleep disorders; diabetes

Introduction

Neurofibromatosis Type 1 (NF1) is one of the most common autosomal dominant genetic disorders with an estimated birth prevalence of 1 in 3,000[1]. While individuals with NF1 are prone to the development of both benign and malignant nervous system tumors, numerous non-malignant neurological conditions including learning disabilities[2] and attention deficits[2-5] have been reported to occur more frequently in people with NF1. In addition, NF1 has been linked to other chronic neurological problems, including epilepsy[6-9], sleep disorders[10-12], multiple sclerosis[13-17], headaches[18, 19], and Parkinson's disease[20, 21]. Most of the latter NF1 associations are derived from case reports and small patient series that are limited by the lack of a non-NF1 comparison group that is needed to assess whether the complications observed in NF1 occur at significantly higher frequencies than in the general population or whether they represent random co-occurrences.

To identify potential associations between NF1 and several chronic neurological conditions in a large population of individuals, we employed administrative claims data from the Truven Health Analytics MarketScan *Commercial Claims and Encounters* database[22]. This database includes de-identified health insurance claims on 88 million Americans from 2006-2010, allowing information to be assembled on the healthcare of thousands of individuals with and without NF1. Using this unique epidemiologic resource, we identified an NF1 group and a comparison group without NF1 to perform the first large-scale study to assess whether specific chronic neurological conditions in individuals with NF1 occur more frequently than in those without NF1.

Materials and Methods

Data source

The study dataset was assembled from the Truven Health Analytics *MarketScan Commercial Claims and Encounters* database that includes de-identified patient-level claims data for healthcare encounters of privately-insured individuals from 2006-2010. The MarketScan database is the largest claims database and represents “real world” healthcare encounters of the privately insured U.S. population[22]. Variables available through MarketScan include demographic data (sex, birth year), enrollment dates, dates of specific claims, 3-digit zip codes, patient age, and *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes for healthcare claims. Race/ethnicity information is not available using MarketScan data. The database differentiates between inpatient and outpatient claims, facility and professional claims, and includes information on health care plan type to identify capitated plans (health maintenance organization (HMO)). All individuals in the commercial database are privately insured and covered by dozens of different health plans across the United States.

Study population

The NF1 cohort was defined using two ICD-9-CM[23] diagnosis codes specific for Neurofibromatosis (NF) (NF1; 237.71) or NF unspecified (237.70). Patients with claims for the ICD-9-CM code 237.72 (Neurofibromatosis Type 2; NF2) were excluded from the study. Subjects were required to have at least two outpatient claims 30 days or more apart or one inpatient claim for the NF ICD-9-CM codes (237.70 or 237.71) to be included in the NF1 cohort. A non-NF1 cohort of individuals was selected from individuals without any ICD-9-CM diagnosis codes for NF (237.70, 237.71, 237.72). The non-NF1 comparison group was frequency-matched to the NF1 group at a 10:1 ratio by one year age group on 1/1/2006 or first enrollment if born after 1/1/2006 and enrollment length in months. Specifically, the sample of NF1 patients and the pool of potential control patients were divided into five subgroups based on 12 month periods of total health insurance enrollment in the database. Within each subgroup of enrollment duration for potential controls, we randomly selected ten patients without replacement so that the age distribution within the control subgroup matched that of the corresponding NF1 subgroup. We matched on enrollment length to control for differences in the number of medical claims due imbalances in enrollment length between the NF1 and non-NF1 groups.

