Chronic rhinitis and its association with headache frequency and disability in persons with migraine: Results of the American Migraine Prevalence and Prevention (AMPP) Study

Vincent T Martin¹, Kristina M Fanning², Daniel Serrano², Dawn C Buse³, Michael L Reed², Jonathan A Bernstein¹,⁴ and Richard B Lipton³,⁵

Abstract

**Background:** Rhinitis is a comorbidity of migraine, but its relationship to migraine headache frequency and headache-related disability is unknown.

**Objectives:** To determine if rhinitis and its subtypes are associated with an increased frequency and associated disability of migraine.

**Methods:** The AMPP Study is a longitudinal study of individuals with “severe” headache from the US population. Respondents meeting ICHD-2 criteria for migraine in 2008 were identified and the presence of rhinitis was determined using the European Community Respiratory Health Survey (ECRHS). Those with rhinitis were subtyped as allergic, non-allergic, mixed and unclassified based on a rhinitis questionnaire. The primary outcome measures were categories of headache-day frequency and headache-related disability as measured by the Migraine Disability Assessment Scale (MIDAS). Logistic regression for ordered categories was used for modeling each outcome separately, adjusted for sociodemographic profile, headache features, headache treatments and comorbidities.

**Results:** The AMPP Study questionnaire was mailed to 17,892 persons and returned by 60.1% of respondents. Among the migraine sample (n = 5849), 66.8% had rhinitis with mixed rhinitis as the most common form. The presence of rhinitis of any type was associated with headache frequency after adjusting for sociodemographic variables only (OR 1.33; 95% CI 1.16, 1.53) and in the fully adjusted model (OR 1.25; 95% CI 1.05–1.49). Headache-related disability (MIDAS category) was associated with rhinitis after adjusting for sociodemographic features (OR 1.30; 95% CI 1.17–1.46), but lost significance in the fully adjusted model (OR 1.10; 95% CI 0.96–1.26). Mixed rhinitis was associated with an increased headache frequency category in the model adjusted for sociodemographics (OR 1.45; 95% CI 1.24–1.70) and in that adjusted for all covariates (OR 1.28; 95% CI 1.05–1.57). The odds ratio for MIDAS categories were similarly increased in both models for the mixed rhinitis group.

**Conclusions:** The frequency and disability of migraine are higher in persons with rhinitis, particularly those with mixed rhinitis. These results, however, should be considered preliminary until confirmed in future studies because of the modest questionnaire response rate in this study.

**Keywords**

Rhinitis, migraine, headache frequency, headache-related disability, comorbidities, depression, allodynia
Introduction

Migraine headache and chronic rhinitis are common, heterogeneous, symptomatic conditions that are more prevalent in women and produce substantial illness related disability (1–5). The population prevalence of migraine in the USA has been estimated to be 11.7%, including 17.1% of women and 5.6% of men (1). Chronic rhinitis prevalence ranges from 24–54% (2–5). Rhinitis symptoms include sneezing, nasal itching and congestion, rhinorrhea and post-nasal drip.

Rhinitis can be categorized into allergic (AR), non-allergic (NAR) and mixed (MR) subtypes. Allergic rhinitis is defined as the presence of a specific IgE mediated immune response to an allergen by skin prick or serologic testing that corresponds with the presence of rhinitis symptoms upon exposure to the allergen. In contrast, in NAR, symptoms are associated with non-allergic triggers (e.g. perfumes, cigarette smoke, diesel fumes, etc.) in conjunction with negative allergy skin and/or serologic testing. Finally, in mixed rhinitis (MR) symptoms occur in response to both allergic and non-allergic triggers. Although the gold standard for distinguishing allergic rhinitis depends upon skin prick or serology testing, symptom-based subtyping has been validated (6–9).

Past studies have reported that AR and hay fever (a surrogate term used to denote a type of seasonal AR) are associated with the prevalence and frequency of migraine headache. Ku and colleagues found that migraine was significantly more prevalent in those with AR (occurring in 34%) compared with non-atopic, non-rhinitis controls (occurring in 2%) (10). Other studies have shown that hay fever is associated with migraine and that the association becomes stronger as headache frequency increases (11–13). Past studies have not assessed the relationship of chronic rhinitis subtypes to headache-related disability in persons with migraine.

This cross-sectional, observational study uses data from the American Migraine Prevalence and Prevention Study (AMPP) Study to assess the association of chronic rhinitis subtypes with the frequency and associated disability of headache in migraineurs. In examining these relations, we adjust for potential confounders including comorbid medical and psychiatric disorders, medication overuse, use of migraine preventive medications and the presence of cutaneous allodynia.

Methods

The AMPP Study is a two-phase, longitudinal, population-based survey of headache epidemiology described in detail elsewhere (1). The phase 1 survey was mailed in June, 2004 to a stratified random sample of 120,000 US households. This survey yielded data for 162,756 household members aged 12 and older. There were 30,721 respondents who reported experiencing “severe headache”. Usable data were obtained from 30,291 individuals, of whom 28,261 reported experiencing “severe headache” in the preceding year. A random sample of 24,000 adults (age 18 and older) was selected from that group to be enrolled in phase 2: a longitudinal follow-up study with surveys mailed annually from 2005–2009.

