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RESEARCH SUBMISSION

Rates and risk factors for migraine progression using multiple definitions of progression: Results of the longitudinal OVERCOME (US) study

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Abstract

Objective: To estimate rates of migraine progression and assess predictors of progression in a large, longitudinal cohort study using the traditional definition and two alternative definitions of migraine progression.

Background: Traditionally, migraine progression is defined as moving from episodic migraine (EM) with ≤ 14 monthly headache days (MHD) to chronic migraine (CM) with ≥ 15 MHDs of which 8 are attributable to migraine. This definition does not take into account changes in the full range of potential headache days, disability, or impact on function.

Methods: The Observational Survey of the Epidemiology, Treatment, and Care of Migraine (OVERCOME) study identified, characterized, and followed a representative sample of adults with migraine in the United States. Migraine was defined based on the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria. We estimated rates of migraine progression at 1 year of follow-up using three definitions: (1) traditional EM-to-CM transition, (2) increase of ≥ 5 MHDs (MHD progression), and (3) increase of ≥ 5 points on the Migraine Disability Assessment (MIDAS) scale (MIDAS progression). The analysis identified sociodemographic, clinical, and migraine-related characteristics associated with each definition of progression from a set of 67 candidates and then determined the association with progression for each candidate predictor and each definition of progression.

Abbreviations: AUC, area under the curve; CI, confidence interval; CM, chronic migraine; EM, episodic migraine; ICHD-3, International Classification of Headache Disorders, 3rd edition; LASSO, least absolute shrinkage and selection operator; MHD, monthly headache day; MIBS-4, Migraine Interictal Burden Scale-4; MIDAS, Migraine Disability Assessment; MSQ, Migraine-Specific Quality of Life Questionnaire v2.1; MSQ-RFR, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Restrictive; MSSS, Migraine Symptom Severity Score; OR, odds ratio; OTC, over the counter; OVERCOME, Observational Survey of the Epidemiology, Treatment and Care of Migraine; RF, random forest; SMD, standardized mean difference; VIF, variance inflation factor.

Results: A total of 11,634 participants met ICHD-3 criteria for migraine at baseline and completed the 1-year follow-up survey. The average age was 48.2 years, and average years living with migraine was 22.8 years. The sample was 75.6% female (8793/11,634), 84.4% White (9814/11,634), 6.5% Black (757/11,634), and 7.6% Hispanic (889/11,634). The majority (89.2%, 10,374/11,634) had EM at baseline, and among these, 4.7% progressed to CM over 1 year of follow-up. Rates of progression at 1 year were higher using other definitions of progression, with 9.6% (1087/11,329) reporting an increase in ≥ 5 MHDs and 21.7% (2519/11,630) reporting an increase of ≥ 5 MIDAS points. Across all three definitions of progression, ever taking preventive medications for migraine placed people at lower odds of progressing (odds ratio [95% confidence interval]: EM-to-CM transition, 0.7 [0.57–0.85]; MHD progression, 0.9 [0.75–1.00]; MIDAS progression, 0.8 [0.73–0.91]), while the presence of depression placed people at higher odds of progressing (odds ratio [95% confidence interval]: EM-to-CM transition, 1.3 [1.05–1.69]; MHD progression, 1.4 [1.21–1.67]; MIDAS progression, 1.2 [1.04–1.34]).

Conclusion: This work expands the concept of migraine progression, exploring two alternative definitions that modify the potential range of MHD changes and take disability into account. This analysis identified never having used preventive medications for migraine and presence of depression as risk factors across all three definitions of progression. This work may more accurately identify persons with progression and at risk of migraine progression, setting the stage for trials of preventive intervention and ultimately more effective practice.

Plain Language Summary

In this study, we used machine learning to examine rates and risk factors for migraine progression using the traditional definition: new onset of chronic migraine with ≥ 15 monthly headache days on average, as well as two novel additional definitions: (1) increase of ≥ 5 monthly headache days and (2) increase in Migraine Disability Assessment (MIDAS) scale of ≥ 5 points. Never having used preventive medication and presence of depression were identified as risk factors for migraine progression across all three definitions of migraine progression. These novel additional definitions of migraine progression may provide new clinical trial endpoints, inform inclusion criteria for clinical trials, and offer insights into prognosis and clinical care.

KEYWORDS
chronification, disability, migraine, progression, risk factors, transformation

BACKGROUND

Migraine is a progressive neurological disease with high prevalence and burden worldwide.[1–6] Migraine progression has traditionally been defined as crossing the threshold from episodic migraine (EM; ≤ 14 monthly headache days [MHDs]) to chronic migraine (CM; ≥ 15 MHDs of which at least 8 are linked to migraine).[2,4,7] The MHD threshold for CM is defined by the International Classification of Headache Disorders, 3rd edition (ICHD-3).[8] Many risk factors have previously been identified, although it is likely that the list of current known risk factors is not exhaustive. Risk factors identified to date for migraine progression can be non-modifiable, such as age, sex, race, and socioeconomic and educational status,[9] or potentially modifiable such as MHD frequency, poor acute treatment optimization, depression, anxiety, and sleep disorders.[2–4,10] Modifiable risk factors may provide valuable targets for future intervention studies.

Migraine progression is recognized as a clinically important phenomenon;[10–12] 2.5% to 14% of people with EM transition to CM from one year to the next.[2,13,14] Preventing progression is a major goal of migraine care;[15] however, the current definition of progression is

restrictive as it may not capture all those who progress and thus imposes a barrier to successful intervention studies and hinders identification of patients in need of appropriate treatment to prevent progression. A more inclusive set of definitions could enhance the field's ability to develop robust studies to prevent progression and better allow clinicians to accurately predict prognosis.

Although the transition from EM to CM has remained the sole indicator of migraine progression since CM or transformed migraine was defined in the 1990s,[16–19] it has been criticized for several reasons. First, in population samples the transition occurs at a low rate, reducing power to identify people at risk and to test treatments intended to prevent progression. Second, the definition does not require consistent levels of change. Neither the transition from 1 to 14 MHDs nor the transition from 15 to 30 MHDs is considered progression despite the significant increase in MHDs and accompanying negative personal, professional, and quality-of-life consequences. This is particularly important given that having EM with a cyclic phenotype has previously been associated with migraine progression.[20,21] Finally, basing EM-to-CM transition solely on MHD frequency does not directly consider the level of disability and impact on function, which are often a focus and priority for patients and health-care professionals as a measure of change in disease severity.[22] Herein, we consider two additional definitions of progression that address some of these issues. These definitions include an increase of ≥ 5 MHDs and/or an increase of ≥ 5 points on the Migraine Disability Assessment (MIDAS) scale. Although we recognize that there are many other potential alternative definitions, the definitions studied herein were selected in part because they address the limitations of crossing the 15-day EM-to-CM transition. Important work on cyclical phenotypes could not be addressed here due to insufficient follow-up.[21]

The goals of this study were to: (1) estimate and compare the rates of migraine progression from one year to the next using three different definitions of progression, (2) identify and compare predictors of progression using the three stated definitions, and (3) consider the implications of these findings for informing future studies designed to test interventions to prevent migraine progression. We hypothesized that the novel definitions we propose would identify people who do not meet the EM-to-CM definition, thus resulting in higher rates of progression; however, we hold that the risk factors identified by all three definitions would be similar and consistent with existing literature. These analyses may inform the design of future studies and suggest strategies for reducing progression in high-risk individuals.

METHODS

Ethics approval and consent to participate

Individuals who were interested in participating in the survey voluntarily provided electronic informed consent. The study was approved by the Sterling Institutional Review Board (IRB ID #6425-001).

Study design

The Observational survey of the Epidemiology, Treatment, and Care of Migraine (OVERCOME United States [US]) study provides an ideal setting to explore rates and predictors of progression using various definitions. In a 1-year longitudinal sample of 11,634 people with migraine, we examined 67 sociodemographic, clinical, and migraine-related characteristic variables using supervised machine learning models to identify characteristics associated with progression using the traditional definition (EM-to-CM transition) and two novel additional definitions of progression (increase of ≥ 5 MHDs and/or increase of ≥ 5 points on MIDAS). OVERCOME (US), a prospective, multicohort, longitudinal, web-based survey, annually (2018–2020) recruited a demographically representative (by geographic region, age, race, sex, and race nested within sex) sample of adults from US consumer panels using quota sampling. Details on study design and recruitment have been published previously.[23] Eligibility requirements were ≥ 18 years of age, US resident, online survey panel member, ability to read/write English, and internet access. Participants who passed demographic screening criteria and indicated having had ≥ 1 headache in the previous 12 months were invited to complete a validated Migraine Diagnostic Module,[13] based on modified ICHD-3 criteria. Individuals meeting criteria for migraine then completed the full OVERCOME questionnaire ($n = 59{,}001$), which included questions related to the impact, consultation, and treatment of migraine. Baseline survey participants were also invited to complete follow-up surveys at 6, 12, 18, and 24 months. The current analyses focus on those who completed baseline and 1-year (i.e., 12-month) follow-up surveys ($n = 11{,}634$).