Variables

Healthcare claims related to neurological and other conditions were identified by the following ICD-9-CM codes using the clinical classification software coding schema (http://www.hcup-us.ahrq.gov/toolssoftware/ccs/AppendixASingleDX.txt) or the 2009 ICD-9-CM manual[23]: epilepsy (345.0-345.91, 780.33, 780.39), migraine headache (346.0-346.93), headache (784.0), multiple sclerosis (340), Parkinson's disease (332.0), sleep disturbances/disorder (780.5×, 327.3×). Of note, we excluded febrile convulsions (780.31) from the epilepsy case definition. Acute urinary infection (UTI) (590.0-590.9, 595.0, 595.89, 595.9, 597.0, 598.0×, 599.0) and diabetes types 1 and 2 (250.01-250.09) were included as negative controls, based on expert knowledge and literature reviews suggesting that these conditions are not related to NF1. For neurological conditions and diabetes, individuals were required to have any combination of at least two outpatient or inpatient claims ≥30 days apart to be classified as having the condition. For UTIs, we required only one claim for classification as having the condition since this is an acute condition.

Variables for conditions specifically linked to NF2 were used for sensitivity analyses to evaluate the robustness of the results when individuals with any evidence of healthcare claims for NF2-related conditions (who were not identified as such by 237.72 ICD-9-CM coded claims) were excluded from analyses. The following diagnosis codes were used for these analyses: benign neoplasm of brain and other parts of nervous system: 225.1 (cranial nerves, acoustic neuroma), 225.2 (cerebral meninges), 225.4 (spinal meninges); malignant neoplasm of other and unspecified parts of the nervous system: 192.1 (cerebral meninges), 192.3 (spinal meninges), 192.0 (cranial nerves); secondary malignant neoplasm of other specified sites: 198.4 (other parts of the nervous system, meninges (cerebral) (spinal)); neoplasm of uncertain behavior of endocrine glands and nervous system: 237.6 (neoplasm of uncertain behavior of endocrine glands and nervous system: meninges), 237.9 (other and unspecified parts of nervous system: cranial nerves); and disorders of the acoustic nerve:

388.5. In addition, we used the following brain tumor codes to assess whether associations between NF1 and neurological conditions (epilepsy, headache, migraine) remained when individuals with healthcare encounters related to brain tumor diagnoses were excluded (malignant neoplasm of brain: 191.0-191.9; benign neoplasm of brain and other parts of nervous system: 225.0-225.9; neoplasms of unspecified nature: 239.6 (brain)).

Healthcare utilization was estimated from the number of outpatient visits using the CPT[24] codes 99201-99205, 99211-99215, and 99241-99245. Approximate age in years at first administrative claim for comorbidities (non-NF1 neurological conditions, diabetes, and UTIs) was determined by taking the difference between the visit year for the first claim for the comorbidity from 2006-2010 and the subject's birth year.

Statistical analysis

Statistical Analysis Software (SAS) (version 9.2; SAS Institute Inc., Cary, NC) was used for all study analyses. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to determine associations between NF1 group membership and each medical condition, adjusting for the frequency matching variables (enrollment time in months and age), sex, and number of healthcare visits. The latter was used to control for differences in healthcare utilization between the two study groups since there would be increased opportunity for medical condition claims in the NF1 group vs. the non-NF1 group due to their increased utilization of the healthcare system. Chi-square and Fisher's exact tests were used to evaluate the statistical significance of differences in the frequency of medical condition claims by sex between the NF1 and non-NF1 groups. The Wilcoxon two sample test (T approximation) was used to test the null hypothesis of no significant difference between the two groups in the age at first healthcare claim during the study period (2006-2010) for specific medical conditions. P-values were considered significant at the $p \leq 0.05$ level.

Results

A total of 8,579 people that met our selection criteria comprised the NF1 group. The non-NF1 comparison group consisted of 85,790 individuals. Subject ages ranged from 0-64 years, with a mean age of 24.4 years (SD= 19.3) for both groups (Table 1). The mean enrollment time, percentage of individuals receiving healthcare through HMO plans, and geographical distribution did not differ appreciably between the two groups. In contrast, the mean healthcare visit number during the study period for the NF1 group was more than twice as high (17.6 ± 17.1 claims) as the comparison group (8.8 ± 11.7 claims). In addition, there was a slightly higher percentage of females in the NF1 group relative to the comparison group (52.3% vs. 50.5%).

