Epidemiologic Study of Smell Disturbance in 2 Medical Insurance Claims Populations

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Objective: To report the rates of medical claims for sense of smell disturbance (SD) and their association with diseases and medications in a managed care population.

Design: Descriptive determination of demographics, prevalence, and incidence of SD and case-control analysis of risk factors. Preselected drug and disease groups were entered into a stepwise regression model to determine risk factors for SD.

Setting: Managed care organizations in the United States.

Patients: Patients identified through medical claims within IMS Health’s LifeLink: Integrated Claims Solution (IMS) and i3 Magnifi Private Managed Care Organizations (MCO) medical insurance databases for 3-year observation periods.

Main Outcome Measures: Prevalence and incidence of smell disturbance; adjusted odds ratios and 95% confidence intervals (CIs) of associated conditions and medications.

Results: The mean annual prevalence rate of SD was 26.2 per 100,000 for IMS (95% CI, 23.1-29.6) and 17.2 per 100,000 for MCO (95% CI, 15.6-18.7). The mean annual incidence per 100,000 was 26.3 for IMS (95% CI, 23.1-29.8) and 15.9 for MCO (95% CI, 14.5-17.5). The 5 strongest risk factors for SD were chronic sinusitis, oropharyngeal inflammatory disorders, other upper respiratory tract disease excluding sinusitis, cerebrovascular disease, and systemic viral disease. The regression model also retained 3 drug groups (corticosteroids, calcium channel blockers, and nasal and/or sinus products) among the significant risk factors for the presence of SD.

Conclusions: The annual prevalence and incidence rates of SD are lower than prior estimates partly owing to reliance on specific medical claims. A number of conditions preceding the diagnosis of SD were significantly associated with the condition. Uses of certain medications were also risk factors for SD compared with controls.

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Olfactory dysfunction or sense of smell disturbance (SD) is a clinical condition often overlooked in many practice settings. This condition includes partial to total loss of sense of smell (anosmia), alterations in sense of smell (dysosmia), and detection of nonexistent odors (phantosmia). Sense of smell disturbance can lead to a reduction in quality of life, and its consequences can be potentially hazardous (ie, inability to detect spoiled foods).1 However, many people do not report lost, diminished, or altered sense of smell to their physicians. In various published case series, more than 200 conditions or exposures have been identified to be associated with changes in olfaction.2-7 The 3 major predisposing conditions include head trauma (9%-32%), upper respiratory tract infections (15%-20%), and nasal or sinus disease (20%-30%).6,8 Increasing age is also a factor in the development of SD.11,12 It is estimated that the crude prevalence of SD ranges from 2.9 to 5.8 million people or 1% to 2% of the US population.13,14 The incidence and prevalence rates of clinically significant SD are not well defined.

Epidemiologic research in SD is limited by the current lack of formal US population-based data defining the prevalence and incidence. Given that many conditions and medications associated with SD are relatively common, a quantification of the population prevalence and incidence rates along with risk factors previously described in the literature would be of value. To better understand the rate of SD diagnosed in managed care populations and its risk factors, an analysis of 2 medical claims insurance databases was conducted.
DATA SOURCES

The study was conducted using 2 databases of medical insurance claims in the United States: IMS Health’s LifeLink: Integrated Claims Solutions (IMS) (Plymouth Meeting, Pennsylvania) and i3 Magnifi (formerly Constella Health Strategies) Private Managed Care Organizations (MCO) (Waltham, Massachusetts). The IMS database is an employer claims database representing the health care experience of approximately 1.6 million employees, dependents, and retirees (1.1 million eligible during 1998). It contains information about both inpatient and outpatient medical care, including diagnoses, therapeutic procedures, and prescriptions (outpatient only). Patients can be tracked longitudinally across multiple sites and providers of care. All age groups are represented because the database contains employees, dependents, and 300,000 retirees with drug benefits. However, the medical claims for patients older than 65 years might not always be complete because, in general, the insurance company is not the primary payer for Medicare-eligible patients. The IMS database has a low turnover rate of approximately 8% per year. Seventy-five percent of the patients are in the Midwest. However, more than 10,000 patients in each of 21 different states in various areas of the country are included.

The MCO database includes longitudinal, member-linked data on medical services provided through commercial health maintenance organization (HMO), preferred provider organization (PPO), Medicare risk, and other indemnity products. This private benefit plan information includes data on approximately 3 million members annually and more than 10 million persons longitudinally since 1991. Health eligibility information is available for 100% of the membership. Approximately 76% of the members in the MCO database belong to commercial HMO or PPO plans. Approximately 21% of the membership is enrolled in Medicare risk products. The remaining membership is enrolled in Medicare supplement and a variety of other specialty and administrative-services-only products. Data for the private benefit plans are complete and available for paid outpatient professional, outpatient facility, and inpatient facility claims from January 1991 through September 2002. For the subset of the population that also has drug benefit coverage, outpatient pharmacy claims are also available.