Variables and measures of interest

Sociodemographic, clinical, and migraine-related characteristics included in the current analysis are outlined in Table S1 in supporting information. Sociodemographic characteristics included age, sex at birth (response options were "male" or "female"; information on gender was not collected), race, ethnicity, education, employment status, health insurance status, rural–urban commuting area, region of residence, annual household income, marital status, number of people in household, and number of children under 18 years of age living in household. Clinical features included presence of self-reported medically diagnosed comorbidities (asthma, allergies, sleep apnea, panic disorder, digestive comorbidity, joint or pain comorbidity, cardiovascular comorbidity, comorbidity that contraindicates triptan use, Framingham Risk Score), depression and/or anxiety assessed via the 4-item Patient Health Questionnaire, marijuana/tobacco use, and height/weight to calculate body mass index. Migraine-associated characteristics included years with migraine, MHD frequency, average headache pain intensity, Migraine Symptom Severity Score (MSSS),[24,25] ictal cutaneous allodynia (assessed via the Allodynia Symptom Checklist-12),[26] migraine-specific quality of life (assessed via the Migraine-Specific Quality of Life Questionnaire v2.1 [MSQ]),[27–30] migraine interictal burden (assessed via the Migraine Interictal Burden Scale-4 [MIBS-4]),[31–33]

migraine-related stigma (assessed via the Migraine-Related Stigma Questionnaire),[34] migraine diagnosis class, interference of migraine symptoms with routine activities, and medication use. Self-reported history of a medical diagnosis of headache was determined by asking participants to report any diagnosis they had received from a health-care professional in the following categories: migraine only, other headaches only, or migraine and other headaches. The medication variables assessed use of acute and preventive medications for migraine. Recommended acute medications for migraine were based on the American Headache Society Consensus statement[35] and included triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan-containing medications, zolmitriptan-containing medications), non-steroidal anti-inflammatory drugs (celecoxib, diclofenac, flurbiprofen, ibuprofen prescription strength, indomethacin, ketoprofen, ketorolac, naproxen), ergotamine derivatives (dihydroergotamine-containing medications, ergotamine, cafergot), gepants (rimegepant, ubrogepant), and lasmiditan. "Start using recommended acute medications" was defined as not taking them at baseline but taking them at the 1-year follow-up. "Still using recommended acute medications" was defined as taking them at baseline and at the 1-year follow-up. "Stop taking recommended acute medications" was defined as taking them at baseline, but not taking them at the 1-year follow-up. Preventive medications included antidepressants (amitriptyline, desvenlafaxine, doxepin, duloxetine, escitalopram oxalate, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, venlafaxine), antiseizure medications (divalproex, gabapentin, pregabalin, topiramate, valproic acid, zonisamide), cardiovascular medications (atenolol, candesartan, lisinopril, metoprolol, nadolol, nifedipine, propranolol, timolol, verapamil), calcitonin gene–related peptide monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab), gepants (rimegepant for prevention, atogepant), and neurotoxins (abotulinumtoxinA, onabotulinumtoxinA). Acute over-the-counter (OTC) medications included acetaminophen, aspirin, ibuprofen, naproxen sodium, and combination migraine or headache formula medications. Overuse was defined as taking ≥ 10 days/month (for prescription medications and OTC combination migraine or headache formulations) or ≥ 15 days/month (for simple analgesics such as acetaminophen, aspirin, ibuprofen, or naproxen sodium).

MIDAS[36,37]

The 5-item MIDAS scale quantifies the number of days an individual missed/had reduced productivity at work/home/social events over the preceding 3 months. Sum core categories were: 0–5 = little/none; 6–10 = mild; 11–20 = moderate; ≥ 21 = severe migraine-related disability.

Definitions of migraine progression

The definitions used were: (1) transition from EM (≤ 14 MHDs) at baseline to CM (≥ 15 MHDs) at 1 year among those with ≤ 14 MHDs at baseline ("EM-to-CM transition"); (2) increase of ≥ 5 MHDs from baseline to 1-year follow-up among those with ≤ 25 MHDs at baseline ("MHD progression"); and (3) increase of ≥ 5 points on MIDAS score from baseline to 1-year follow-up ("MIDAS progression") among those with a MIDAS score of ≤ 265 at baseline. The rationale for MHD progression was supported by recent work characterizing smaller groups of MHD frequencies, often using group sizes that span approximately 5 MHDs, which showed that disability, comorbidity, and life impact change dramatically as people with migraine progress to the next higher category.[38,39] Further, the recent American Headache Society consensus statement on migraine[15] recommends considering preventive medication for people with ≥ 5 MHDs and no disability. Last, several US Food and Drug Administration–approved preventive treatments for migraine report a change in ~5 MHDs over the trial period.[40–43] The rationale for MIDAS progression was supported by previous research showing this to be a clinically meaningful change in people with at least high-frequency EM.[44]

Statistical analysis

Sociodemographic, clinical, and migraine-related characteristics were summarized with means (± standard deviation) for continuous variables, with percentages for dichotomous variables, or with proportions in ordinal categorical variables. All included variables are listed in Table S1. Standardized mean differences (SMDs) were used to compare characteristics between groups: < 0.2 = no difference, 0.2–0.49 = small difference, 0.5–0.79 = moderate difference, and > 0.8 = large difference.

Supervised machine learning was used for variable selection by assessing the degree of association for 67 sociodemographic, migraine-related, and clinical variables with migraine progression according to each of the above definitions, followed by quantification of the level of association for each of the selected variables. Two complementary machine learning methods were used: first, a random forest (RF) consisting of 1000 trees and, second, a main effects linear model under a least absolute shrinkage and selection operator (LASSO) algorithm.[45] Both methods can be useful tools for variable selection in large population-based samples.[46,47] RFs with bootstrap aggregation (bagging) generalize single tree prediction ability and provide variable importance measures (using the RF algorithm in SAS) used to rank variables in order of predictive importance. This method was chosen for its ability to efficiently handle large data sets with highly complex and nonlinear relationships. All variables that demonstrated a substantial impact on the model's predictive accuracy, as indicated by the greatest out-of-bag Gini values out of the ranked set for all variables, were evaluated further. The LASSO algorithm conducts variable selection by shrinking coefficients for nonpredictive variables to zero so that the terms that are left have the most important predictive value. LASSO was chosen because it has a simpler structure based on a linear model and can handle multicollinearity; LASSO is also commonly used for variable selection. The variables identified by RF and/or LASSO were then used in a logistic regression for each definition of migraine

progression (EM-to-CM transition, MHD progression, MIDAS progression) to evaluate the odds ratio (OR) for each variable in the regression adjusting for the other predictors. The logistic model for computing ORs included all the predicting factors; hence, all ORs are adjusted. All continuous variables were standardized for the logistic regression model. ORs are presented with 95% confidence intervals (CIs) and were considered statistically significant at the 5% level of significance if the 95% CI for the OR did not include 1 using a two-tailed hypothesis test. Variance inflation factors (VIFs) were calculated to understand the degree of multicollinearity between the variables in the logistic regression models. To assess model accuracy, we used a test sample of 40% of the data to determine area under the curve (AUC) values of the RF model. For LASSO, the penalty parameter lambda was calculated using AUC. All analyses used SAS Enterprise Guide version 8.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Among the participants in OVERCOME (US) who met ICHD-3 criteria for migraine at baseline, 11,634 completed the 1-year follow-up survey and were included in this analysis (Figure S1 in supporting information). With an average age of 48.2 years, this population had migraine for an average of 22.8 years. The majority were female (n = 8793/11,634, 75.6%), 84.4% (n = 9814/11,634) identified as White, 6.5% (n = 757/11,634) identified as Black, 7.6% (n = 889/11,634) identified as Hispanic, and 90.1% (n = 10,482/11,634) identified as non-Hispanic (Table 1). Sociodemographic characteristics were similar among those groups who progressed according to each definition compared to those who did not. As would be expected, a larger proportion of respondents who progressed had more MHDs than those who did not progress (SMD > 0.2). Furthermore, respondents who progressed according to the EM-to-CM transition and MHD progression definitions were more likely to have higher MIBS-4 and MIDAS scores and lower quality of life (SMD > 0.2). Some differences in comorbidities and medication use were also observed (Table 1).

Rates of migraine progression

Among the 11,634 participants who completed the baseline and 1-year follow-up OVERCOME surveys, 89.2% (n = 10,374/11,634) had EM at baseline and were eligible for assessing the rate of EM-to-CM transition; of these participants, 4.7% (n = 486/10,374) met this definition of progression according to the current ICHD-3 definition of CM (Figure 1A). For MHD progression, those with ≤ 25 MHDs at baseline (n = 11,329) were eligible as those with ≥ 26 MHDs could not have an increase of 5 MHDs. Using the MHD progression definition, 9.6% (n = 1087/11,329) progressed at the 1-year follow-up period (Figure 1A). For MIDAS progression, those with MIDAS scores ≤ 265 (n = 11,630) were eligible, as those with ≥ 266 could not have an increase of 5 MIDAS points. Using the MIDAS progression definition, 21.7% (n = 2519/11,630) progressed (Figure 1A). There was overlap with some participants meeting more than one definition of progression (Figure 1B). Of the 486 individuals who underwent the EM-to-CM transition, 462 (95.1%) met at least one of the alternative definitions. Of the 1087 individuals who met the increase of ≥ 5 MHDs definition, 751 (69.1%) met at least one of the alternative definitions. Of the 2519 individuals who met the ≥ 5 MIDAS point increase definition, 567 (22.5%) met at least one other definition of progression.

Of note, rates of progression using each of the three progression definitions changed in relation to specific variables in a stepwise fashion and were lower with increases in annual household income, and higher with increases in average MHD frequency, interictal burden (MIBS-4), disability (MIDAS), body mass index, and types and numbers of comorbid conditions (Table 2).

Factors associated with transition from EM at baseline to CM at 1-year follow-up

We defined 67 sociodemographic, clinical, and migraine-related variables a priori as potential predictors of progression. Supervised machine learning models (RF and LASSO) were utilized to determine which factors were most associated with transition from EM to CM (Table 3). Logistic regression models including the factors identified by RF and/or LASSO assessed the predictive validity of risk factors using each definition of progression. The VIFs among the variables in this model were < 4, indicating that a high degree of multicollinearity was not present. Figures 2 and 3 show that people with EM at baseline who overused acute OTC medication had higher odds of transitioning to CM at 1 year of follow-up (OR = 3.00; 95% CI = 2.36–3.80), as well as those with higher MIDAS at baseline (severe vs. little or none: OR = 2.08, 95% CI = 1.56–2.76; moderate vs. little or none: OR = 1.45, 95% CI = 1.09–1.94) and those with depression at baseline (OR = 1.33, 95% CI = 1.05–1.69). The analysis also showed that those who had ever taken a preventive medication for migraine were at lower odds of progressing to CM (OR = 0.69, 95% CI = 0.57–0.85). For both the RF and LASSO models, the AUC was 0.7, suggesting good model performance.