In general, subjects in the NF1 group had significantly higher odds of health insurance claims for all neurological conditions evaluated (Table 2). This finding was also observed when we adjusted for HMO membership; for this reason, this variable was not included in the final model. Individuals in the NF1 group had a higher odds of health insurance claims related to epilepsy (OR=7.3; 95% CI 6.4-8.3), migraine (OR=2.6; 95% CI 2.2-2.9), headache (including migraine) (OR=2.9; 95% CI 2.6-3.1), multiple sclerosis (OR=1.9; 95%

CI 1.2-2.9), Parkinson's disease (OR=3.1; 95% CI 1.3-7.5), and sleep disturbances/disorder (OR=1.4; 95% CI 1.2-2.6). While there was no association between NF1 and healthcare claims for acute UTIs (OR=1.0; 95% CI 0.96-1.1), individuals in the NF1 vs. the non-NF1 group exhibited a significantly lower odds of diabetes claims (OR=0.4, 95% CI 0.3-0.4). When individuals with claims for conditions that could indicate NF2 (but who did not have claims for this condition) were excluded, the results were not materially different (data not shown).

To address the possibility that associations between NF1 and epilepsy, migraine, or headaches were mediated by brain tumors, we conducted analyses that excluded individuals with brain tumor claims. For epilepsy, the overall association was slightly weaker, but still significant (OR=6.7; 95% CI 5.8-7.8). Associations for headache (including migraine) and migraine were similar to the analyses that did not exclude these individuals (headache (including migraine): OR=2.7, 95% CI 2.4-2.9; migraine: OR=2.6, 95% CI 2.3-3.0).

We also sought to determine whether there were any differences in the health insurance claims patterns for each medical condition as a function of age. As expected, there were no individuals in the younger age category in the NF1 group with claims for Parkinson's disease or multiple sclerosis. For other neurological conditions, the magnitude of the association was stronger for migraines, headache (includes migraine), and sleep disturbances/disorders in the younger vs. older age group, while the opposite was true for epilepsy.

For each medical condition category, we also assessed whether there was any evidence for differences in the sex distribution and the mean age at first healthcare claim between the NF1 vs. the non-NF1 group (Table 3). Among those identified with two or more healthcare claims for epilepsy, migraine, Parkinson's disease, sleep disturbances, or diabetes, there was no significant difference in the percentage of females between the NF1 and non-NF1 groups. In contrast, there was a significantly lower percentage of females among those with claims for headache (including migraine) (64.6% vs. 73.2%), multiple sclerosis (60% and 78.7%), and UTIs (77.5% and. 84.5%) in the NF1 vs. the non-NF1 group, respectively. Individuals in the NF1 group were on average younger at their first administrative claim for headache (including migraine) (29.9 vs. 34.2 years, $p<0.0001$), migraine (31.1 vs. 36.4 years, $p<0.0001$), and sleep disturbances/disorders (41.2 vs. 44.5 years, $P=0.0113$), and older for UTIs than those in the non-NF1 group (35.2 vs. 32.4 years, $p<0.0001$).

Discussion

We observed a significantly higher odds of healthcare claims related to epilepsy, migraine, headache (including migraine), sleep disorders, multiple sclerosis, and Parkinson's disease in individuals with NF1 than in those without NF1 who were identified using administrative claims data. These findings substantiate prior evidence from case reports and clinical series that have suggested causative associations between these neurological problems and NF1.

An increased prevalence of epilepsy or unprovoked seizures in individuals with NF1 has been described in previous smaller studies, where the prevalence has been estimated between 5.9% and 9.5%[6-8]. In the current study, we found that the prevalence of two or

more epilepsy related claims thirty days or more apart was 5.6% in the NF1 group vs. 0.6% in the non-NF1 group with evidence suggesting that both children and adults with NF1 are at risk for developing epilepsy. The propensity for individuals with NF1 to seek medical attention for seizures may be partially due to the presence of central nervous system tumors, as we have recently reported[8]. However, the observation that the positive association between NF1 and epilepsy persisted after exclusion of individuals with brain tumor healthcare claims suggests that other etiologies may account for epilepsy in this at-risk population[6-8].