STUDY SAMPLE

Patient records were selected from 3-year intervals for each database: IMS from January 1, 2000, to December 31, 2002; MCO from October 1, 1999, to September 30, 2002. Patients had continuous eligibility for drug and medical coverage throughout the study period.

DESCRIPTIVE ANALYSIS

All cases of SD were identified by the presence of at least 1 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for “Disturbances of sensation of smell and taste” (781.1) or “Injury to other specified cranial nerves, including Olfactory—1st cranial—nerve” (951.8).

The cohort was described on the basis of the following characteristics:

- Annual prevalence of ICD-9-CM 781.1 or 951.8, annualized from all available years, with 95% confidence intervals (CIs).
- Annual incidence of ICD-9-CM 781.1 or 951.8. Incident cases were determined by collecting all cases in the second and third years of the 3-year study period and eliminating any that had the study diagnosis indicated in the first year. These cases were divided into the base population for their respective year to derive an incidence rate along with a 95% CI. The average annual incidence was calculated for these data.

EXPOSURES MEASURED

Risk factors (specifically drug and disease and/or accident exposures) were selected based on prior reports in the medical literature and hypothesized clinical association with the outcome. Other exposures not preselected but found to be statistically associated with SD were noted solely for hypothesis generation. Diseases, injuries, or procedures were then grouped a priori into 31 categories to be analyzed for the relationship with SD (Table 1). Likewise, 12 drug class groupings were selected as possible risk factors for SD (Table 2).

STATISTICAL ANALYSIS

Data sets from IMS and MCO were evaluated for completeness and analyzed using SAS software, version 8.02 (SAS Institute, Cary, North Carolina). For the 3 preceding time periods, univariate analyses were performed. Cases and controls were paired and matched for the study criteria. A combined model was constructed using the 31 disease and/or symptom and 12 drug groups as predicted risk fac-
tors. Univariate conditional logistic regression was performed on disease and drug data to identify the best fitting parameters for multivariate analysis. The data were then entered into multivariate regression analysis using a stepwise algorithm. The magnitude of each risk factor is expressed as an adjusted odds ratio (ie, adjusted for the influence of all other variables in the model).

### RESULTS

After eligibility exclusions, 727 patients (416 women and 311 men) in the IMS database and 1338 (798 women and 540 men) in the MCO database met the selection criteria. The mean ages were 62.2 years (median age, 63.0 years; age range, 5-88 years) and 55.7 years (median age, 57.0 years; age range, 1-89 years) for IMS and MCO groups, respectively. Most patients with SD were 50 years or older (84.7% of IMS cases and 66.1% of MCO cases). There were more women than men in each age band starting at 20 years or older. Overall, women outnumbered men by approximately 3 to 2 in both cohorts. This proportion of women to men remained constant for age 50 years or older (Figure 1). Common chronic conditions such as diabetes, hypertension, hyperlipidemia, and osteoarthritis each appeared in higher proportions in the IMS group than in the MCO group. In the prevalence population, SD was most frequently coded by otolaryngologists (24.4% for IMS, 38.7% for MCO), followed by other specialties including family practice physicians, internists, radiologists, and neurologists. Over 3 years, SD was coded a total of 1176 and 2211 times in the IMS and MCO groups, respectively. Most patients with SD were 50 years or older (84.7% of IMS cases and 66.1% of MCO cases). There were more women than men in each age band starting at 20 years or older. Overall, women outnumbered men by approximately 3 to 2 in both cohorts. This proportion of women to men remained constant for age 50 years or older (Table 3).

### PREVALENCE

For the 3-year period between January 1, 2000, and December 31, 2002, the mean annual prevalence of SD in IMS was 26.2 cases per 100 000 (95% CI, 23.1-29.6) in an eligible population of 2 911 547. Likewise, for the period between October 1, 1999, and September 30, 2002, the mean annual SD prevalence in MCO was 17.2 cases per 100 000 (95% CI, 15.6-18.7) in an eligible population of 2 782 145.

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### Table 1. Preselected ICD-9-CM Disease Groupings Used as Covariates of Smell Disturbance