Non-responders to the AMPP Study tend to be older and more likely to be female than responders, common patterns in a broad range of survey research (14). Non-response bias has been explored in the AMPP Study sample previously and patterns are typical for survey research in general (15). There is no evidence for selective participation by migraine or rhinitis status.

The current study analyzed data from 2008, the only year to include a rhinitis questionnaire. Study respondents who met International Classification of Headache Disorders-II (ICHD-II) criteria for migraine and completed the rhinitis questionnaire were included in analyses (16). This study was approved by the Albert Einstein College of Medicine Institutional Review Board.

Rhinitis groups

All participants completed a rhinitis questionnaire, developed to ascertain information about nasal allergies, seasonal allergies and hay fever. It also assesses the frequency of five rhinitis symptoms (stuffy nose, runny nose, itchy nose, sneezing, post-nasal drip) and the frequency of eight allergic and non-allergic triggers (online Supplementary material).

A diagnosis of rhinitis was defined as a response of “yes” to the presence of nasal allergies, seasonal allergies or hay fever. This question was obtained from the validated European Community Respiratory Health Survey (ECRHS) and is one of the most commonly used questions to define rhinitis within past epidemiologic studies (17–19). An affirmative response to this question significantly increases the risk of AR as a recent study demonstrated a positive likelihood ratio of 8.1 for atopy as determined by skin prick testing (19). Other studies using “hay fever” as a sole question also report positive likelihood ratios ranging from 4.8–11.7 in the diagnosis of atopy (20,21). However, a positive response does not exclude the possibility of NAR as seasonal exacerbations of rhinitis symptoms commonly occur with this type of rhinitis and are often misinterpreted by the patient as seasonal allergies (22). A diagnosis of rhinitis also required a response of “sometimes”, “very often” or “always” to at least two rhinitis symptoms, which represent the symptoms
used by the Joint Task Force on Practice Parameters to define rhinitis (23). The second question was added to confirm that rhinitis symptoms were present in this group. Non-rhinitis controls were defined as those that answered “no” to the presence of nasal allergies, seasonal allergies or hay fever.

Participants with rhinitis were subdivided into allergic, non-allergic, mixed and unclassified rhinitis categories based upon their response to questions regarding specific allergic and non-allergic rhinitis triggers. While the definitions of the rhinitis subtypes have not been validated, the individual questions used in these definitions have demonstrated positive likelihood ratios ranging from 1.69–6.8 and negative likelihood ratios ranging from 0.28–0.81 for diagnosis of AR and NAR subtypes (6,9,21,22). For example, the provocation of rhinitis symptoms by cats or dogs has a positive likelihood ratio of 4.2 for the diagnosis of AR in one past study (6). Allergic triggers included a worsening of rhinitis symptoms with seasonal outdoor exposure (spring, summer, fall), cat/dog and mold, whereas non-allergic triggers included strong odors (perfumes, cleaning agents, gasoline fumes), temperature/weather changes and cigarette smoke. Allergic rhinitis (AR) was defined as a response of “very often” or “always” to at least one of the questions representing AR triggers and “never” or “rarely” to all of the non-allergic triggers. Non-allergic rhinitis was defined as a response of “very often” or “always” to at least one of the questions representing non-allergic rhinitis triggers and “never” or “rarely” to all of the allergic triggers. Mixed rhinitis was defined as a response of “very often” or “always” to at least one of the questions representing non-allergic rhinitis triggers and “very often” or “always” to at least one of the questions representing non-allergic rhinitis triggers. Unclassified rhinitis (UR) was defined as those rhinitis patients that did not self-report allergic or non-allergic triggers.

Outcome measures

Headache-related disability was assessed with the Migraine Disability Assessment Questionnaire (MIDAS) (24). The MIDAS is a five-item, self-administered questionnaire that assesses days of missed or substantially reduced activity caused by headache in the preceding 3 months in three domains: schoolwork/paid employment, household work or chores, and non-work (family, social, and leisure) activities. Responses (number of days per question) are summed and coded into one of four grades of headache-related disability: Grade I, little or no disability (0–5); Grade II, mild disability (6–10); Grade III, moderate disability (11–20); Grade IV, severe disability (≥21).

The frequency of headache days was obtained from the MIDAS Questionnaire, which included a question asking the number of headache days over the preceding 3 months. Monthly headache days were determined by dividing the number of headache days over the preceding 3 months by three. Monthly headache days were divided into categories of low frequency episodic migraine: 0–4, moderate frequency episodic migraine: 5–9, high frequency episodic migraine: 10–14, and chronic migraine: ≥15 days of headache per month.

Definitions of covariates

Sociodemographic measures included age, sex, race, income, and height and weight (which were used to calculate body mass index [BMI] using a standard formula). Current smoking was ascertained with a single question to assess current smoking habits. The presence of comorbid medical and psychiatric disorders was also ascertained for each respondent by validated questionnaires or by patient self-report of a past physician diagnosis.