NF1 has been evaluated as a risk factor for headache in studies surveying NF1 patients about headaches[18, 19], with mixed results. We observed a significantly higher odds of healthcare claims related to headaches and migraines in individuals in the NF1 vs. non-NF1 group. Consistent with studies demonstrating that headaches in NF1 do not necessarily result from intracranial tumors[18, 19], the association between headaches/migraines and NF1 did not change following the exclusion of individuals with brain tumor claims. Since headaches can severely compromise quality of life, further research is warranted to examine the etiology and impact of headaches in people with NF1.

Previous case reports have also revealed a potential association between NF1 and multiple sclerosis (MS)[13-17]. However, our study suggests that MS is a rare complication of NF1 (<1.0% individuals with NF1), with a two-fold increased odds of MS-related health insurance claims in people with NF1. While it is not clear why MS should be over-represented in people with NF1, several lines of evidence suggest that this association has a biological basis. First, the *OMG* (oligodendrocyte-myelin glycoprotein) gene[25] lies within an intron of the *NF1* gene, raising the intriguing possibility that impaired *OMG* function could affect myelination, predisposing some individuals with NF1 to MS[15]. However, *OMG* mutations are neither necessary nor sufficient for primary progressive MS[25]. Second, the *NF1* gene is highly expressed in oligodendrocytes, the primary cell type affected in MS[26]. Third, *Nf1* gene inactivation results in increased oligodendrocyte precursor numbers in mice[27] and zebrafish[28], and leads to deregulated nitric oxide-mediated blood-brain barrier defects in *Nf1* genetically-engineered mouse models[29]. Further investigation will be required to establish a mechanistic connection between NF1 and MS pathogenesis.

To our knowledge, there are only two published case reports of Parkinson's disease (PD) in individuals with NF1[20, 21]. PD results from insufficient striatal dopamine production resulting in a variety of movement abnormalities[30]. While we observed a three-fold increased odds of PD claims in people in the NF1 group vs. the non-NF1 group, there were only seven individuals in the NF1 group who had repeated claims for PD, suggesting that PD occurs very rarely in individuals with NF1. However, the potential association between NF1 and PD is intriguing in light of recent studies demonstrating that the *Nf1* protein, neurofibromin, regulates striatal dopamine levels in genetically-engineered mouse (GEM) models[31]. In this regard, *Nf1* GEM strains exhibit attention and learning deficits that are responsive to dopamine restoration[31-33]. Additional research will be required to establish a biological basis for this interesting association.

An increased prevalence of abnormal sleep patterns in people with NF1 has also been reported[10-12]. In the current study, we observed a two-fold higher odds of claims for sleep disturbances/disorder in individuals with NF1. While little is known about the mechanism underlying sleep disturbances in mammals using *Nf1* genetically engineered models, elegant studies in *Drosophila* have demonstrated that the *Nf1* gene is critical for maintaining fruit fly circadian rhythm [34].

Unexpectedly, we observed a significantly lower odds of diabetes-related healthcare claims in people with NF1 vs. the non-NF1 group. This inverse relationship is intriguing, and has been noted in an anecdotal expert report[35]. While two prior studies have reported diabetes cases in individuals with NF1, the authors of both papers indicated that this is a rare occurrence[36, 37]. It is not clear why NF1 would be associated with lower risk of diabetes; however, it is possible that this reflects de-regulated Protein Kinase B (AKT)/mammalian target of rapamycin (mTOR) activity, resulting from defective neurofibromin AKT/mTOR control[38, 39]. Further studies will be required to establish a mechanistic connection between these two conditions.