<table>
<thead>
<tr>
<th>ICD-9-CM Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>042-079</td>
<td>Systemic viral diseases</td>
</tr>
<tr>
<td>141-149</td>
<td>Malignant neoplasms of lip, oral cavity, and pharynx</td>
</tr>
<tr>
<td>150-199</td>
<td>Other malignant neoplasms</td>
</tr>
<tr>
<td>200-208</td>
<td>Malignant neoplasms of the lymphatic and hematopoietic tissue</td>
</tr>
<tr>
<td>250</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>272</td>
<td>Disorders of lipid metabolism</td>
</tr>
<tr>
<td>276</td>
<td>Disorders of fluid, electrolyte, and acid-base balance</td>
</tr>
<tr>
<td>294-298</td>
<td>Organic and nonorganic psychoses; schizophrenic, affective psychoses, delusional disorders</td>
</tr>
<tr>
<td>300-309</td>
<td>Neurosis, dependence, personality, and other nonpsychotic mental disorders</td>
</tr>
<tr>
<td>331-334</td>
<td>Cerebral degeneration, Parkinson disease, other extrapyramidal and abnormal movement disorders, spinocebellar disease</td>
</tr>
<tr>
<td>335-349</td>
<td>Other organic disorders of the central nervous system</td>
</tr>
<tr>
<td>350-352</td>
<td>Trigeminal, facial, and other cranial nerve disorders</td>
</tr>
<tr>
<td>380-389</td>
<td>Diseases of the ear and mastoid process</td>
</tr>
<tr>
<td>401-405</td>
<td>Hypertensive disease</td>
</tr>
<tr>
<td>410-414</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>415-429</td>
<td>Diseases of pulmonary circulation and other heart diseases</td>
</tr>
<tr>
<td>430-438</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>461</td>
<td>Acute sinusitis</td>
</tr>
<tr>
<td>473</td>
<td>Chronic sinusitis</td>
</tr>
<tr>
<td>477</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>460, 462-472, 474, 476, 478</td>
<td>Other upper respiratory disease: acute respiratory infections; chronic disease of the pharynx, larynx, and tonsils; other diseases of the upper respiratory tract</td>
</tr>
<tr>
<td>480-487</td>
<td>Pneumonia and influenza</td>
</tr>
<tr>
<td>580-588</td>
<td>Kidney diseases</td>
</tr>
<tr>
<td>784</td>
<td>Symptoms involving the head and neck</td>
</tr>
<tr>
<td>786</td>
<td>Respiratory system and other chest symptoms</td>
</tr>
<tr>
<td>790</td>
<td>Abnormal findings on blood examination (nonspecific)</td>
</tr>
<tr>
<td>801-803, 850-851, 854, 873, 900, 920</td>
<td>All head injuries. Includes skull fractures, nonfracture intracranial injury, open head wounds, injury to blood vessels of the head or neck, and head contusions without fracture or wound</td>
</tr>
<tr>
<td>E860-E869</td>
<td>Accidental poisonings by nondrug solids, liquids, gas, or vapors</td>
</tr>
<tr>
<td>V10</td>
<td>Medical history of malignant neoplasms</td>
</tr>
<tr>
<td>V72</td>
<td>Special examinations</td>
</tr>
<tr>
<td>V76</td>
<td>Screening for malignant neoplasms</td>
</tr>
</tbody>
</table>


### Table 2. Preselected Medication Groups Used as Covariates of Smell Disturbance

<table>
<thead>
<tr>
<th>Drug Category Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Quinolone antibiotics</td>
</tr>
<tr>
<td>245, 123, 127</td>
<td>Nasal steroids, oral antihistamines, oral decongestants</td>
</tr>
<tr>
<td>20</td>
<td>Antineoplastics</td>
</tr>
<tr>
<td>42</td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>47</td>
<td>ß-Blockers</td>
</tr>
<tr>
<td>48</td>
<td>Calcium channel blocking agents</td>
</tr>
<tr>
<td>43, 44, 49, 53, 55, 56</td>
<td>Other antihypertensive agents (diuretics, central adrenergic blockers, angiotension II inhibitors, and combination products)</td>
</tr>
<tr>
<td>173</td>
<td>HMG-CoA reductase inhibitors</td>
</tr>
<tr>
<td>124, 128, 132</td>
<td>Cough and cold treatments (expectorants, antitussives, and respiratory combinations)</td>
</tr>
<tr>
<td>215</td>
<td>Insulin products</td>
</tr>
<tr>
<td>301</td>
<td>Systemic glucocorticoids</td>
</tr>
</tbody>
</table>

Abbreviation: HMG-CoA, hydroxy-3-methylglutaryl coenzyme A. 

Codes are based on the Cerner Multum Lexicon database (Denver, Colorado).
INCIDENCE

For the 2-year period between January 1, 2001, and December 31, 2002, the mean annualized incidence rate of SD for IMS was 26.3 cases per 100,000 (95% CI, 23.1-29.8) in an eligible population of 941,362. Likewise for the period between October 1, 2000, and September 30, 2002, the mean annualized rate for MCO was 15.9 cases per 100,000 (95% CI, 14.5-17.5) in an eligible population of 2,782,145. The MCO population data were available for the period of October 1, 2000, to September 30, 2002, allowing for incidence calculations stratified by age and sex (Table 4). Overall, the incidence rate was greater in women than in men (17.2 vs 14.4 per 100,000), while subjects older than 50 years had rates twice that of younger subjects (22.0 vs 10.9 per 100,000). In both sexes, incidence rates were highest between ages 50 and 69 years.

CASE-CONTROL ANALYSIS

Incident cases in the second and third years of the cohort were found in 491 patients in the IMS and 852 patients in the MCO populations. Matched controls totaled 1,473 for IMS and 2,556 for MCO. The proportion of subjects older than 50 years in both groups remained nearly the same. Similar to the characteristics of the SD prevalent group, more IMS subjects had chronic diseases such as hypertension and osteoarthritis.