Factors associated with increase of ≥ 5 MHDs at 1-year follow-up

When we evaluated factors associated with the MHD progression definition (increase of ≥ 5 MHDs at the 1-year follow-up), the identified factors were similar to those associated with EM-to-CM transition (Table 4; Figure 2). Specifically, those overusing acute OTC medications (OR = 1.55; 95% CI = 1.30–1.85), those with higher MIDAS (severe vs. little or none: OR = 1.48, 95% CI = 1.21–1.81; moderate vs. little or none: OR = 1.53, 95% CI = 1.26–1.87) at baseline, and those with depression (OR = 1.42, 95% CI = 1.21–1.67) were at higher risk of progressing to ≥ 5 MHDs at 1 year (Figure 4). In addition, the analysis demonstrated that consulting in primary care resulted in higher odds

TABLE 1 Demographics at baseline among those who experienced migraine disease progression based on increase in MHDs and/or MIDAS score at 1-year follow-up.

	EM-to-CM transition		MHD progression		MIDAS progression		Total
Variable	**Yes (*n* = 486)**	**No (*n* = 9888)**	**Yes (*n* = 1087)**	**No (*n* = 10,242)**	**Yes (*n* = 2519)**	**No (*n* = 9111)**	***N* = 11,634**
Sociodemographic characteristics							
Age, mean (SD)	48.8 (13.3)	48.1 (14.2)	47.8 (13.6)	48.2 (14.2)	46.4 (13.5)	48.7 (14.2)	48.2 (14.1)
Years with migraine, mean (SD)	23.5 (16.8)	22.7 (16.2)	22.6 (16.1)	22.8 (16.2)	21.9 (15.3)	23.1 (16.4)	22.8 (16.2)
Sex assigned at birth, *n* (%)							
Female	390 (80.2)	7383 (74.7)	840 (77.3)	7714 (75.3)	1982 (78.7)	6807 (74.7)	8793 (75.6)
Male	96 (19.8)	2505 (25.3)	247 (22.7)	2528 (24.7)	537 (21.3)	2304 (25.3)	2841 (24.4)
Urban/rural commuting area, *n* (%)							
Urban	390 (80.2)	8185 (82.8)	873 (80.3)	8469 (82.7)	2047 (81.3)	7523 (82.6)	9574 (82.3)
Race[a], *n* (%)							
White or Caucasian	429 (88.3)	8267 (83.6)	922 (84.8)	8620 (84.2)	2143 (85.1)	7668 (84.2)	9814 (84.4)
Black or African American	19 (3.9)	678 (6.9)	54 (5.0)	690 (6.7)	158 (6.3)	599 (6.6)	757 (6.5)
Asian	9 (1.9)	329 (3.3)	27 (2.5)	318 (3.1)	62 (2.5)	283 (3.1)	345 (3.0)
Other	28 (5.8)	570 (5.8)	78 (7.2)	572 (5.6)	142 (5.6)	527 (5.8)	670 (5.8)
Prefer not to answer	1 (0.2)	44 (0.4)	6 (0.6)	42 (0.4)	14 (0.6)	34 (0.4)	48 (0.4)
Ethnicity, *n* (%)							
Hispanic, Latino/a, or Spanish	37 (7.6)	778 (7.9)	80 (7.4)	794 (7.8)	184 (7.3)	705 (7.7)	889 (7.6)
Not Hispanic, Latino/a, or Spanish	435 (89.5)	8895 (90.0)	987 (90.8)	9215 (90.0)	2275 (90.3)	8203 (90.0)	10,482 (90.1)
Prefer not to answer	14 (2.9)	215 (2.2)	20 (1.8)	233 (2.3)	60 (2.4)	203 (2.2)	263 (2.3)
Children under 18 years living in household, *n* (%)							
Yes	87 (17.9)	1559 (15.8)	198 (18.2)	1622 (15.8)	436 (17.3)	1429 (15.7)	3962 (34.1)
Married/living with partner, *n* (%)							
Yes	290 (59.7)	5864 (59.3)	642 (59.1)	6079 (59.4)	1433 (56.9)	5455 (59.9)	6889 (59.2)
Household income, *n* (%)							
<$50,000	241 (49.6)	4312 (43.7)	543 (50.0)	4527 (44.2)	1267 (50.2)	3974 (43.8)	5244 (45.0)
$50,000–$99,999	149 (30.7)	3348 (33.8)	341 (31.4)	3469 (33.8)	819 (32.5)	3075 (33.7)	3895 (33.5)
≥$100,000	78 (16.1)	1930 (19.5)	167 (15.3)	1946 (19.0)	364 (14.5)	1786 (19.5)	2150 (18.5)
Education status, *n* (%)							
College degree	164 (33.7)	4000 (40.5)	386 (35.5)	4081 (39.8)	866 (34.4)	3705 (40.7)	4572 (39.3)
Employment status, *n* (%)							
Full-time employed	165 (34.0)*	4318 (43.7)*	407 (37.4)	4406 (43.0)	1002 (39.8)	3896 (42.8)	4898 (42.1)
Part-time employed	60 (12.3)	1251 (12.7)	117 (10.8)	1290 (12.6)	317 (12.6)	1126 (12.4)	1443 (12.4)
Health insurance, *n* (%)							
Yes	426 (87.7)	8837 (89.4)	945 (86.9)	9157 (89.4)	2230 (88.5)	8131 (89.2)	10,364 (89.1)
Migraine-related characteristics							
MHDs, *n* (%)							
0–3	134 (27.6)***	6834 (69.1)***	489 (45.0)*	6479 (63.3)*	1307 (51.9)*	5661 (62.1)*	6968 (59.9)
4–7	155 (31.9)*	2096 (21.2)*	307 (28.2)*	1944 (19.0)*	573 (22.7)	1678 (18.4)	2251 (19.3)
8–14	197 (40.5)**	958 (9.7)**	173 (15.9)	982 (9.6)	300 (11.9)	854 (9.4)	1155 (9.9)
≥15	–	–	118 (10.9)	837 (8.2)	339 (13.5)	918 (10.1)	1260 (10.8)
Migraine diagnosis class, *n* (%)							
Migraine diagnosis only	77 (15.8)	1953 (19.8)	178 (16.4)	2037 (19.9)	457 (18.1)	1810 (19.9)	2268 (19.5)
Other headache[b] diagnosis only	109 (22.4)	2280 (23.1)	260 (23.9)	2291 (22.4)	535 (21.2)	2066 (22.7)	2601 (22.4)

TABLE 1 (Continued)

Variable	EM-to-CM transition		MHD progression		MIDAS progression		Total
	Yes ($n=486$)	No ($n=9888$)	Yes ($n=1087$)	No ($n=10,242$)	Yes ($n=2519$)	No ($n=9111$)	$N=11,634$
No migraine or headache diagnosis	61 (12.6)*	2355 (23.8)*	170 (15.6)	2352 (23.0)	412 (16.4)	2138 (23.5)	2550 (21.9)
Migraine plus other headache diagnosis	239 (49.2)*	3300 (33.4)*	479 (44.1)	3562 (34.8)	1115 (44.3)	3097 (34.0)	4215 (36.2)
MIBS-4[c], *n* (%)							
None (score 0)	122 (25.1)*	3722 (37.6)*	282 (25.9)*	3726 (36.4)*	647 (25.7)*	3420 (37.5)*	4067 (35.0)
Mild (score 1–2)	91 (18.7)	1792 (18.1)	195 (17.9)	1858 (18.1)	465 (18.5)	1633 (17.9)	2098 (18.0)
Moderate (score 3–4)	74 (15.2)	1470 (14.9)	187 (17.2)	1508 (14.7)	437 (17.3)	1306 (14.3)	1743 (15.0)
Severe (score ≥5)	199 (40.9)*	2904 (29.4)*	423 (38.9)	3150 (30.8)	970 (38.5)	2752 (30.2)	3726 (32.0)
MIDAS[d], *n* (%)							
Little or none (score 0–5)	146 (30.0)**	5122 (51.8)**	355 (32.7)*	5074 (49.5)*	1076 (42.7)	4421 (48.5)	5497 (47.2)
Mild (score 6–10)	59 (12.1)	1752 (17.7)	164 (15.1)	1713 (16.7)	459 (18.2)	1433 (15.7)	1892 (16.3)
Moderate (score 11–20)	98 (20.2)	1505 (15.2)	227 (20.9)	1513 (14.8)	482 (19.1)	1290 (14.2)	1772 (15.2)
Severe (score ≥ 21)	183 (37.7)**	1509 (15.3)**	341 (31.4)	1942 (19.0)	502 (19.9)	1967 (21.6)	2473 (21.3)
MSQ-RFR[e], mean (SD)	48.6 (23.4)*	59.8 (23.6)*	50.6 (23.4)*	58.6 (24.0)*	51.3 (23.2)*	59.1 (24.3)*	57.4 (24.3)
MSQ-RFP[e], mean (SD)	61.5 (26.3)*	70.3 (25.3)*	62.0 (26.4)*	69.5 (25.7)*	62.4 (26.1)*	70.1 (25.7)*	68.4 (26.0)
MSQ-EF[e], mean (SD)	54.0 (29.7)**	68.1 (27.6)**	56.5 (29.4)*	66.6 (28.4)*	58.2 (29.1)*	67.0 (28.6)*	65.1 (29.0)
Clinical characteristics and comorbidities							
Any tobacco use, *n* (%)							
Yes	144 (29.6)	2505 (25.3)	335 (30.8)	2652 (25.9)	809 (32.1)	2261 (24.8)	3071 (26.4)
Marijuana use, *n* (%)							
Yes	108 (22.2)	1972 (19.9)	240 (22.1)	2066 (20.2)	579 (23.0)	1781 (19.5)	2361 (20.3)
Body mass index group, *n* (%)							
Did not report weight/height	24 (4.9)	468 (4.7)	42 (3.9)	490 (4.8)	118 (4.7)	431 (4.7)	133 (1.1)
Underweight/normal	139 (28.6)	3354 (33.9)	333 (30.6)	3461 (33.8)	803 (31.9)	3073 (33.7)	4363 (37.5)
Overweight	133 (27.4)	2822 (28.5)	304 (28.0)	2888 (28.2)	662 (26.3)	2609 (28.6)	3203 (27.5)
Obese	190 (39.1)	3244 (32.8)	408 (37.5)	3403 (33.2)	936 (37.2)	2998 (32.9)	3935 (33.8)
Number of self-reported cardiovascular comorbidity[f], *n* (%)							
None	205 (42.2)	4867 (49.2)	487 (44.8)	4989 (48.7)	1184 (47.0)	4399 (48.3)	2855 (24.5)
1	124 (25.5)	2409 (24.4)	270 (24.8)	2502 (24.4)	600 (23.8)	2255 (24.8)	3194 (27.5)
≥2	157 (32.3)	2612 (26.4)	330 (30.4)	2751 (26.9)	735 (29.2)	2457 (27.0)	5585 (48.0)
Self-reported comorbidity that is a contraindication for triptans[g], *n* (%)	103 (21.2)	1444 (14.6)	202 (18.6)	1559 (15.2)	445 (17.7)	1386 (15.2)	1833 (15.8)
Number of self-reported joint or pain comorbidity[h], *n* (%)							
None	252 (51.9)*	6587 (66.6)*	607 (55.8)	6682 (65.2)	1431 (56.8)	5984 (65.7)	7416 (63.7)
1	126 (25.9)	2148 (21.7)	280 (25.8)	2260 (22.1)	647 (25.7)	1972 (21.6)	2620 (22.5)
≥2	108 (22.2)*	1153 (11.7)*	200 (18.4)	1300 (12.7)	441 (17.5)	1155 (12.7)	1598 (13.7)
Anxiety[i], yes, *n* (%)	369 (75.9)	6654 (67.3)	840 (77.3)*	6949 (67.8)*	1938 (76.9)*	6080 (66.7)*	8021 (68.9)
Depression[i], yes, *n* (%)	383 (78.8)*	6308 (63.8)*	846 (77.8)*	6628 (64.7)*	1890 (75.0)*	5827 (64.0)*	7721 (66.4)
Allergies, yes, *n* (%)	218 (44.9)	3732 (37.7)	493 (45.4)	3879 (37.9)	1027 (40.8)	3492 (38.3)	4521 (38.9)
Treatment related							
Sought care for migraine in the previous 12 months, *n* (%)	380 (78.2)*	6601 (66.8)*	807 (74.2)	6965 (68.0)	1877 (74.5)	6152 (67.5)	7985 (68.6)
Sought care in primary care	224 (46.1)*	3154 (31.9)*	484 (44.5)*	3413 (33.3)*	1065 (42.3)*	2983 (32.7)*	4050 (34.8)