Strengths of this study include its large size and the use of an age- and length of enrollment-matched comparison group that allows for more accurate estimation of relative differences in the prevalence of chronic neurological conditions in individuals with vs. without NF1. In addition, we controlled for healthcare utilization to minimize the concern that associations were confounded by this factor. The lack of an association between acute urinary tract infections and NF1 and the inverse association between diabetes and NF1 reinforces the concept that the positive associations detected between neurological conditions and NF1 were not due to increased surveillance for medical conditions in this population.

There are also limitations to the use of administrative claims data. Using health insurance claims as markers of medical diagnoses (NF1 and comorbidities), rather than physical examinations and laboratory tests, may result in misclassification of individuals with respect to NF1. Misclassification can result from coding errors, coding to rule-out conditions, and under- and over-coding. We attempted to minimize misclassification through the application of strict selection criteria that are used in administrative data analyses by only considering individuals to have the chronic medical conditions if they had ≥2 codes for the condition in the outpatient/inpatient setting 30 or more days apart. However, we note that this approach could miss cases of NF1. In addition, it was recently recommended as a result of a systematic review of ICD codes for the study of neurological conditions that fewer than three ICD codes can be used with sufficient accuracy for identifying cases of epilepsy and MS in administrative data; insufficient data was found for PD to make recommendations[40]. Further, although we excluded people with NF2 and NF2-related healthcare claims from analyses, it is possible that some individuals with NF2 were not identifiable by ICD-9-CM codes. NF2 is estimated to be ten-fold less common than NF1[41], and therefore, failure to exclude all subjects with NF2 is unlikely to materially impact on our findings. Finally, the generalizability of this study is limited to privately insured working adults and dependent children with NF1. In addition, since MarketScan predominantly assembles claims data from larger U.S. employers, these results may not be generalizable to individuals who are privately insured through small to medium size employers[22].

In conclusion, this large administrative health insurance claims study strengthens existing evidence from uncontrolled studies that individuals with NF1 are at significantly elevated risk for a number of neurological conditions compared to the general population. In addition, our results suggest that individuals with NF1 are at lower risk for diabetes. Additional research will be required to validate these results, mechanistically study these associations, and identify the specific factors that distinguish individuals with NF1 who are at risk for these neurological complications.

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Table 1

Demographics of 2006-2010 MarketScan sample population.

Characteristic	NF1 group (n=8579)	Non-NF1 group n=85790)
Age category years (No., %)		
0-9	2,668 (31.1)	26,680 (31.1)
10-19	1,816 (21.2)	18,160 (21.2)
20-29	762 (8.9)	7,620 (8.9)
30-39	889 (10.4)	8,890 (10.4)
40-49	1,105 (12.9)	11,050 (12.9)
50-59	1,113 (13.0)	11,130 (13.0)
60-69	226 (2.6)	2,260 (2.6)
Enrollment, months		
Mean (SD)	35.3 (17.1)	34.6 (17.8)
Median	36	36
Number of visits		
Mean (SD)	17.6 (17.2)	8.8 (11.7)
Median	13	5
Sex (No., %)		
Female	4,486 (52.3)	43,365 (50.6)
Male	4,093 (47.7)	42,425 (49.5)
HMO membership (No., %)		
Yes	1,507 (17.6)	15,122 (17.6)
No	7,072 (82.4)	70,668 (82.4)
Region (No., %)[a]		
New England	468 (5.5)	3,473 (4.1)
Middle Atlantic	903 (10.5)	7,840 (9.1)
East North Central	1,677 (19.6)	16,356 (19.1)
West North Central	593 (6.9)	5,958 (6.9)
South Atlantic	1,684 (19.6)	17,328 (20.2)
East South Central	365 (4.3)	4,622 (5.4)
West South Central	1,284 (15.0)	14,352 (16.7)
Mountain	419 (4.9)	4,470 (5.2)
Pacific	838 (9.8)	10,277 (12.0)
Missing	342 (4.0)	1,051 (1.2)
Other	6 (0.1)	63 (0.1)