Univariate analyses revealed several trends in risk factors that were shared between the 2 databases and across 3 time periods preceding the index date. Seven predefined classes of drugs were associated with SD, including 2 classes of antibiotics and 3 classes of agents that can be used for respiratory symptoms (including corticosteroids). Additionally, narcotic analgesic combinations and proton pump inhibitors were significantly associated with SD (Figure 2). With each class, there was a rising likelihood of association as the time periods got closer to the index date. The same analysis showed 3 predefined disease categories appearing in both databases and across all time periods: acute sinusitis, hypertensive disease, and respiratory tract and other chest symptoms (Figure 3).

In the multivariate analysis for the IMS database, 15 of 31 preselected disease groupings were retained along with 2 of 12 drug groups. The 5 strongest risk factors of SD were chronic sinusitis, oropharyngeal inflammatory disorders, other upper respiratory tract disease not including sinusitis, cerebrovascular disease, and systemic viral disease (Table 5). In the MCO group, 12 of 31 disease groupings and 2 of 12 drug groups were retained in the multivariate model. The risk factors most highly associated with SD in either category were chronic sinusitis, cerebral degeneration, allergic rhinitis, and acute sinusitis (Table 5). The drug group consisting of nasal corticosteroids, antihistamines, and decongestants was among the significant risk factors in both IMS (odds ratio [OR], 3.5; 95% CI,
### Table 3. Frequency of Medical Specialty or Setting Coding for Sense of Smell Disturbances in the 2 Database Groups

<table>
<thead>
<tr>
<th>Specialty or Setting</th>
<th>IMS Health LifeLink Database</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Otology</td>
<td>285 (24.4)</td>
<td></td>
</tr>
<tr>
<td>Acute care hospital</td>
<td>205 (17.5)</td>
<td></td>
</tr>
<tr>
<td>Radiology x-ray</td>
<td>163 (14.4)</td>
<td></td>
</tr>
<tr>
<td>Internal medicine</td>
<td>81 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Family practice</td>
<td>74 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>57 (4.9)</td>
<td></td>
</tr>
<tr>
<td>Neurology</td>
<td>48 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>48 (4.1)</td>
<td></td>
</tr>
<tr>
<td>General practice</td>
<td>46 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Independent laboratory</td>
<td>26 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Obstetrics/gynecology</td>
<td>19 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Extended care</td>
<td>17 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Dermatology</td>
<td>16 (1.4)</td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td>9 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td>8 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>7 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>6 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>5 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>5 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>5 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Urology</td>
<td>5 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Neurology surgery</td>
<td>4 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Endocrinology</td>
<td>4 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Ambulance-free</td>
<td>4 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Pediatrics</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Physical medicine</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Other medical care</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Specialty hospital</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Ambulatory service</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Podiatrist</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric hospital</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1169</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Distribution and Incidence of Sense of Smell Disturbance in Patients From the MCO Database by Age and Sex From October 1, 2000, to September 30, 2002

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Incident Cases, No. (%)</th>
<th>MCO Population, No. (%)</th>
<th>Annual Incidence per 100 000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td>519 (58.5) / 1507 492 (54.2)</td>
<td>4 (0.5) / 121 117 (4.4)</td>
<td>17.2 (15.8-18.8)</td>
</tr>
<tr>
<td>10-19</td>
<td>10 (12) / 160 936 (5.6)</td>
<td>10 (1.2) / 160 936 (5.6)</td>
<td>3.2 (1.6-5.9)</td>
</tr>
<tr>
<td>20-29</td>
<td>29 (3.3) / 110 764 (4.0)</td>
<td>29 (3.3) / 110 764 (4.0)</td>
<td>13.1 (8.8-18.8)</td>
</tr>
<tr>
<td>30-39</td>
<td>54 (6.1) / 177 140 (6.4)</td>
<td>54 (6.1) / 177 140 (6.4)</td>
<td>15.2 (11.4-19.9)</td>
</tr>
<tr>
<td>40-49</td>
<td>91 (10.3) / 228 759 (8.2)</td>
<td>91 (10.3) / 228 759 (8.2)</td>
<td>20.0 (16.1-24.5)</td>
</tr>
<tr>
<td>50-59</td>
<td>120 (13.6) / 193 517 (7.0)</td>
<td>120 (13.6) / 193 517 (7.0)</td>
<td>31.1 (25.8-37.2)</td>
</tr>
<tr>
<td>60-69</td>
<td>98 (11.0) / 157 395 (5.7)</td>
<td>98 (11.0) / 157 395 (5.7)</td>
<td>31.0 (25.1-37.8)</td>
</tr>
<tr>
<td>70-79</td>
<td>83 (9.4) / 224 364 (8.1)</td>
<td>83 (9.4) / 224 364 (8.1)</td>
<td>18.5 (14.7-22.9)</td>
</tr>
<tr>
<td>80+</td>
<td>29 (3.3) / 133 502 (4.8)</td>
<td>29 (3.3) / 133 502 (4.8)</td>
<td>10.9 (7.3-15.6)</td>
</tr>
<tr>
<td>Male</td>
<td>367 (41.5) / 1 274 653 (45.8)</td>
<td>367 (41.5) / 1 274 653 (45.8)</td>
<td>14.4 (13.0-16.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MCO, i3 Magnifi Private Managed Care Organizations database (Waltham, Massachusetts).