(Continues)

TABLE 1 (Continued)

Variable	EM-to-CM transition		MHD progression		MIDAS progression		Total
	Yes ($n=486$)	No ($n=9888$)	Yes ($n=1087$)	No ($n=10,242$)	Yes ($n=2519$)	No ($n=9111$)	$N=11,634$
Medication use, *n* (%)							
Start using recommended acute medications[j] during 1-year follow-up	13 (2.7)	113 (1.1)	19 (1.7)	116 (1.1)	42 (1.7)	95 (1.0)	137 (1.2)
Still using recommended acute medications[j] that were used at baseline at 1-year follow-up	369 (75.9)*	6534 (66.1)*	830 (76.4)*	6791 (66.3)*	1866 (74.1)	5954 (65.4)	7824 (67.3)
Stop using recommended acute medications[j] during 1-year follow-up	45 (9.3)*	1783 (18.0)*	112 (10.3)*	1837 (17.9)*	304 (12.1)	1688 (18.5)	1992 (17.1)
Ever used any preventive medication[k] for migraine	200 (41.2)*	2451 (24.8)*	397 (36.5)*	2718 (26.5)*	916 (36.4)*	2361 (25.9)*	3281 (28.2)
Acute OTC medication overuse[l] at baseline, *n* (%)	114 (23.5)*	634 (6.4)*	208 (19.1)*	1022 (10.0)*	384 (15.2)	1003 (11.0)	1388 (11.9)

Note: Percents indicate column percent for each characteristic; for row percent, please see Table 2. Standardized mean difference (SMD) was calculated to compare groups. All were not different (SMD <0.2), except where indicated. *Indicates a small difference (SMD = 0.2–0.49); **Indicates a moderate difference (SMD = 0.5–0.79); ***Indicates a large difference (SMD ≥0.8).

Abbreviations: CM, chronic migraine; EM, episodic migraine; MHD, monthly headache day; MIBS-4, Migraine Interictal Burden Scale-4; MIDAS, Migraine Disability Assessment; MSQ-EF, Migraine-Specific Quality of Life Questionnaire v2.1 Emotional Function; MSQ-RFP, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Preventive; MSQ-RFR, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Restrictive; OTC, over the counter; SD, standard deviation.

[a]Participants could select all that applied from a list, which included the following options: (1) Asian Indian or Alaska Native, (2) Asian or Asian American (for example, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese), (3) Black or African American, (4) Native Hawaiian or Asian or Pacific Islander, (5) White or Caucasian, (6) Other, and (7) Prefer not to answer. "Other" in this table includes those who selected options 1, 4, 6, or multiple options.

[b]Other headache types included cervicogenic headache, chronic daily headache, cluster headache, new daily persistent headache, medication overuse headache or rebound headache, menstrual headache or menstrual migraine, post-traumatic headache or post-concussion headache, sinus headache stress headache, tension type headache, or tension headache.

[c]Migraine burden in between attacks (interictal) was assessed via the MIBS-4.

[d]Migraine-related disability was assessed via the MIDAS scale.

[e]The functional impact of migraine over the previous 4 weeks was measured using the 7-item MSQ-RFR, the 4-item MSQ-RFP, and the 3-item MSQ-EF. Each item contains 6 response options ranging from "none of the time" to "all of the time" and the raw score for each domain is transformed to a score of 0 to 100, with higher scores indicating better function.

[f]Cardiovascular comorbidities included self-reported medical diagnosis of prediabetes, diabetes, high cholesterol, and hypertension.

[g]Contraindication for triptans included presence of aneurysm, angina, cerebral hemorrhage, claudication, myocardial infarction, stroke, transient ischemic attack, blood clots in legs/lungs.

[h]Joint or pain comorbidities included chronic back pain, fibromyalgia, osteoarthritis, and rheumatoid arthritis.

[i]Presence of depression and anxiety were determined by the 4-item Patient Health Questionnaire.

[j]Recommended acute medications for migraine were based on the American Headache Society Consensus statement[35] and included triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan-containing medications, zolmitriptan-containing medications), non-steroidal anti-inflammatory drugs (celecoxib, diclofenac, flurbiprofen, ibuprofen prescription strength, indomethacin, ketoprofen, ketorolac, naproxen), ergotamine derivatives (dihydroergotamine-containing medications, ergotamine, cafergot), gepants (rimegepant, ubrogepant), and lasmiditan. "Start using recommended acute medications" was defined as not taking them at baseline but taking them at the 1-year follow-up. "Still using recommended acute medications" was defined as taking them at baseline and at the 1-year follow-up. "Stop taking recommended acute medications" was defined as taking them at baseline but not taking them at the 1-year follow-up.

[k]Acute OTC medications included acetaminophen, aspirin, ibuprofen, naproxen sodium, and combination migraine or headache formula medications. Overuse was defined as taking ≥ 10 days/month (combination migraine or headache formula medications) or ≥ 15 days/month (acetaminophen, aspirin, ibuprofen, naproxen sodium).

[l]Preventive medications included antidepressants (amitriptyline, desvenlafaxine, doxepin, duloxetine, escitalopram oxalate, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, venlafaxine), antiseizure medications (divalproex, gabapentin, pregabalin, topiramate, valproic acid, zonisamide), cardiovascular medications (atenolol, candesartan, lisinopril, metoprolol, nadolol, nifedipine, propranolol, timolol, verapamil), calcitonin gene-related peptide monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab), gepants (rimegepant for prevention, atogepant), and neurotoxins (abotulinumtoxinA, onabotulinumtoxinA).