NF1, neurofibromatosis type 1; SD, standard deviation; HMO, Health Maintenance Organization

[a]New England (Maine, New Hampshire, Vermont, Massachusetts, and Connecticut); Middle Atlantic (New York, New Jersey, and Pennsylvania); East North Central (Wisconsin, Michigan, Illinois, Indiana, and Ohio); West North Central (North Dakota, South Dakota, Minnesota, Nebraska, Iowa, Kansas, and Missouri), South Atlantic (Maryland, Delaware, District of Columbia, West Virginia, Virginia, North Carolina, South Carolina, Georgia, and Florida); East South Central (Kentucky, Tennessee, Mississippi, Alabama); West South Central (Oklahoma, Arkansas, Texas, and

Louisiana); Mountain (Montana, Idaho, Wyoming, Nevada, Utah, Colorado, Arizona, and New Mexico); Pacific (Washington, Oregon, California, Alaska, and Hawaii); Other (includes military regions, Puerto Rico, and Guam)

Table 2

Associations between NF1 and medical conditions overall and by age group.

	All subjects				<18 years[a]				≥18 years[a]			
Condition[b]	**NF1 group N (%)**	**Non-NF1 group N (%)**	**OR[b]**	**95% CI**	**NF1 group N (%)**	**Non-NF1 group N (%)**	**OR[c]**	**95% CI**	**NF1 group N (%)**	**Non-NF1 group No (%)**	**OR[c]**	**95% CI**
Epilepsy												
No	7,837 (94.4)	84,644 (99.4)	1.0	Ref.	3,943 (95.1)	42,308 (99.4)	1.0	Ref.	3,894 (93.7)	42,336 (99.4)	1.0	Ref.
Yes	467 (5.6)	536 (0.6)	7.3	6.4-8.3	204 (4.9)	259 (0.6)	5.6	4.6-6.9	263 (6.3)	277 (0.7)	8.4	7.1-10.1
Migraine												
No	7,843 (95.8)	83,233 (98.8)	1.0	Ref.	4,033 (97.4)	42,284 (99.5)	1.0	Ref.	3,810 (94.1)	40,949 (98.1)	1.0	Ref.
Yes	345 (4.2)	1010 (1.2)	2.6	2.2-2.9	108 (2.6)	207 (0.5)	3.9	3.0-5.1	237 (5.9)	803 (1.9)	2.1	1.8-2.5
Headache (including migraine)												
No	6,505 (87.6)	77,586 (96.8)	1.0	Ref.	3,446 (90.9)	39,894 (98.2)	1.0	Ref.	3,059 (84.2)	37,692 (95.3)	1.0	Ref.
Yes	921 (12.4)	2,592 (3.2)	2.9	2.6-3.1	347 (9.2)	751(1.9)	3.4	2.9-3.9	574 (15.8)	1,841 (4.7)	2.5	2.3-2.8
Multiple sclerosis												
No	8,527 (99.7)	85,615 (99.9)	1.0	Ref.	4,291 (100)	42,916 (100)	ND	ND	4,236 (99.4)	42,699 (99.8)	1.0	Ref.
Yes	25 (0.3)	108 (0.1)	1.9	1.2-2.9	0 (0.0)	5 (0.01)	ND	ND	25 (0.6)	103 (0.2)	1.9	1.2-3.0
Parkinson's disease												
No	8,562 (99.9)	85,762 (100.0)	1.0	Ref.	4,292 (100)	42,927 (100)	ND	ND	4,270 (99.8)	42,835 (100)	1.0	Ref.
Yes	7 (0.08)	19 (0.02)	3.1	1.3-7.5	0 (0.0)	1 (0.0)	ND	ND	7 (0.2)	18 (0.04)	3.3	1.4-7.9
Sleep disturbances/disorder												
No	7,842 (96.2)	82,029 (98.2)	1.0	Ref.	4,139 (98.8)	42,298 (99.6)	1.0	Ref.	3,703 (93.4)	39,731 (96.7)	1.0	Ref.
Yes	311 (3.8)	1,499 (1.8)	1.4	1.2-2.6	49 (1.2)	155 (0.4)	1.8	1.2-2.5	262 (6.6)	1,344 (3.3)	1.4	1.2-1.6
Acute urinary infection												
No	7,408 (86.4)	77,735 (90.6)	1.0	Ref.	3,964 (92.3)	40,136 (93.5)	1.0	Ref.	3,444 (80.4)	37,599 (87.7)	1.0	Ref.
Yes	1,171 (13.7)	8,055 (9.4)	1.0	0.96-1.1	329 (7.7)	2794 (6.5)	0.7	0.6-0.8	842 (19.7)	5,261 (12.3)	1.2	1.1-1.3
Diabetes[d]												
No	8,220 (97.6)	81,473 (96.3)	1.0	Ref.	4268 (99.8)	42714 (99.7)	1.0	Ref.	3,952 (95.3)	38,759 (92.7)	1.0	Ref.
Yes	201 (2.4)	3,167 (3.7)	0.4	0.3-0.4	7 (0.2)	126 (0.3)	0.3	0.1-0.6	194 (4.7)	3,041 (7.3)	0.4	0.3-0.4