This analysis captured medical claims for SD, most likely representing the proportion of the population with SD that specifically sought medical care for this condition. In this initial descriptive analysis within 2 claims databases from managed care organizations, the annual prevalence of this proportion of those with claims for SD was 17.1 and 26.2 cases per 100 000 patients for MCO and IMS, respectively. The annual incidence for claims for the same disorder was 15.9 and 26.3 cases per 100 000 patients for MCO and IMS, respectively. In the MCO population, age- and sex-specific data showed that incidence rates were higher with increasing age and were greater in women than men. These results correspond with studies done in other settings. 

2.1-6.1) and MCO (OR, 3.9; 95% CI, 1.6-9.3). Systemic corticosteroids were also twice as likely to be used in patients with SD in the IMS group (OR, 2.0; 95% CI, 1.1-3.9). In the MCO group, calcium channel blocker antihypertensives were found to be significantly associated with SD. Disease groups found in both databases were disorders of lipid metabolism, cerebral degenerative conditions, and other cardiopulmonary diseases (excluding heart disease and hypertension).
higher likelihood of SD in women. The number of claims coded for ICD-9-CM 781.1 and/or 951.8 was 1.6 per person over 3 years for both databases, which appears to be a relatively low rate of repeated claims. Further analysis compared with a chronic disease state such as hypertension would help to index the duration. A higher rate of SD in the IMS population could be expected, since IMS subjects were notably older (Figure 1).

Most epidemiologic studies of SD have been cross-sectional or descriptive case series in design. In 1987, National Geographic published a nonrandom survey of 1.2 million persons by Gilbert and Wysocki\textsuperscript{14} showing that 1% of respondents could not smell 3 of 6 odorants on a scratch-and-sniff test. Since the survey was cross-sectional and not controlled, the data could not provide a reliable prevalence estimate.

The National Institutes of Health National Institute on Deafness and Other Communication Disorders and the National Center for Health Statistics\textsuperscript{27} used the Disability Supplement of the National Health Interview Survey (NHIS)\textsuperscript{28} to obtain information about SD in 42,000 randomly selected households representing 80,000 adults older than 18 years. Hoffman and colleagues\textsuperscript{13} analyzed these data and reported an adjusted prevalence of 2.7 million adults (1.4%, 1,420 per 100,000) with chronic sense of smell problems. Taste disturbances were also analyzed, since they are largely associated with dysfunctions of smell. When taste disturbances were included, a prevalence of 3.2 million people or 1.65% was found. The NHIS was limited owing to its household survey methodology,\textsuperscript{28} which added a dimension of recall bias. This approach captures a broad spectrum of reported SDs in the general population, but the source lacks the sensitivity or specificity elicited from a medical examination. Our study reflects that portion of SDs that are medically diagnosed and accompanied by information on prior exposure to diseases or drugs. While not comparable, both studies provide population-based estimates that contribute to our understanding of different components of SD.

Prevalence rates for SD claims for our study were approximately 50- to 80-fold smaller than the estimates by Hoffman and colleagues.\textsuperscript{13} However, there were major differences in design and conduct between our study and the NHIS.\textsuperscript{28} One difference is the natural bias inherent in medical claims, which might have selected for more patients with ear, nose, and throat disorders for which specialists would make the diagnosis, more patients with viral upper respiratory tract infections, and fewer cases that might be due to other causes. The present analysis could not identify those who did not seek medical care for SD for a number of reasons (patient lack of awareness, low patient perception of severity, and symptomatically minor or transient events). Analysis of medical claims likely includes only patients with SD severe enough to seek medical care. Our results are most representative of patients who have insurance with managed care organizations, including those with Medicare. It might not be entirely generalizable to the broader population, which includes patients without insurance or covered by

![Figure 2. Drug classes associated with sense of smell disturbance in 3 preindex time periods in both the IMS Health LifeLink (Plymouth Meeting, Pennsylvania) (IMS) (A) and the i3 Magni Private Managed Care Organizations (Waltham, Massachusetts) (MCO) (B) databases. With each class, there was a rising likelihood of association as the time periods approached the index date. Error brackets indicate 95% confidence intervals.](image-url)
Medicaid, since these patients might be less likely to seek care for such a disorder.