Depression was assessed using the Patient Health Questionnaire Depression module (PHQ-9), a validated measure of major depressive disorder (25). The PHQ-9 assesses depressive symptomology over the preceding 2 weeks based on nine items with four response options, which are summed for a total score (ranging from 0–27). Major depression was defined using a standard cut score of at least 10. Anxiety was assessed using the PRIME-MD Anxiety module of the Primary Care Evaluation of Mental Disorders (PRIME-MD), which evaluates seven symptoms of anxiety experienced over the preceding 4 weeks (26). Respondents who reported, “feeling nervous, anxious, on edge, or worrying about a lot of different things” and at least three additional symptoms on “more than half the days” were given a diagnosis of anxiety. A diagnosis of asthma was based on the European Community Respiratory Health Survey-II, a validated questionnaire for the diagnosis of asthma and bronchial hyper-responsiveness (27). A response of “yes” to two of three of the following questions was defined as an asthma diagnosis: 1) wheezing/whistling in your chest in the past 12 months and breathlessness when the wheezing noise was present or woken up by attack of shortness of breath (SOB) anytime in the past 12 months, 2) attack of asthma in the past 12 months and 3) currently taking any physician prescribed medication for asthma. Additional comorbid conditions, including diabetes and hypertension, were assessed by respondent endorsement if they have ever received a medical diagnosis by a health professional for a list of 36 medical and psychiatric conditions.

Cutaneous allodynia (defined as pain normally non-noxious stimuli) was assessed using the Allodynia
Symptom Checklist-12 (ASC-12) (28). Sum scores on the ASC-12 range from 0 to 24 and a standard cut score of at least three was used to define the presence of allodynia.

The AMPP Study survey includes a comprehensive list of acute and preventative medications, both generic and brand names, used by respondents to treat their “most severe type of headaches”. The acute medication list includes both non-prescription and prescription medications. Medication overuse was defined when non-steroidal anti-inflammatories or simple analgesics were used for at least 15 days/month or triptan, ergots or narcotics for at least 10 days per month (29). Preventive medication use was defined as currently taking a medication to prevent headaches or not using a preventive, which was the reference for this variable.

Analyses
Analyses were performed using IBM SPSS Statistics Version 20.0.0 (IBM, Armonk, NY, USA; 2011). A p value of ≤0.05 was used to identify statistically significant effects and all tests were two-tailed. Descriptive statistics were generated for all dependent variables by total rhinitis, each of the rhinitis subgroups and non-rhinitis control. Unadjusted binary regression analysis was performed comparing the total rhinitis group and each rhinitis subgroup to the non-rhinitis control OR and 95% CI were provided. For continuous variables, linear regression was used to compare the total rhinitis and each rhinitis subgroup (AR, NR, MR, UR) against a non-rhinitis control; regression coefficients (B) and 95% CI were provided.

Ordinal logistic regression was used to assess differences between total rhinitis group and rhinitis subgroups compared with the non-rhinitis control group on headache days and disability (MIDAS) categories. Regression models were run both adjusted for sociodemographics only (age, sex, income) and adjusted for sociodemographics, comorbid conditions (anxiety, depression, asthma, diabetes and hypertension), BMI, smoking, allodynia, preventative medication use and medication overuse. The inclusion of sociodemographic variables and other covariates in the models can adjust for imbalances between comparison groups at baseline.

Results
In 2008, the AMPP Study survey was mailed to 17,892 AMPP Study participants and returned by 10,745 individuals (60.1% response rate), of whom 10,720 provided complete data and were eligible for analysis. The sample for the current analysis includes 5849 respondents age 18 or older who met a case definition for migraine and completed the rhinitis questionnaire. Among eligible respondents, one-third (1940; 33.2%) did not meet any of the rhinitis criteria and were treated as a non-rhinitis control group; overall two-thirds (3909; 66.8%) met the criteria for rhinitis. Among those with rhinitis, 737 (18.9%) met criteria for AR, 379 (9.7%) for NAR, 1869 (47.8%) for MR and 924 (23.6%) for UR (Figure 1).

Sociodemographic data and clinical characteristics of the sample are presented in Table 1. The total rhinitis and non-rhinitis groups did not differ in age but persons with rhinitis were more likely to be female, less likely to be a current smoker and had higher BMIs. In comparison with controls free of rhinitis, the rhinitis group was more likely to have allodynia (OR 1.40, 95% CI 1.25–1.57), asthma (OR 3.75, 95% CI 3.11–4.52), anxiety (OR 1.32, 95% CI 1.07–1.64), depression (OR 1.25, 95% CI 1.08–1.43), diabetes (OR 1.22, 95% CI 1.04–1.44) and hypertension (OR 1.28, 95% CI 1.14–1.44). Those with mixed rhinitis had the highest rates of these covariates and differed from non-rhinitis controls for allodynia, asthma, anxiety, depression and hypertension.

Missing data
Missing data were permitted and not imputed because of the heterogeneous response distributions of covariates. Case deletion was not employed to achieve a synthetic balanced design across models and outcomes. Consequently, we have slightly different sample sizes across models and outcomes. Our approach is unbiased if data are missing complete at random (MCAR). If this assumption is false, standard errors may be reduced resulting in liberal test statistics. For the headache frequency outcome, the available sample was 6213 (out of a possible 6377). Of these 6213, 5699 contributed to model 1, because 678 cases were missing the data on the rhinitis. In model 2, 4017 cases were available for analysis and 1696 additional cases were missing data required for model 2. Data on preventive medication use was missing most frequently, accounting for 888 (52%) of the missing data. For the MIDAS outcome, the available sample was 6205 out of 6377. Of these 6377 individuals, 678 were missing rhinitis data, leaving 5699 individuals eligible for model 1. For model 2, an additional 1692 persons were missing information on the covariate set in model 2. Again, data on preventive medication were most frequently missing (N=877, 52%).