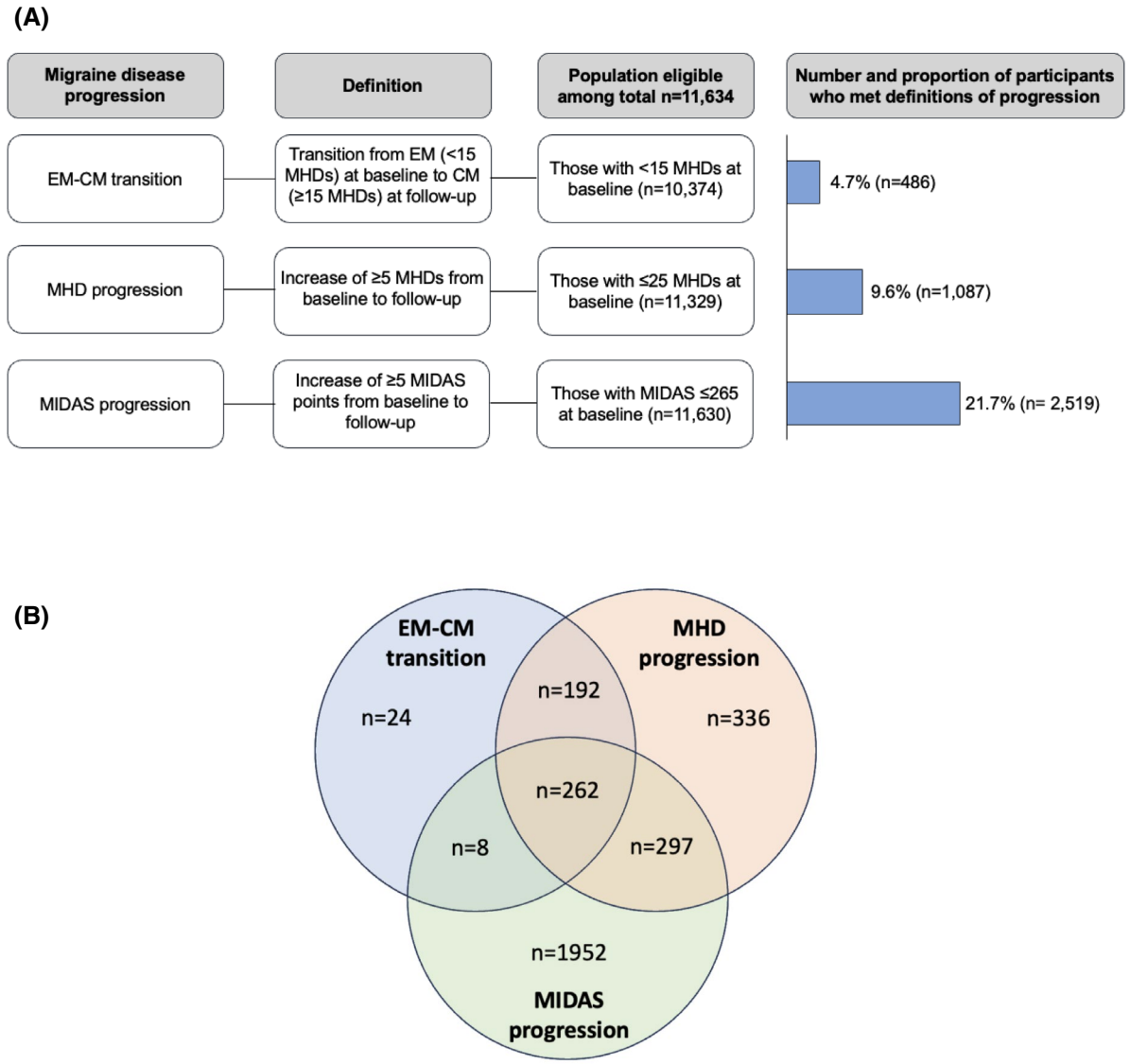

FIGURE 1 (A) Description of definitions of migraine disease progression and proportion of participants who met these definitions. (B) Breakdown of number of participants who met one, two, or all three definitions of progression. Figure not to scale. CM, chronic migraine; EM, episodic migraine, MHD, monthly headache day; MIDAS, Migraine Disability Assessment. [Colour figure can be viewed at wileyonlinelibrary.com]

of experiencing migraine progression (OR = 1.17, 95% CI = 1.02–1.35) and that those who stopped using recommended acute medications had lower odds of experiencing an increase in ≥ 5 MHDs (OR = 0.65, 95% CI = 0.50–0.85). Similarly, multicollinearity was also not present among variables in this logistic regression model for this analysis with a VIF of <4 for all variables. The AUC was 0.7 for RF and 0.6 for LASSO, suggesting good model performance.

Factors associated with progression in MIDAS at 1-year follow-up

When we evaluated factors associated with MIDAS progression (increase of ≥ 5 MIDAS points at the 1-year follow-up), some factors associated with MIDAS progression identified by RF and LASSO were similar to those associated with increases in MHDs and EM-to-CM transition (Table 5; Figure 2). Additional factors were MIBS-4 category at baseline, ictal cutaneous allodynia category at baseline, MSSS total score at baseline, MSQ Role Function-Restrictive (MSQ-RFR) domain score at baseline, care seeking, migraine diagnosis class at baseline, acute medication use status, and presence of joint or pain comorbidities. Specifically, those who had depression (OR = 1.18, 95% CI = 1.04–1.34) or anxiety (OR = 1.24, 95% CI = 1.09–1.40) at baseline, those with moderate MIBS-4 (vs. none: OR = 1.28, 95% CI = 1.10–1.48) or mild MIBS-4 (vs. none: OR = 1.22, 95% CI = 1.06–1.40) at baseline, those with mild allodynia at baseline (vs. none: OR = 1.24, 95% CI = 1.10–1.39), and those with higher MSSS total score at baseline (OR = 1.03, 95% CI = 1.01–1.05) had higher odds of increasing ≥ 5 MIDAS points at 1 year (Figure 5). Further, having a diagnosis of migraine and other headaches (vs. no diagnosis: OR = 1.19,

TABLE 2 Rates of progression.

	EM-to-CM transition		MHD progression		MIDAS progression	
Variable	**Yes (*n* = 486)**	**No (*n* = 9888)**	**Yes (*n* = 1087)**	**No (*n* = 10,242)**	**Yes (*n* = 2519)**	**No (*n* = 9111)**
Sociodemographic characteristics						
Sex assigned at birth, *n* (%)						
Female	390 (5.0)	7383 (95.0)	840 (9.8)	7714 (90.2)	1982 (22.6)	6807 (77.4)
Male	96 (3.7)	2505 (96.3)	247 (8.9)	2528 (91.1)	537 (18.9)	2304 (81.1)
Urban/rural commuting area, *n* (%)						
Urban	390 (4.5)	8185 (95.5)	873 (9.3)	8469 (90.7)	2047 (21.4)	7523 (78.6)
Race[a], *n* (%)						
White or Caucasian	429 (4.9)	8267 (95.1)	922 (9.7)	8620 (90.3)	2143 (21.8)	7668 (78.2)
Black or African American	19 (2.7)	678 (97.3)	54 (7.3)	690 (92.7)	158 (20.9)	599 (79.1)
Asian	9 (2.7)	329 (97.3)	27 (7.8)	318 (92.2)	62 (18.0)	283 (82.0)
Other	28 (4.7)	570 (95.3)	78 (12.0)	572 (88.0)	142 (21.2)	527 (78.8)
Prefer not to answer	1 (2.2)	44 (97.8)	6 (12.5)	42 (87.5)	14 (29.2)	34 (70.8)
Ethnicity, *n* (%)						
Hispanic, Latino/a, or Spanish	37 (4.5)	778 (95.5)	80 (9.2)	794 (90.8)	184 (20.7)	705 (79.3)
Not Hispanic, Latino/a, or Spanish	435 (4.7)	8895 (95.3)	987 (9.7)	9215 (90.3)	2275 (21.7)	8203 (78.3)
Prefer not to answer	14 (6.1)	215 (93.9)	20 (7.9)	233 (92.1)	60 (22.8)	203 (77.2)
Children under 18 years living in household, *n* (%)						
Yes	87 (5.3)	1559 (94.7)	198 (10.9)	1622 (89.1)	436 (23.4)	1429 (76.6)
Married/living with partner, *n* (%)						
Yes	290 (4.7)	5864 (95.3)	642 (9.6)	6079 (90.4)	1433 (20.8)	5455 (79.2)
Household income, *n* (%)						
<$50,000	241 (5.3)	4312 (94.7)	543 (10.7)	4527 (89.3)	1267 (24.2)	3974 (75.8)
$50,000–$99,999	149 (4.3)	3348 (95.7)	341 (9.0)	3469 (91.0)	819 (21.0)	3075 (79.0)
≥$100,000	78 (3.9)	1930 (96.1)	167 (7.9)	1946 (82.1)	364 (16.9)	1786 (83.1)
Education status, *n* (%)						
College degree	164 (3.9)	4000 (96.1)	386 (8.6)	4081 (91.4)	866 (18.9)	3705 (81.1)
Employment status, *n* (%)						
Full time employed	165 (3.7)	4318 (96.3)	407 (8.5)	4406 (91.5)	1002 (20.5)	3896 (79.5)
Part time employed	60 (4.6)	1251 (95.4)	117 (8.3)	1290 (91.7)	317 (22)	1126 (78)
Health insurance, *n* (%)						
Yes	426 (4.6)	8837 (95.4)	945 (9.4)	9157 (90.6)	2230 (21.5)	8131 (78.5)
Migraine-related characteristics						
MHDs, *n* (%)						
0–3	134 (1.9)	6834 (98.1)	489 (7.0)	6479 (93.0)	1307 (18.8)	5661 (81.2)
4–7	155 (6.9)	2096 (93.1)	307 (13.6)	1944 (86.4)	573 (25.5)	1678 (74.5)
8–14	197 (17.1)	958 (82.9)	173 (15.0)	982 (85.0)	300 (26.0)	854 (74.0)
≥15	–	–	118 (12.4)	837 (87.6)	339 (27.0)	918 (73.0)
Migraine diagnosis class, *n* (%)						
Migraine diagnosis only	77 (3.8)	1953 (96.2)	178 (8.0)	2037 (92.0)	457 (20.2)	1810 (79.8)
Other headache[b] diagnosis only	109 (4.6)	2280 (95.4)	260 (10.2)	2291 (89.8)	535 (20.6)	2066 (79.4)
No migraine or headache diagnosis	61 (2.5)	2355 (97.5)	170 (6.7)	2352 (93.3)	412 (16.2)	2138 (83.8)
Migraine plus other headache diagnosis	239 (6.8)	3300 (93.2)	479 (11.9)	3562 (88.1)	1115 (26.5)	3097 (73.5)

TABLE 2 (Continued)