The National Health Interview Survey of Disability also revealed a distinct age-related trend in the prevalence of reported olfactory dysfunction. People older than 65 years accounted for 1.07 million of the 2.7 million adults who reported olfactory dysfunction, an overall prevalence of 0.55%. The prevalence increased with each age group: 1.99%, 2.65%, and 4.60% for age groups 55 to 64 years, 65 to 74 years, and 75 years or older, respectively. Murphy et al showed a similar trend but a higher prevalence: 6.1%, 17.3%, and 29.2% for age groups 53 to 59 years, 60 to 69 years, and 70 to 79 years, respectively. Our study cohort also had a large proportion of patients in the upper age ranges, with 84.7% of IMS cases and 66.1% of MCO cases older than 50 years.

Sex differences were apparent in our study. In both databases, about 60% of diagnoses for SD were in women. This predominance occurred across all age groups. By contrast, Murphy and colleagues demonstrated a higher proportion and a higher prevalence of olfactory dysfunction among men. This difference might be owing to the nature of managed care settings where women are more likely to seek medical services. Other epidemiologic studies have found mixed results for sex distribution.

Murphy and colleagues evaluated the prevalence of olfactory impairment in a cohort of older participants of the 5-year follow-up examination for the Epidemiology of Hearing Loss Study. Subjects (N = 2491) aged between 53 and 84 years completed the San Diego Odor Identification Test, an 8-item test that uses commonly found odors. The authors described an SD prevalence of 24.5% based on testing, and 9.3% from self-report in these older patients. It was noted that self-reporting was a positive risk factor in 1 of every 5 people who had olfactory dysfunction. The authors suggested that many people might be unaware that a problem even existed. This lack of awareness would have excluded a large number of cases in our claims study. Thus, the lower rate in our study might indicate the selection of cases with more severe olfactory dysfunction that prompted patients to seek medical attention. The lack of self-report reliability has also been reported by others. Another possible contributor might be the low detection rate of SD in primary care practices.

Several epidemiologic studies outside the United States also provide insight into the prevalence of SD. Olsson and colleagues randomly surveyed 10,670 participants in Stockholm County, Sweden. Reduced olfactory sense described as “often” was reported in 1.9% of healthy subjects, 2.2% of subjects with allergic rhinoconjunctivitis, and 8.4% of subjects with nonallergic rhinitis. The Skovde Population-Based Study examined 1387 volunteers using the Scandinavian Odor Identification Test. Investigators reported a 13.3% prevalence of hyposmia and 5.8% prevalence of anosmia among these volunteers. Test performance declined significantly with age. In Dresden, Germany, Landis and colleagues recruited 1240 subjects without sinonasal disease for odor identification testing. Sixteen percent of subjects were found to have hyposmia, while 4.7% were reported to be functionally anosmic.

Harris and colleagues performed a case series examination on 1000 consecutive patients presenting to a specialized smell and taste clinic in San Diego, California. Subjects provided medical histories and were administered psychophysical olfactory tests. Each subject was also given an ear, nose, and throat examination along with a com-

Figure 3. Three disease categories were associated with sense of smell disturbance in 3 preindex time periods in both the IMS Health LifeLink (Plymouth Meeting, Pennsylvania) (IMS) (A) and the i3 Magnifi Private Managed Care Organizations (Waltham, Massachusetts) (MCO) (B) databases: acute sinusitis (ICD-9-CM code 461), respiratory symptoms (ICD-9-CM code 786), and hypertensive disease (ICD-9-CM codes 401-405). ICD-9-CM indicates International Classification of Diseases, Ninth Revision, Clinical Modification. Error brackets indicate 95% confidence intervals.
puted tomography scan. Patients answered a 22-item questionnaire to rate various symptoms associated with sense of smell loss. The investigators found that 41.4% of patients were 50 years or older, and the numbers of men and women were approximately equal. The percentages of the populations older than 50 years in our study were 84.7% and 66.1% in the IMS and MCO databases, respectively; women outnumbered men in both databases in our study. Overall, Harris and colleagues\(^\text{34}\) reported that SD was most frequently caused by viral infections and inflammatory processes. Nearly half of SD cases due to head trauma were found in those younger than 50 years. In the present study, SD was attributed to many of the conditions we found to be significant risk factors. However, our study cannot be directly compared with the non-population-based case series by Harris et al\(^\text{34}\) because subjects in our study were identified from a defined large population of managed care enrollees. This allowed for the quantification of other possible risk factors such as drug exposure. However, the case series provides a detailed clinical picture of patients referred to a specialty clinic, who likely require more thorough workup and care owing to the severity of their condition.