Headache frequency and disability
The total rhinitis group significantly differed from controls in both headache frequency category and
The odds of being in a higher headache days/month category were 33% greater for the total rhinitis group in models adjusted for sociodemographic variables (OR 1.33, 95% CI 1.16–1.53) and 25% greater in the fully adjusted models (OR 1.25, 95% CI 1.05–1.49). Covariates like medication overuse (OR 3.55, 95% CI 2.99–4.22), allodynia (OR 1.22, 95% CI 1.04–1.44) and depression (OR 1.49, 95% CI 1.21–1.84) were all significant predictors of increased headache days/month. Rhinitis was associated with the headache-related disability (MIDAS) category in the model adjusted for sociodemographic variables (OR 1.30, 95% CI 1.17–1.46), although significance was lost in the fully adjusted model.

We next examined the influence of rhinitis subtypes on headache frequency category (Table 3). Effects were most consistent for MR. After adjusting for sociodemographic variables, only the relative odds of being in a higher headache frequency category for the MR group were elevated (OR 1.45; 95% CI 1.24–1.70). Results were similar for the fully adjusted model (OR 1.28; 95% CI 1.05–1.57). Medication overuse, allodynia and depression were also significant predictors of headache frequency categories (Table 3). Unclassified rhinitis was also associated with headache frequency in both models (Figure 2).

We then determined the influence of rhinitis subtype on headache-related disability using MIDAS category as the outcome. MR was associated with MIDAS disability category after adjusting for sociodemographic variables (OR 1.60, 95% CI 1.41–1.81; Figure 2) and in the fully adjusted model (OR 1.31; 95% CI 1.03–1.67). Numerous covariates in the fully adjusted model were associated with disability including allodynia, comorbidities, medication overuse and preventive medications (Table 3).

**Discussion**

This study shows that two-thirds of individuals with migraine meet a case definition for rhinitis. Those with rhinitis of any type were approximately one-third more likely to be in higher headache frequency and disability categories in models adjusted for sociodemographic features. The association between rhinitis and headache frequency remained significant in fully adjusted models, but lost significance for headache-related disability after adjustment for these covariates. This could suggest that rhinitis is associated with increased vulnerability to attacks, but may have little effect on headache-related disability once an attack begins. Alternatively, the association between rhinitis and headache-related disability may be mediated or...
Table 1. Sociodemographic and clinical characteristics of study population.

<table>
<thead>
<tr>
<th>N</th>
<th>Non-rhinitis</th>
<th>Total rhinitis</th>
<th>AR</th>
<th>NAR</th>
<th>MR</th>
<th>UR</th>
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<tbody>
<tr>
<td></td>
<td>1940 M(SD)</td>
<td>3909 M(SD)</td>
<td>737 M(SD)</td>
<td>379 M(SD)</td>
<td>1869 M(SD)</td>
<td>924 M(SD)</td>
</tr>
<tr>
<td>Age (mean, SD) B (95% CI)</td>
<td>49.8 (12.5)</td>
<td>47.7 (12.2)</td>
<td>51.5 (12.4)</td>
<td>49.8 (12.3)</td>
<td>50.7 (12.5)</td>
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<tr>
<td>BMI (mean, SD) B (95% CI)</td>
<td>29.0 (7.7)</td>
<td>30.2 (8.2)</td>
<td>29.8 (8.0)</td>
<td>30.1 (8.6)</td>
<td>30.7 (8.3)</td>
<td>29.5 (7.9)</td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
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<td>n (%)</td>
</tr>
<tr>
<td>Female (Contrasts LR)</td>
<td>1509 (77.8%) Ref</td>
<td>3192 (81.7%)</td>
<td>558 (75.7%)</td>
<td>321 (84.7%)</td>
<td>1602 (85.7%)</td>
<td>711 (76.9%)</td>
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<tr>
<td>Caucasian</td>
<td>1738 (89.6%)</td>
<td>3447 (88.2%)</td>
<td>660 (98.6%)</td>
<td>337 (88.9%)</td>
<td>1640 (87.7%)</td>
<td>810 (87.7%)</td>
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<td>African American</td>
<td>103 (5.3%)</td>
<td>248 (6.3%)</td>
<td>32 (4.3%)</td>
<td>21 (5.5%)</td>
<td>160 (7.0%)</td>
<td>65 (7.0%)</td>
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<td>Other/unclassified</td>
<td>99 (5.1%) Ref</td>
<td>214 (5.5%)</td>
<td>45 (6.1%)</td>
<td>21 (5.5%)</td>
<td>99 (5.3%)</td>
<td>49 (5.3%)</td>
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<td>Income ≥ $30,000</td>
<td>1379 (71.1%) Ref</td>
<td>2765 (70.7%)</td>
<td>579 (78.6%)</td>
<td>1207 (76.7%)</td>
<td>1270 (68.0%)</td>
<td>636 (68.8%)</td>
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<tr>
<td>Current smoking</td>
<td>349 (18.3%) Ref</td>
<td>580 (15.1%)</td>
<td>122 (16.7%)</td>
<td>53 (14.1%)</td>
<td>233 (12.7%)</td>
<td>172 (18.9%)</td>
</tr>
<tr>
<td>Current use of migraine preventatives</td>
<td>195 (11.9%) Ref</td>
<td>409 (12.6%)</td>
<td>74 (11.3%)</td>
<td>42 (13.1%)</td>
<td>214 (14.1%)</td>
<td>79 (10.3%)</td>
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<td>Medication overuse (Contrasts LR)</td>
<td>445 (25.7%) Ref</td>
<td>1105 (31.1%)</td>
<td>188 (27.5%)</td>
<td>104 (29.9%)</td>
<td>583 (34.4%)</td>
<td>230 (27.8%)</td>
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<tr>
<td>Allodynia (Contrasts LR)</td>
<td>953 (50.2%) Ref</td>
<td>2254 (58.6%)</td>
<td>402 (54.8%)</td>
<td>208 (55.8%)</td>
<td>1221 (66.1%)</td>
<td>423 (47.3%)</td>
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<td>Comorbid conditions</td>
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<tr>
<td>Asthma (Contrasts LR)</td>
<td>142 (7.7%) Ref</td>
<td>903 (23.8%)</td>
<td>118 (16.5%)</td>
<td>64 (17.4%)</td>
<td>599 (32.8%)</td>
<td>122 (13.7%)</td>
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<td>Anxiety (Contrasts LR)</td>
<td>126 (6.6%) Ref</td>
<td>375 (31.1%)</td>
<td>238 (18.3%)</td>
<td>253 (18.4%)</td>
<td>587 (38.2%)</td>
<td>191 (14.8%)</td>
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<td>Depression (Contrasts LR)</td>
<td>344 (17.8%) Ref</td>
<td>824 (21.2%)</td>
<td>129 (17.6%)</td>
<td>70 (18.6%)</td>
<td>472 (25.4%)</td>
<td>153 (16.7%)</td>
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<td>Diabetes (Contrasts LR)</td>
<td>248 (12.8%) Ref</td>
<td>595 (15.2%)</td>
<td>99 (13.4%)</td>
<td>61 (16.1%)</td>
<td>298 (15.9%)</td>
<td>137 (14.8%)</td>
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<td>Hypertension (Contrasts LR)</td>
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<td>1501 (38.4%)</td>
<td>257 (34.9%)</td>
<td>144 (38.0%)</td>
<td>751 (40.2%)</td>
<td>349 (37.8%)</td>
</tr>
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(continued)
confounded by the association between rhinitis and comorbid medical/psychiatric disorders, medication overuse, allodynia and/or smoking.