Variable	EM-to-CM transition		MHD progression		MIDAS progression	
	Yes ($n=486$)	No ($n=9888$)	Yes ($n=1087$)	No ($n=10,242$)	Yes ($n=2519$)	No ($n=9111$)
MIBS-4[c], *n* (%)						
None (score 0)	122 (3.2)	3722 (96.8)	282 (7.0)	3726 (93.0)	647 (15.9)	3420 (84.1)
Mild (score 1–2)	91 (4.8)	1792 (95.2)	195 (9.5)	1858 (90.5)	465 (22.2)	1633 (77.8)
Moderate (score 3–4)	74 (4.8)	1470 (95.2)	187 (11.0)	1508 (89.0)	437 (25.1)	1306 (74.9)
Severe (score ≥5)	199 (6.4)	2904 (93.6)	423 (11.8)	3150 (88.2)	970 (26.1)	2752 (73.9)
MIDAS[d], *n* (%)						
Little or none (score 0–5)	146 (2.8)	5122 (97.2)	355 (6.5)	5074 (93.5)	1076 (19.6)	4421 (80.4)
Mild (score 6–10)	59 (3.3)	1752 (96.7)	164 (8.7)	1713 (91.3)	459 (24.3)	1433 (75.7)
Moderate (score 11–20)	98 (6.1)	1505 (93.9)	227 (13.0)	1513 (87.0)	482 (27.2)	1290 (72.8)
Severe (score ≥ 21)	183 (10.8)	1509 (89.2)	341 (14.9)	1942 (85.1)	502 (20.3)	1967 (79.7)
Clinical characteristics and comorbidities						
Any tobacco use, *n* (%)						
Yes	144 (5.4)	2505 (94.6)	335 (11.2)	2652 (88.8)	809 (26.4)	2261 (73.6)
Marijuana use, *n* (%)						
Yes	108 (5.2)	1972 (94.8)	240 (10.4)	2066 (89.6)	579 (24.5)	1781 (75.5)
Body mass index group, *n* (%)						
Did not report weight/height	24 (4.9)	468 (95.1)	42 (7.9)	490 (92.1)	118 (21.5)	431 (78.5)
Underweight/normal	139 (4.0)	3354 (96.0)	333 (8.8)	3461 (91.2)	803 (20.7)	3073 (79.3)
Overweight	133 (4.5)	2822 (95.5)	304 (9.5)	2888 (90.5)	662 (20.2)	2609 (79.8)
Obese	190 (5.5)	3244 (94.5)	408 (10.7)	3403 (89.3)	936 (23.8)	2998 (76.2)
Self-reported cardiovascular comorbidity[e], *n* (%)						
None	205 (4.0)	4867 (96.0)	487 (8.9)	4989 (91.1)	1184 (21.2)	4399 (78.8)
1	124 (4.9)	2409 (95.1)	270 (9.7)	2502 (90.3)	600 (21.0)	2255 (79.0)
≥2	157 (5.7)	2612 (94.3)	330 (10.7)	2751 (89.3)	735 (23.0)	2457 (77.0)
Self-reported comorbidity that is a contraindication for triptans[f], *n* (%)	103 (6.7)	1444 (93.3)	202 (11.5)	1559 (88.5)	445 (24.3)	1386 (75.7)
Self-reported joint or pain comorbidity[g], *n* (%)						
None	252 (3.7)	6587 (96.3)	607 (8.3)	6682 (91.7)	1431 (19.3)	5984 (80.7)
1	126 (5.5)	2148 (94.5)	280 (11.0)	2260 (89.0)	647 (24.7)	1972 (75.3)
≥2	108 (8.6)	1153 (91.4)	200 (13.3)	1300 (86.7)	441 (27.6)	1155 (72.4)
Anxiety[h], yes, *n* (%)	369 (5.3)	6654 (94.7)	840 (10.8)	6949 (89.2)	1938 (24.2)	6080 (75.8)
Depression[h], yes, *n* (%)	383 (5.7)	6308 (94.3)	846 (11.3)	6628 (88.7)	1890 (24.5)	5827 (75.5)
Allergies, yes, *n* (%)	218 (5.5)	3732 (94.5)	493 (11.3)	3879 (88.7)	1027 (22.7)	3492 (77.3)
Treatment related						
Sought care for migraine in the previous 12 months, *n* (%)	380 (5.4)	6601 (94.6)	807 (10.4)	6965 (89.6)	1877 (23.4)	6152 (76.6)
Sought care in primary care	224 (6.6)	3154 (93.4)	484 (12.4)	3413 (87.6)	1065 (26.3)	2983 (73.7)
Medication use, *n* (%)						
Start using recommended acute medications[i] during 1-year follow-up	13 (10.3)	113 (89.7)	19 (14.1)	116 (85.9)	42 (30.7)	95 (69.3)
Still using recommended acute medications[i] that were used at baseline at 1-year follow-up	369 (5.3)	6534 (94.7)	830 (10.9)	6791 (89.1)	1866 (23.9)	5954 (76.1)

(Continues)

TABLE 2 (Continued)

Variable	EM-to-CM transition		MHD progression		MIDAS progression	
	Yes ($n=486$)	No ($n=9888$)	Yes ($n=1087$)	No ($n=10,242$)	Yes ($n=2519$)	No ($n=9111$)
Stop using recommended acute medications[i] during 1-year follow-up	45 (2.5)	1783 (97.5)	112 (5.7)	1837 (94.3)	304 (15.3)	1688 (84.7)
Ever taken any preventive medication[j] for migraine	200 (7.5)	2451 (92.5)	397 (12.7)	2718 (87.3)	916 (28.0)	2361 (72.0)
Acute OTC medication overuse[k] at baseline, *n* (%)	114 (15.2)	634 (84.8)	208 (16.9)	1022 (83.1)	384 (27.7)	1003 (72.3)

Note: The table shows rates of progression among those who experienced migraine disease progression based on increases in MHDs and/or MIDAS score at 1-year follow-up. Percents indicate row percent for each definition of progression.

Abbreviations: CM, chronic migraine; EM, episodic migraine; MHD, monthly headache day; MIBS-4, Migraine Interictal Burden Scale-4; MIDAS, Migraine Disability Assessment; OTC, over the counter.

[a]Participants could select all that applied from a list, which included the following options: (1) Asian Indian or Alaska Native, (2) Asian or Asian American (for example, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese), (3) Black or African American, (4) Native Hawaiian or Asian or Pacific Islander, (5) White or Caucasian; (6) Other, and (7) Prefer not to answer. "Other" in this table includes those who selected options 1, 4, 6, or multiple options.

[b]Other headache types included cervicogenic headache, chronic daily headache, cluster headache, new daily persistent headache, medication overuse headache or rebound headache, menstrual headache or menstrual migraine, post-traumatic headache or post-concussion headache, sinus headache stress headache, tension type headache, or tension headache.

[c]Migraine burden in between attacks (interictal) was assessed via the MIBS-4.

[d]Migraine-related disability was assessed via the MIDAS scale.

[e]Cardiovascular comorbidities included self-reported medical diagnosis of prediabetes, diabetes, high cholesterol, and hypertension.

[f]Contraindication for triptan included presence of aneurysm, angina, cerebral hemorrhage, claudication, myocardial infarction, stroke, transient ischemic attack, blood clots in legs/lungs.

[g]Joint or pain comorbidities included chronic back pain, fibromyalgia, osteoarthritis, and rheumatoid arthritis.

[h]Presence of depression and anxiety were determined by the 4-item Patient Health Questionnaire.

[i]Recommended acute medications for migraine were based on the American Headache Society Consensus statement[35] and included triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan-containing medications, zolmitriptan-containing medications), non-steroidal anti-inflammatory drugs (celecoxib, diclofenac, flurbiprofen, ibuprofen prescription strength, indomethacin, ketoprofen, ketorolac, naproxen), ergotamine derivatives (dihydroergotamine-containing medications, ergotamine, cafergot), gepants (rimegepant, ubrogepant), and lasmiditan. "Start using recommended acute medications" was defined as not taking them at baseline but taking them at the 1-year follow-up. "Still using recommended acute medications" was defined as taking them at baseline and at the 1-year follow-up. "Stop taking recommended acute medications" was defined as taking them at baseline, but not taking them at the 1-year follow-up.

[j]Preventive medications included antidepressants (amitriptyline, desvenlafaxine, doxepin, duloxetine, escitalopram oxalate, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, venlafaxine), antiseizure medications (divalproex, gabapentin, pregabalin, topiramate, valproic acid, zonisamide), cardiovascular medications (atenolol, candesartan, lisinopril, metoprolol, nadolol, nifedipine, propranolol, timolol, verapamil), calcitonin gene-related peptide monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab), gepants (rimegepant for prevention, atogepant), and neurotoxins (abotulinumtoxinA, onabotulinumtoxinA).

[k]Acute OTC medications included acetaminophen, aspirin, ibuprofen, naproxen sodium, and combination migraine or headache formula medications. Overuse was defined as taking ≥ 10 days/month (combination migraine or headache formula medications) or ≥ 15 days/month (acetaminophen, aspirin, ibuprofen, naproxen sodium).

95% CI = 1.03–1.38), having joint or pain comorbidities at baseline (≥ 2 vs. none: OR = 1.30, 95% CI = 1.14–1.48; 1 vs. none: OR = 1.24, 95% CI = 1.11–1.38), and using recommended acute medications (started using during follow-up: OR = 1.70, 95% CI = 1.15–2.51; using at baseline and follow-up: OR = 1.18, 95% CI = 1.03–1.36) resulted in higher odds of progression in MIDAS. On the other hand, those who reported that they had ever taken preventive medication (OR = 0.82, 95% CI = 0.73–0.91) and those who stopped using recommended acute medications during the follow-up period (OR = 0.73, 95% CI = 0.62–0.88) had lower odds of progression. VIFs for this model were also < 4 for all variables, suggesting that high levels of multicollinearity were not present. The AUC was 0.6 for both models (RF and LASSO), suggesting good model performance.

DISCUSSION

This study explored rates and risk factors for progression using three different theoretically grounded definitions for progression: the traditional definition of progression (EM-to-CM transition) and two additional definitions (MHD progression and MIDAS progression). Rates of progression were lowest for the EM-to-CM transition (4.7%), intermediate for the MHD increase (9.6%), and highest for MIDAS progression (21.7%). We will consider these alternative definitions of progression and their predictors one at a time.

The current study found that the EM-to-CM transition rate at 1 year was 4.7%, slightly higher than in previous epidemiological studies.[2,11,13,14] Using machine learning, we confirmed previously

TABLE 3 Factors associated with EM-to-CM transition.