A number of grouped drug and disease classifications that we selected were found to be significantly associated with SD in this case-control analysis. Conditions documented to be related to SD such as malignancies, psychoses, cerebrovascular accidents, and upper respiratory tract diseases were also shown to be preceding conditions to SD in our study.\(^\text{2,5,9}\) Other conditions such as head injuries and metabolic disorders did not achieve statistical significance despite their general association with olfactory dysfunction.\(^\text{10}\)

Our disease groupings were selected based on documented evidence of an effect on olfactory function or on the basis of drug therapies that might increase the risk of SD. Nasal polyps have been reported to impair the sense of smell in 47% of patients tested.\(^\text{21}\) Patients with cancer typically report the loss of taste and smell, which compounds or contributes to their critical malnutrition, and which might relate to the tumor condition or the chemotherapy that also alters the sense of smell.\(^\text{4}\) Olfactory disorders associated with neuropsychiatric conditions such as schizophrenia have been documented.\(^\text{5,35}\)

The category of hypertensive diseases was significantly associated with SD in both databases. The diagnoses for hypertension and lipid disorders are possibly markers for antihypertensive or lipid-lowering drug-induced disorders of olfaction. However, our regression model favored the diseases themselves over the drug categories. Doty and colleagues\(^\text{2}\) recently reviewed the labeling of 92 antihypertensive and antihyperlipidemic agents for their effect on smell and taste. It was noted that SD was reported in 36% of the group. The review also discussed possible related mechanisms for each drug class.

A recent study by DiBaise and colleagues\(^\text{36}\) showed that 81% of patients with chronic sinusitis also had gastroesophageal reflux. Several mechanisms have been proposed, including direct insult to the nasal mucosa, a vagal neurogenic effect, and an infectious role of *Helicobacter pylori*.\(^\text{37}\) This might help explain the finding of an association with proton pump inhibitors. Numerous unexplained associations with SD such as these demonstrate the need for further studies in this area. One additional mechanism for SD related to sinusitis might be found in the therapy. Nasal steroids in particular have been associated with the development of and treatment for SD; however, there is clear temporal confounding that might make it difficult to disentangle therapy from the underlying disease.

### Table 5. Multivariate Analysis of Disease and Drug\(^\text{a}\) Categories Associated With Sense of Smell Disturbance

<table>
<thead>
<tr>
<th>Disease or Drug Grouping</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMS</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>204.4 (22.8-1834.7)</td>
</tr>
<tr>
<td>Systemic viral diseases</td>
<td>71.0 (11.7-431.8)</td>
</tr>
<tr>
<td>Diseases of the ear and mastoid process</td>
<td>20.4 (7.9-52.8)</td>
</tr>
<tr>
<td>Symptoms involving the head or neck</td>
<td>19.4 (5.2-71.8)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>16.9 (5.5-52.0)</td>
</tr>
<tr>
<td>Other upper respiratory tract disease: acute respiratory tract infections; chronic disease of the pharynx, larynx, and tonsils; other diseases of the upper respiratory tract</td>
<td>9.5 (3.9-22.9)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>8.5 (1.7-42.1)</td>
</tr>
<tr>
<td>Other organic central nervous system diseases</td>
<td>6.9 (1.0-47.2)</td>
</tr>
<tr>
<td>Psychoses, including schizophrenia</td>
<td>6.2 (2.0-19.7)</td>
</tr>
<tr>
<td>Cerebral degeneration, including Alzheimer disease</td>
<td>6.1 (1.0-35.2)</td>
</tr>
<tr>
<td>Other malignant neoplasms</td>
<td>4.3 (2.0-9.3)</td>
</tr>
<tr>
<td>Nasal steroids, antihistamines, decongestant products</td>
<td>3.5 (2.1-6.1)</td>
</tr>
<tr>
<td>Respiratory and other chest symptoms</td>
<td>3.3 (1.8-6.2)</td>
</tr>
<tr>
<td>Diseases of pulmonary circulation and other heart diseases</td>
<td>2.7 (1.3-5.6)</td>
</tr>
<tr>
<td>Disorders of lipid metabolism (hyperlipidemia)</td>
<td>2.3 (1.2-4.2)</td>
</tr>
<tr>
<td>Glucocorticosteroids</td>
<td>2.0 (1.1-3.9)</td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td>1.9 (1.1-3.2)</td>
</tr>
<tr>
<td><strong>MCO</strong></td>
<td></td>
</tr>
<tr>
<td>Symptoms involving the head or neck</td>
<td>44.3 (6.7-293.5)</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>31.6 (4.3-233.5)</td>
</tr>
<tr>
<td>Cerebral degeneration, including Alzheimer disease</td>
<td>18.4 (1.6-207.5)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>15.5 (4.3-56.2)</td>
</tr>
<tr>
<td>Diseases of the ear and mastoid process</td>
<td>10.4 (3.1-34.9)</td>
</tr>
<tr>
<td>Acute sinusitis</td>
<td>13.6 (2.4-78.4)</td>
</tr>
<tr>
<td>Other upper respiratory tract disease: acute respiratory tract infections; chronic disease of the pharynx, larynx, and tonsils; other diseases of the upper respiratory tract</td>
<td>10.3 (4.7-22.6)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>9.7 (1.2-76.2)</td>
</tr>
<tr>
<td>Neurosis, dependence, personality, and other nonpsychotic mental disorders, including tobacco addiction</td>
<td>7.5 (2.2-25.9)</td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td>4.0 (2.2-7.1)</td>
</tr>
<tr>
<td>Nasal steroids, antihistamines, decongestant products</td>
<td>3.9 (1.6-9.3)</td>
</tr>
<tr>
<td>Diseases of pulmonary circulation and other heart diseases</td>
<td>3.7 (1.4-9.4)</td>
</tr>
<tr>
<td>Disorders of lipid metabolism (hyperlipidemia)</td>
<td>3.4 (1.8-6.4)</td>
</tr>
<tr>
<td>Calcium channel blocking agents</td>
<td>1.9 (1.1-3.5)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IMS, IMS Health LifeLink claims database (Plymouth Meeting, Pennsylvania) MCO, i3 Magni Private Managed Care Organizations database (Waltham, Massachusetts).  
\(^a\)Drug categories are listed in italics.
There has long been evidence of a relationship between SD and psychosis or schizophrenia. In the present study, schizophrenia and psychosis were strongly associated with SD in the IMS cohort (OR, 6.2; 95% CI, 2.0-19.7). Though not retained in the multivariable model this database shows that schizophrenia was more likely to be found in patients with SD (OR, 5.9; 95% CI, 1.5-22.6). McLean and colleagues recently discovered that schizophrenics with diminished olfaction had their ability to smell attenuated by smoking. Both of these factors alone are typically thought to have negative effects on olfaction. Such a situation could not have been explained by our study and serves as a good example for using caution in arriving at conclusions based solely on claims data.