Our findings are consistent with prior reports that chronic rhinitis and rhinosinusitis are associated with increased headache frequency. Aamodt and colleagues (13) reported that hay fever was associated with the frequency of migraine headaches. The relative odds of migraine given rhinitis were 1.5 for migraine less than 7 days per month, 1.9 for migraine 7–14 days per month and 2.6 for migraine 15 or more days per month. In addition, persons with chronic rhinosinusitis were nine times more likely to experience chronic headaches (i.e. ≥15 headache days per month) (30). We are not aware of prior data addressing the association between rhinitis and headache-related disability.

Of the rhinitis subtypes, the mixed rhinitis (MR) group demonstrated the strongest associations with headache frequency and disability categories. Persons with MR were 45% more likely to report higher headache frequency categories and 60% more likely to report higher headache-related disability categories than controls in models adjusted for sociodemographic variables. The ORs were attenuated but remained statistically significant in fully adjusted models. In addition, the percentages of patients with allodynia, comorbid medical and psychiatric conditions, and medication overuse were numerically higher in the MR group than in the other rhinitis groups.

Unclassified rhinitis (UR) was associated with migraine headache frequency but not with headache-related disability. The unclassified group includes persons with rhinitis that do not report the presence of allergic or non-allergic triggers. It is not evident why patients with UR would have an increased frequency of headache, whereas those with AR and NAR did not have an increased frequency of headache. Whereas those with AR and NAR did not have an increased frequency of headache, persons with MR would have an increased frequency of headache, whereas those with MR and NAR did not have an increased frequency of headache. The MR group includes persons with MR and NAR who do not report the presence of allergic or non-allergic triggers.

Table 1. Continued.