Factors identified by LASSO	
MSQ-EF domain score at baseline	
Acute OTC medication overuse	
Seeking care for migraine	
Using any preventive medication for migraine	
MIDAS score at baseline	
Factors identified by random forest	**OOB Gini**
Acute OTC medication overuse	60.2×10^{-5}
MIDAS score at baseline	40.9×10^{-5}
MSQ-EF domain score at baseline	4.9×10^{-5}
Ever taking any preventive medication for migraine	4.0×10^{-5}
MSQ-RFR domain score at baseline	3.2×10^{-5}
Depression at baseline	0.3×10^{-5}

Note: Factors were identified by LASSO and random forest (presented in order of association).

Abbreviations: CM, chronic migraine; EM, episodic migraine; LASSO, least absolute shrinkage and selection operator; MIDAS, Migraine Disability Assessment; MSQ-EF, Migraine-Specific Quality of Life Questionnaire v2.1 Emotional Function; MSQ-RFR, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Restrictive; OOB, out of bag; OTC, over the counter.

identified factors and identified novel factors associated with the EM-to-CM transition. Key risk factors identified were higher MIDAS score, overusing acute OTC medications for migraine, never having used migraine preventive treatments, and comorbid depression. While comorbid depression and overusing acute OTC medications have been reported previously,[48,49] the current analysis illustrates that higher migraine-specific disability and not taking preventive treatment are also important risk factors. While it is yet to be established if modifying risk factors prevents progression, addressing modifiable risk factors as we await the results of specifically designed trials is a worthy consideration in migraine management. In contrast to the results of the current study, previous analyses identified high MHD frequency, comorbid pain disorders, allodynia, and various demographic characteristics as risk factors for EM-to-CM transition.[2,4,49–51] While these studies took a candidate approach to analyzing risk factors, the use of machine learning algorithms in the current study allowed us to consider 67 sociodemographic, clinical, and migraine-related variables to determine those most associated with risk of progression. Although previous studies had specifically selected sociodemographic variables as risk candidates, they did not emerge as important predictors of the EM-to-CM transition in the current study; this is likely a reflection of the relative importance of migraine-related and clinical factors compared to sociodemographic factors in whether an individual experiences migraine progression.

We also defined progression as a 5-day increase in MHDs. Compared to those who transitioned from EM to CM, a higher proportion of people met the MHD progression definition at 1-year follow-up (9.6%). Identifying individuals with EM whose MHDs increased but who did not cross the 15-day threshold as well as people with CM who experienced an increase in MHDs likely accounts for the higher rates of progression using this definition. The majority of those who met the EM-to-CM transition definition also met the MHD increase definition (93.4%, $n=454/486$), but less than half of those who met the MHD increase definition also met the EM-to-CM transition definition (41.8%, $n=454/1087$). The model evaluating risk factors for MHD progression identified the same four risk factors as the EM-to-CM transition model (higher MIDAS score, overusing acute OTC medications for migraine, never having taken migraine preventive treatments, and depression), highlighting the importance of these four risk factors. The MHD progression model also identified two additional risk factors; those who consulted for migraine/headache in primary care had higher odds of progression and those who stopped using acute recommended medications had lower odds of progression. It is unclear if these variables are a cause or consequence of progression (i.e., did those individuals who stopped using acute medication during the 1-year follow-up do so because they felt that it was no longer working or did their migraine worsen because they stopped taking acute medications), highlighting that these results do not fully assess causality and directionality. There may be shared underlying factors and a range of other explanations for the relationships seen between what we refer to as risk factors and outcomes. Nevertheless, both highlight important steps in the migraine care pathway that may affect migraine progression. These findings should be replicated in an independent sample. In addition, for risk factors that are modifiable, randomized trials could be used to assess the benefits of risk factor modification on progression using various progression definitions.

More than 1 in 5 people in this analysis experienced MIDAS progression (21.7%). While measures of MHDs and MIDAS scores are correlated, the relationship is not linear.[52] MHD frequency accounts for only 45% of the variance in MIDAS score.[52] There may be additional variables and individual characteristics that change the strength of the relationship, and it could be that changes in disability are more impactful to the person with migraine than increases in MHDs. In addition, the correlation between disability and MHDs may change over time, and there may be a lead–lag relationship in which it takes more time for one variable to show change compared to the other.[53] In fact, among those who met the MIDAS progression definition ($n=2519$), the majority (77.5%, $n=1952$) met only this definition and not the others; overlap with the MHD-based definitions occurred in 22.2% ($n=559$) and with the EM-to-CM transition definition in just 10.7% ($n=270$). For comparison, 336 participants met the MHD progression definition only and just 24 met the EM-to-CM transition definition only. MIDAS may play a unique role in identifying people who progress from a disability perspective without meeting the MHD-based criteria. The MIDAS progression model identified two factors observed in the EM-to-CM transition and MHD progression models (never having used migraine preventive treatment and comorbid depression). It also identified the largest list of risk factors. Risk factors included several migraine-related patient-reported outcome measures (e.g., mild/moderate MIBS-4 vs. none, mild/moderate allodynia vs. none, higher MSSS score, MSQ-RFR score), having

	EM-to-CM transition[a]	MHD progression[b]	MIDAS progression[c]
Migraine-related factors			
Moderate MIDAS at baseline	OR 1.5 (1.09-1.94)	OR 1.5 (1.26-1.87)	
Severe MIDAS at baseline	OR 2.1 (1.56-2.76)	OR 1.5 (1.21-1.81)	
Mild MIBS-4 at baseline			OR 1.2 (1.06-1.40)
Moderate MIBS-4 at baseline			OR 1.3 (1.10-1.48)
Mild ictal cutaneous allodynia at baseline			OR 1.2 (1.10-1.39)
Higher MSSS total score at baseline			OR 1.0 (1.01-1.05)
MSQ-RFR score at baseline			OR 1.0 (0.99-1.00)
Having a migraine and other headache diagnosis			OR 1.2 (1.03-1.38)
Treatment-related factors			
Overusing acute OTC medications for migraine	OR 3.0 (2.36-3.80)	OR 1.6 (1.30-1.85)	
Start using recommended acute medication for migraine			OR 1.7 (1.15-2.51)
Still using recommended acute medication for migraine			OR 1.2 (1.03-1.36)
Stop using recommended acute medication for migraine		OR 0.7 (0.50-0.85)	OR 0.7 (0.62-0.88)
Ever having used preventive medication for migraine	**OR 0.7 (0.57-0.85)**	**OR 0.9 (0.75-1.00*)**	**OR 0.8 (0.73-0.91)**
Consulting at primary care for migraine		OR 1.2 (1.02-1.35)	
Clinical factors			
Presence of depression at baseline	**OR 1.3 (1.05-1.69)**	**OR 1.4 (1.21-1.67)**	**OR 1.2 (1.04-1.34)**
Presence of anxiety at baseline			OR 1.2 (1.09-1.40)
Presence of 1 joint or pain comorbidities at baseline			OR 1.2 (1.11-1.38)
Presence of ≥2 joint or pain comorbidities at baseline			OR 1.3 (1.14-1.48)

FIGURE 2 Summary of migraine-related, treatment-related, and clinical factors identified by machine learning associated with each definition of migraine progression. Data are shown as ORs (95% CIs). Underlined text indicates factors selected by two out of three models. Bold and underlined text indicates factors selected by all three models. *Actual value is <1 but is rounded to two decimal places. [a]Reference group: Those who did not transition from EM to CM at 1-year follow-up. The model was adjusted for the following covariates identified by machine learning as predictors of EM-to-CM transition: mild MIDAS at baseline, MSQ-RFR score at baseline, MSQ-EF score at baseline, and sought care for migraine. [b]Reference group: Those who did not experience an increase of ≥ 5 MHDs at 1-year follow-up. The model was adjusted for the following covariates identified by machine learning as predictors of MHD progression: mild MIDAS at baseline, MSQ-RFR score at baseline, MSQ-EF score at baseline, MSQ-RFP score at baseline, start using recommended acute medication for migraine, and still using recommended acute medication for migraine. Recommended acute and preventive medications were used as defined by Ailani et al. in the 2021 American Headache Society Consensus Statement.[35] [c]Reference group: Those who did not experience an increase of ≥ 5 points in MIDAS score at 1-year follow-up. The model was adjusted for the following covariates identified by machine learning as predictors of MIDAS progression: moderate MIBS-4 at baseline, severe MIBS-4 at baseline, MSQ-EF score at baseline, MSQ-RFP score at baseline, moderate ictal cutaneous allodynia at baseline, severe ictal cutaneous allodynia at baseline, migraine diagnosis or migraine and other headache diagnosis, and sought care for migraine. CI, confidence interval; CM, chronic migraine; EM, episodic migraine, MHD, monthly headache day; MIBS-4, Migraine Interictal Burden Scale-4; MIDAS, Migraine Disability Assessment; MSQ-EF, Migraine-Specific Quality of Life Questionnaire v2.1 Emotional Function; MSQ-RFP, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Preventive; MSQ-RFR, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Restrictive; MSSS, Migraine Symptom Severity Scale; OR, odds ratio; OTC, over the counter.

a migraine and other headache diagnosis, and using recommended acute medications for migraine. Clinical risk factors included comorbidities (e.g., presence of anxiety and/or joint or pain comorbidities) not present in the other two models (Figure 5). The increased identification of risk factors may result from the larger number of progression outcomes, providing more power to detect risk factors. Having a large sample size increases power to identify predictors of progression; having a large set of candidate predictors increased the probability of novel discoveries but also false-positive discoveries.

It is highly likely that some potentially important risk factors (e.g., anxiety, joint or pain comorbidities, and allodynia) were not identified in the current study.[4,50,54] Of note, the model showed that mild and moderate MIBS-4 (vs. none) and mild and moderate allodynia (vs. none) were risk factors for MIDAS progression. The dose–response relationship may reflect the smaller sample size at extreme values of MIBS-4 and allodynia. In addition, severe allodynia is associated with higher frequency and more disabling migraine; this may attenuate rates of MIDAS progression in this most disabled group.