Similar to the findings in schizophrenia, we did not find full conformity between the 2 databases for other factors in our multivariable analysis. In the IMS database, 17 factors were found to be significantly associated with SD, as were 14 factors in the MCO group. Among these, 11 factors were common to both groups making up about 65% of IMS and 79% of MCO factors. This appears to be a fairly high concordance between databases. Many of the risk factors that were not significant in both databases were significant in our intermediate conditional regression analyses. However, the multivariable regression removed them from the final model. This might be explained by insufficient statistical power for these conditions. Systematic or administrative differences between the 2 managed care databases such as prior authorization or capitated reimbursement might also be a reason for differences in results. We intentionally chose to examine 2 managed care databases to draw from a heterogeneous population. We noted that the IMS group was generally older than the MCO group. Each database also reflected slightly different geographic regions and different health plans.

We performed univariate analyses in time periods of 0 to 30, 31 to 90, and 91 to 180 days preceding the index date. These exploratory analyses identified a number of drug classes associated with SD in each of the 3 preceding periods. β-Lactamase inhibitors and quinolone antibiotics are commonly used agents for upper respiratory tract infections. Upper respiratory tract infections were also strongly associated with SD, but it is unclear if there is confounding by indication to the antibiotics or if there is a true association.

The present study is subject to some limitations. The population examined represents patients eligible for health insurance coverage. All patients in our cohort were seeking health care and thus might differ somewhat from the larger general population. These rates are useful because they arise from the population seen by many physicians participating in health plans. Specificity was also limited by the ICD-9-CM code for “Disturbances of sensation of smell and taste” (781.1) because it does not distinguish between smell and taste. Thus, uncertainty remains about which outcome a risk factor influences. However, clinical attribution of significant risk factors to disturbances of smell, taste, or both can be made. Most taste alterations are a function of smell disorders since flavors are influenced by olfaction. Our early univariate analyses showed a predominance of significant factors related to smell rather than taste.

Although a significant number of visits were coded by nonotolaryngologist physicians, SD was most frequently coded by otolaryngologists. This included multiple diagnoses made in the same patient. However, SD would logically be clustered with the type of conditions seen by this specialty, and this might be an incidental finding. It is not known from our study how the initial diagnosis for SD is influenced by examination by an otolaryngologist vs other health care providers. It is possible that members of the case group in this study were more likely to see their otolaryngologist physicians for their upper respiratory tract conditions. This would have increased the likelihood that SD be detected either by patient report or by greater awareness on the part of the specialist. In a managed care environment, patients with more complicated or severe conditions—reflected in greater comorbidities—tend to be referred to specialists. We did not have sufficient power to examine this subgroup; however, such a study would complement findings from studies in specialty clinics like those conducted by Harris and colleagues and Deems et al. Further studies on the relationship between otolaryngologists and risk factors for SD are warranted.

In conclusion, this descriptive analysis of medical claims in patients diagnosed as having SD is most relevant for those who have a clinically significant disorder. The rates found, based on analysis of 3 years of data (for prevalence estimates) were much lower than those previously reported in the literature. This is in part a reflection of the data source that does not include patients who do not report this condition to their physicians and/or do not have their complaints registered as a claim. As in previous studies, cases tended to be found in older patients, but in our study, SD tended to occur more frequently in women than in men.

The results of this case-control study confirm a number of suspected associations between specific groups of diseases and drugs and the incidence of SD. A regression model combining drug and disease predictive groups that were selected a priori removed all but 3 drug groups. This suggests the greater influence of disease states as predisposing factors in patients with SD. Multivariate analyses helped to determine the combined influence of diseases and drugs on the occurrence of SD.

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