<table>
<thead>
<tr>
<th></th>
<th>Non-rhinitis</th>
<th>Total rhinitis</th>
<th>AR</th>
<th>NAR</th>
<th>MR</th>
<th>UR</th>
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<td>N</td>
<td>1940 (SD)</td>
<td>3909 (SD)</td>
<td>737 (SD)</td>
<td>379 (SD)</td>
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<td>Headache-related disability (MIDAS category)</td>
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<td>Little or no disability</td>
<td>1183 (62.8%)</td>
<td>2119 (55.6%)</td>
<td>418 (57.4%)</td>
<td>217 (59.5%)</td>
<td>907 (49.6%)</td>
<td>577 (64.8%)</td>
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<td>Mild disability</td>
<td>279 (14.8%)</td>
<td>667 (17.5%)</td>
<td>140 (19.2%)</td>
<td>60 (16.4%)</td>
<td>346 (18.9%)</td>
<td>121 (13.6%)</td>
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<td>Moderate disability</td>
<td>214 (11.4%)</td>
<td>503 (13.2%)</td>
<td>98 (13.5%)</td>
<td>42 (11.5%)</td>
<td>277 (15.1%)</td>
<td>86 (9.7%)</td>
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<td>Severe disability</td>
<td>209 (11.1%)</td>
<td>525 (13.8%)</td>
<td>72 (9.9%)</td>
<td>46 (12.6%)</td>
<td>300 (16.4%)</td>
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<tr>
<td>0–4</td>
<td>1548 (82.2%)</td>
<td>2959 (77.5%)</td>
<td>583 (79.8%)</td>
<td>288 (78.5%)</td>
<td>1,386 (75.8%)</td>
<td>702 (78.9%)</td>
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<td>5–9</td>
<td>186 (9.9%)</td>
<td>464 (12.2%)</td>
<td>89 (12.2%)</td>
<td>45 (12.3%)</td>
<td>231 (12.6%)</td>
<td>99 (11.1%)</td>
</tr>
<tr>
<td>10–14</td>
<td>72 (3.8%)</td>
<td>169 (4.4%)</td>
<td>26 (3.6%)</td>
<td>15 (4.1%)</td>
<td>90 (4.9%)</td>
<td>38 (4.3%)</td>
</tr>
<tr>
<td>≥15</td>
<td>77 (4.1%)</td>
<td>224 (5.9%)</td>
<td>33 (4.5%)</td>
<td>19 (5.2%)</td>
<td>121 (6.6%)</td>
<td>51 (5.7%)</td>
</tr>
</tbody>
</table>

LR: logistic regression.
Linear, logistic and ordered regression was used to test specific contrasts against controls; p < 0.5 or OR with 95% CI that did not include 1.0 were considered significant. Models were unadjusted.

See unadjusted contrast on Tables 3 and 5.

Comorbid depression and allodynia

Past studies have demonstrated that comorbid psychiatric and headache conditions are independent in patients with chronic rhinitis and rhinosinusitis. Our findings are consistent with prior reports that chronic rhinitis and rhinosinusitis are associated with increased headache frequency. Aamodt and colleagues (13) reported that hay fever was associated with the frequency of migraine headaches. The relative odds of migraine given rhinitis were 1.5 for migraine less than 7 days per month, 1.9 for migraine 7–14 days per month and 2.6 for migraine 15 or more days per month. In addition, persons with chronic rhinosinusitis were nine times more likely to experience chronic headaches (i.e. ≥15 headache days per month) (30). We are not aware of prior data addressing the association between rhinitis and headache-related disability.

Of the rhinitis subtypes, the mixed rhinitis (MR) group demonstrated the strongest associations with headache frequency and disability categories. Persons with MR were 45% more likely to report higher headache frequency categories and 60% more likely to report higher headache-related disability categories than controls in models adjusted for sociodemographic variables. The ORs were attenuated but remained statistically significant in fully adjusted models. In addition, the percentages of patients with allodynia, comorbid medical and psychiatric conditions, and medication overuse were numerically higher in the MR group than in the other rhinitis groups.

Unclassified rhinitis (UR) was associated with migraine headache frequency but not with headache-related disability. The unclassified group includes persons with rhinitis that do not report the presence of allergic or non-allergic triggers. It is not evident why patients with UR would have an increased frequency of headache, whereas those with AR and NAR did not have an increased likelihood of this outcome measure. However, it is possible that people with AR and NAR did not have an increased frequency of headache, whereas those with MR would have an increased frequency of headache, whereas those with MR and NAR did not have an increased frequency of headache. The MR group includes persons with MR and NAR who do not report the presence of allergic or non-allergic triggers. The MR group includes persons with MR and NAR who do not report the presence of allergic or non-allergic triggers. The MR group includes persons with MR and NAR who do not report the presence of allergic or non-allergic triggers.
We found that depression was associated with a 49% increase in the odds of being in a higher headache frequency category and a 93% increase in the odds of being in a higher headache-related disability category. This is consistent with the results of a recent longitudinal analysis from the AMPP Study, which reported that depression among persons with EM at baseline was associated with significantly increased risk for the development of chronic migraine 1–2 years later (33).

The presence of cutaneous allodynia (CA) was associated with an increased likelihood of being in higher frequency and headache-related disability categories in multivariate models. This is also consistent with past studies demonstrating an increased headache frequency in migraineurs with cutaneous allodynia (28,35). Patients with chronic rhinitis were 1.2–1.94 times more likely to experience CA than controls with the largest odds ratios in the MR group. The inclusion of allodynia in the fully adjusted models did not significantly attenuate the ORs for headache frequency in the rhinitis groups, which might suggest that the increased headache frequency associated with chronic rhinitis is not solely explained by the presence of allodynic symptoms.

### Potential mechanisms

In any association study, selection bias or unmeasured confounding variables can distort measured relationships. Selection bias is unlikely because preferential participation by people with frequent or disabling migraine and rhinitis would be required to generate spurious results. Although we cannot exclude the possibility of unmeasured or residual confounding variables, we endeavored to measure and adjust for potential confounders.