OR, odds ratio; CI, confidence interval; NF1, Neurofibromatosis Type 1; ND, Not Determined

[a] Age on 1/1/2006 or at enrollment if birth occurred after 1/1/2006

[b] Individuals with only one ICD-9-CM code for the medical condition during the study period were excluded from the analysis

[c] Adjusted for age, enrollment time, number of healthcare visits, and sex

[d] Includes Diabetes types I and II

Table 3

Differences in sex and mean age at for first healthcare claim between the NF1 and non-NF1 groups by medical condition.

	Females with medical condition			Age at first healthcare claim for condition[a]		
Medical condition (Number of cases in NF1/non-NF1 group, respectively)	**NF1 group (% female)[b]**	**Non-NF1 group (% female)[b]**	**P-value[c]**	**NF1 group mean (SD)**	**Non-NF1 group mean (SD)**	**P-value[e]**
Epilepsy (467, 536)	48.8	50.8	0.5433	27.1 (18.5)	27.6 (19.7)	0.9806
Headache (including migraine) (921, 2592)	64.6	73.2	<0.0001	29.9 (17.3)	34.2 (16.7)	<0.0001
Migraine (345, 1010)	71.2	74.5	0.1324	31.0 (15.5)	36.4 (15.4)	<0.0001
Multiple sclerosis (25, 108)	60.0	78.7	0.0510	45.2 (10.4)	44.9 (12.4)	0.9039
Parkinson's disease (7, 19)	42.9	47.4	1.0[d]	56.0 (5.2)	53.9 (12.5)	0.9771
Sleep disturbances/disorder (311, 1499)	47.3	46.4	0.7715	41.2 (17.4)	44.4 (15.4)	0.0416
UTI (1171, 8055)	77.5	84.5	<0.0001	35.2 (19.4)	32.4 (19.4)	<0.0001
Diabetes (201, 3167)	50.3	48.9	0.7194	50.4 (12.0)	50.2 (11.8)	0.6566

N, number; NF1, neurofibromatosis type 1; SD, standard deviation

[a] Age was estimated as the difference between the year of the healthcare claim for the condition during 2006-2010 and the patient's birth year

[b] Percent female in NF1/non-NF1 group in those with medical condition listed in column 1.

[c] Chi-square test p-value

[d] Fisher's exact test two-sided p-value

[e] Based on Wilcoxon Two-sample Test (T-approximation)