Because this is a cross-sectional study, our findings are consistent with several mechanistic possibilities. First, unidirectional causal relationships are possible. That is, rhinitis may result in increased migraine frequency and disability, or frequent and disabling migraine could contribute to the development of...
rhinitis. Second, the disorders may have shared underlying genetic or environmental risk factors. Finally, the disorders may be linked by shared biological mechanisms. These are not mutually exclusive but complementary possibilities.

Under a unidirectional causal model, the biology of rhinitis may contribute to the development of more frequent migraine attacks. Allergic triggers could result in mast cell degranulation and release of inflammatory mediators in the nares and perhaps the dura matter. These processes might sensitize peripheral or central trigeminal nociceptors or central sensory pathways leading to more frequent or severe attacks. In support of this hypothesis, a recent study in atopic migraineurs found that immunotherapy (allergy shots) was associated with a 52% reduction in the frequency of migraine and a 45% reduction in the number of days with headache-related disability (36). Non-allergic triggers might directly activate trigeminal afferents by binding to Transient Receptor Potential (TRP) receptors located on these neurons. Perhaps persons with mixed rhinitis have more frequent and disabling migraine as a result of their susceptibility to both allergic and non-allergic triggers. Alternatively, frequent attacks of migraine could up-regulate cranial parasympathetic neurons leading to more frequent rhinitis symptoms, as discussed below. In support of this theory, symptoms which reflect parasympathetic activation commonly occur during attacks of migraine (37). In fact, we cannot exclude the possibility that these cranial autonomic symptoms might be confused with rhinitis symptoms and lead to an erroneous diagnosis of rhinitis in persons with migraine. It is also possible that each disorder exacerbates the other through bidirectional influences.

The second possibility, shared environmental or genetic factors, is attractive. For example, both migraine

### Table 3. Association of rhinitis subtypes with headache frequency and MIDAS disability categories among persons with migraine: Results from ordinal logistic regression models adjusted for sociodemographics, comorbid conditions and headache features.

<table>
<thead>
<tr>
<th>Covariates used in models</th>
<th>Headache frequency category[a]</th>
<th>MIDAS disability category[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for sociodemographics</td>
<td>Adjusted for all covariates</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)c</td>
<td>OR (95% CI)c</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>1.18 (0.95–1.46)</td>
<td>1.14 (0.89–1.47)</td>
</tr>
<tr>
<td>Non-allergic rhinitis</td>
<td>1.26 (0.96–1.66)</td>
<td>1.20 (0.86–1.67)</td>
</tr>
<tr>
<td>Mixed rhinitis</td>
<td>1.45 (1.24–1.70)</td>
<td>1.28 (1.05–1.57)</td>
</tr>
<tr>
<td>Unclassified rhinitis</td>
<td>1.25 (1.02–1.52)</td>
<td>1.31 (1.03–1.67)</td>
</tr>
<tr>
<td>Controls[d]</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Age (10-year intervals)[e]</td>
<td>0.98 (0.93–1.03)</td>
<td>0.93 (0.87–1.00)</td>
</tr>
<tr>
<td>Household income (continuous)</td>
<td>0.91 (0.86–0.96)</td>
<td>0.98 (0.91–1.05)</td>
</tr>
<tr>
<td>Female sex (yes)</td>
<td>1.18 (1.00–1.40)</td>
<td>1.11 (0.90–1.36)</td>
</tr>
<tr>
<td>BMI (5 point intervals)[f]</td>
<td>0.96 (0.91–1.01)</td>
<td></td>
</tr>
<tr>
<td>Migraine preventives (yes)</td>
<td>1.16 (0.93–1.44)</td>
<td></td>
</tr>
<tr>
<td>Medication overuse (yes)</td>
<td>3.56 (3.00–4.23)</td>
<td></td>
</tr>
<tr>
<td>Allodynia (yes)</td>
<td>1.22 (1.04–1.44)</td>
<td></td>
</tr>
<tr>
<td>Asthma (yes)</td>
<td>1.17 (0.95–1.43)</td>
<td></td>
</tr>
<tr>
<td>Anxiety (yes)</td>
<td>1.24 (0.92–1.66)</td>
<td></td>
</tr>
<tr>
<td>Depression (yes)</td>
<td>1.49 (1.21–1.84)</td>
<td></td>
</tr>
<tr>
<td>Current smoking (yes)</td>
<td>1.01 (0.81–1.25)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (yes)</td>
<td>0.88 (0.69–1.13)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (yes)</td>
<td>0.90 (0.74–1.08)</td>
<td></td>
</tr>
</tbody>
</table>

[a] Headache frequency was divided into categories of 0–4, 5–9, 10–14, and ≥15 days of headache per month.
[b] Headache-related disability was assessed with the Migraine Disability Assessment Questionnaire (MIDAS). Responses were summed and coded into one of four grades of headache-related disability: Grade I, little or no disability (0–5); Grade II, mild disability (6–10); Grade III, moderate disability (11–20); Grade IV: severe disability (≥21).
[c] Multivariate models were adjusted for the covariates listed in the table.
[d] Ref = reference group.
[e] The odds ratio depicts the effect of age on headache frequency and headache-related disability for each 10-year increase in age.
[f] The odds ratio depicts the effect of body mass index (BMI) on headache frequency and headache-related disability for each five point change in BMI.
and rhinitis have been associated with polymorphisms in the toll-like receptor 4 (TLR-4); certain variants may result in higher IgE and cytokine levels in persons with AR, potentially contributing to migraine exacerbation (38,39). Agonists of the TLR-4 activate microglial cells and produce allodynia; their blockade with naloxone reduces mechanical allodynia in experimental pain models in rats (40). Polymorphisms of vanilloid receptor genes (e.g. TRPV1 and TRPV3) are associated with migraine and with vulnerability to environmental irritants that trigger non-allergic rhinitis (41). In a recent clinical trial, the TRPV1 agonist, intranasal capsaicin, improved rhinitis symptoms as well as headache in patients with non-allergic rhinitis subtypes (42). Perhaps genetic variations in vanilloid or toll-like 4 receptors predispose to both rhinitis and severe migraine and contribute to the association we report herein.

Genetic and environmental risk factors could operate through biological mechanisms that predispose to both disorders. Autonomic dysfunction is one such possible biological mechanism as there is evidence for parasympathetic hyperfunction (37,43–45) and sympathetic hypofunction (46–48) in patients with rhinitis as well as migraine. Persons with migraine and chronic rhinitis may represent a group with “parasympathetic predominance” caused by either hyperfunction of the parasympathetic nervous system or hypofunction of the sympathetic nervous system, which may increase the frequency and disability of migraine attacks.

**Strengths and limitations**

Strengths of this study include the large sample size, the population-based sample, and the use of validated instruments from the AMP4 Study including the headache diagnosis module which is based on ICHD-2 criteria, MIDAS to measure headache-related disability and the PHQ-9 and PRIME-MD to measure depression and anxiety. Results of this study should have broad generalization as the sociodemographic features of the study population approximate those typically found in migraineurs within the USA. Second, we used a more stringent definition of rhinitis that is typically used in rhinitis studies, which included the presence of nasal allergies, seasonal allergies or hay fever as well as two or more rhinitis symptoms. Most past rhinitis studies used “hay fever” as a definition of rhinitis and there was never any corroboration of rhinitis symptoms. Third, we controlled for comorbid medical and psychiatric disorders as well as allodynia, which could confound the association between rhinitis and migraine days or disability. After controlling for these variables, the ORs for rhinitis group were attenuated, but remained statistically significant in most of the fully adjusted models, which is a testament to the consistency of these findings.

The study has a number of limitations. First, all data are self-reported. We do not have allergy testing or medical records to confirm subtypes; therefore, some of our study participants with rhinitis subtypes could have been misclassified. However, the use of self-report of symptoms is a common practice in population-based, epidemiological studies and our instruments asked questions that resemble standard diagnostic criteria. Second, the frequency and disability of headache were determined by patient self-report obtained from questionnaires and not verified by daily diary data. However, we think that it is unlikely that this significantly influenced our data as recent studies have shown that self-report of headache frequency and disability are highly correlated with results obtained from daily diaries (49,50). Third, the questionnaire was completed in June or July of 2008 and the MIDAS questionnaire queried headache frequency and disability during the preceding 3 months. Therefore, our headache outcome measures were sampled during the springtime. If our outcome measures increased during time periods of fall allergens (e.g. mold) then this could have been missed with our sampling period. This could have decreased the ORs for our outcome measures in persons with MR and AR. Fourth, the statistical analyses were not corrected for multiple comparisons and...
therefore these results should be considered exploratory until confirmed in future studies. Fifth, AMPP participants were identified as experiencing “severe headaches” prior to assigning a diagnosis of migraine and thus the sample may not be completely representative of those with migraine in the general population. Sixth, we cannot rule out the possibility of “non-response” bias as 39% of the study population did not return the questionnaire. This type of bias occurs when the results of the questionnaire differ between those that did and did not return the questionnaire. We believe that this type of bias is less likely to have occurred given that the ORs reported in this manuscript are of a similar direction and magnitude to those obtained in past studies (13,51). Seventh, there was a modest amount of missing data particularly within the analyses involving all covariates and therefore these analyses should be considered “hypothesis generating” rather than conclusive.

**Conclusions**

Chronic rhinitis is modestly associated with an increased frequency and disability of headache in migraineurs sampled from the general population. Among chronic rhinitis subtypes, the MR subtype was most consistently related to these outcome measures suggesting that the presence of allergic and non-allergic rhinitis symptoms identifies a subgroup of patients with a more severe clinical phenotype of migraine headache. The mechanisms to explain this association are unknown, but could relate to autonomic dysfunction, mast cell degranulation or shared genetic factors between these two disorders. The authors recommend caution in interpreting these results of this study because of its limitations, but nonetheless these findings are intriguing and require confirmation in future cross-sectional and longitudinal studies.

**Clinical implications**

- Chronic rhinitis is common in people with migraine, occurring in 67% of a general US population sample of individuals with migraine.
- The frequency and headache-related disability of migraine are higher in persons with rhinitis overall and especially in those with a mixed rhinitis subtype.
- The mechanisms and the directionality of these associations are unknown. Because mixed rhinitis is associated with more robust changes in frequency than headache-related disability, we suggest that rhinitis may lower the threshold for migraine initiation, perhaps as a result of inflammation, mast cell degranulation or autonomic dysfunction. Shared biological predisposition is possible.

**Supplementary material (online)**

Rhinitis Questionnaire (9,19).

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**Conflict of interest**

None declared.

**References**