Importantly, two risk factors were associated with progression for all three definitions: (1) never having taken a preventive medication for migraine and (2) the presence of depression. In this and other studies, less than one-third of people with migraine are ever treated with preventive medications, and depression is a common comorbidity previously associated with an increased risk of progression.[48,55] As preventive treatment is standard of care in migraine

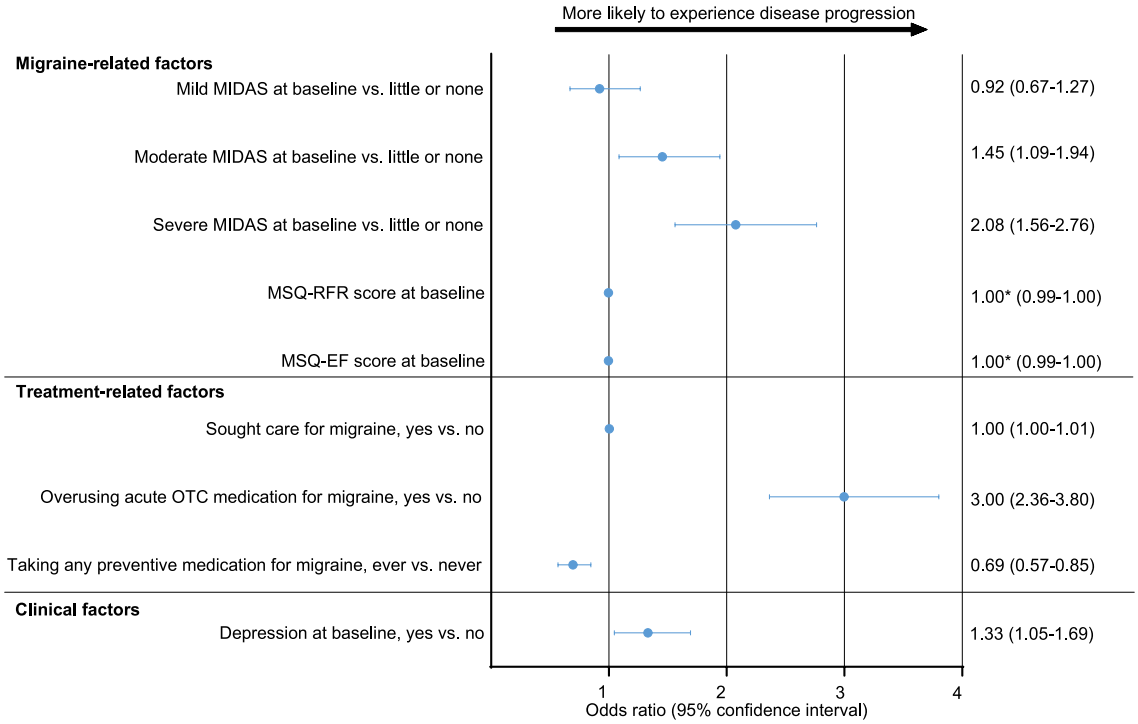

FIGURE 3 Factors associated with EM-to-CM transition. The factors most strongly associated with EM-to-CM transition at 1 year are shown in this forest plot. Continuous variables were standardized. Note that data points without evident error bars mean that the 95% CIs are contained within the width of the point shown. *Actual value is <1 but is rounded to two decimal places. CI, confidence interval; CM, chronic migraine; EM, episodic migraine; MIDAS, Migraine Disability Assessment; MSQ-EF, Migraine-Specific Quality of Life Questionnaire v2.1 Emotional Function; MSQ-RFR, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Restrictive; OTC, over the counter. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Factors associated with MHD progression.

Factors identified by LASSO	
MSQ-EF domain score at baseline	
Acute OTC medication overuse	
MIDAS score at baseline	
Factors identified by random forest	**OOB Gini**
MIDAS score at baseline	57.1×10^{-5}
Acute OTC medication overuse	31.1×10^{-5}
MSQ-EF domain score at baseline	14.4×10^{-5}
Depression at baseline	14.2×10^{-5}
MSQ-RFR domain score at baseline	8.1×10^{-5}
Consulting in primary care for migraine	5.2×10^{-5}
Recommended acute medication use status	3.3×10^{-5}
MSQ-RFP domain score at baseline	1.3×10^{-5}
Ever taking any preventive medication for migraine	1.1×10^{-5}

Note: Factors were identified by LASSO and random forest (presented in order of association).

Abbreviations: LASSO, least absolute shrinkage and selection operator; MHD, monthly headache day; MIDAS, Migraine Disability Assessment; MSQ-EF, Migraine-Specific Quality of Life Questionnaire v2.1 Emotional Function; MSQ-RFP, Migraine Specific Quality of Life Questionnaire v2.1 Role Function-Preventive; MSQ-RFR, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Restrictive; OOB, out of bag; OTC, over the counter.

management for those who meet MHD frequency/disability criteria and depression is highly treatable, more focus should be given to highlighting the clinical utility of addressing these risk factors for preventing migraine progression.

This study has many strengths. OVERCOME (US) is the largest longitudinal population-based study among adults with migraine to date. Supervised machine learning methods provide a largely unbiased method to determine factors associated with migraine progression as they effectively handle complex datasets. While clinician–scientists had identified candidate risk factors and tested them as predictors in previous risk factor analyses, the use of machine learning in the current study identified novel risk factors, providing opportunities for the development, identification, and testing of interventions to prevent migraine progression and improve outcomes. Moreover, this study has also tested three approaches to defining migraine disease progression, which may be used to expand the conceptualization of disease progression.

This study has several limitations. Although we assessed three definitions of progression, we did not examine other clinically plausible definitions (i.e., a 30% increase in MIDAS score or MHDs), nor did we use machine learning or latent trajectory modeling to identify natural subgroups that differed in prognosis and use those as novel definitions of progression. We did not consider the clinical stability of various definitions of progression

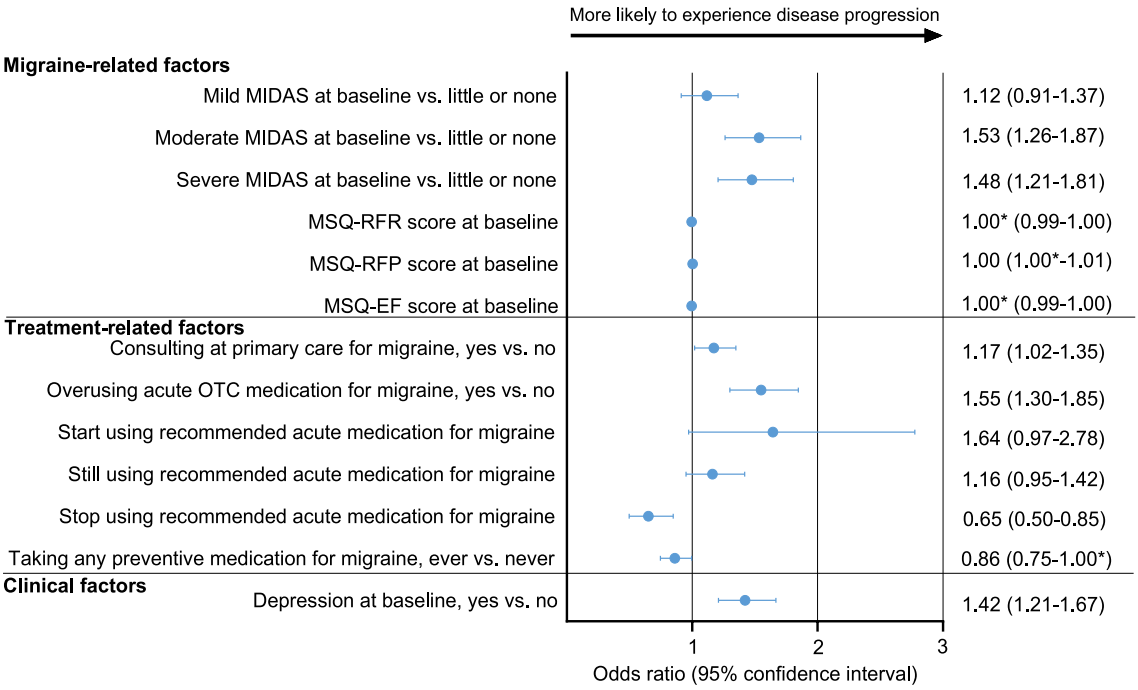

FIGURE 4 Factors associated with MHD progression. The factors most strongly associated with MHD progression at 1 year are shown in this forest plot. Continuous variables were standardized. Note that data points without evident error bars mean that the 95% CIs are contained within the width of the point shown. *Actual value is <1 but is rounded to two decimal places. CI, confidence interval; MHD, monthly headache day; MIDAS, Migraine Disability Assessment; MSQ-EF, Migraine-Specific Quality of Life Questionnaire v2.1 Emotional Function; MSQ-RFP, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Preventive; MSQ-RFR, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Restrictive; OTC, over the counter [Colour figure can be viewed at wileyonlinelibrary.com].

TABLE 5 Factors associated with MIDAS progression.

Factors identified by LASSO	
MSQ-EF domain score at baseline	
MSQ-RFR domain score at baseline	
Factors identified by random forest	**OOB Gini**
MSQ-RFR domain score at baseline	77.2×10^{-5}
MSQ-EF domain score at baseline	72.2×10^{-5}
MSQ-RFP domain score at baseline	57.1×10^{-5}
Ever taking any preventive medication for migraine	41.3×10^{-5}
Depression at baseline	35.4×10^{-5}
Recommended acute medication use status	25.4×10^{-5}
Anxiety at baseline	23.3×10^{-5}
MIBS-4 category at baseline	21.3×10^{-5}
Ictal cutaneous allodynia category at baseline	14.3×10^{-5}
MSSS total score at baseline	10.0×10^{-5}
Seeking care for migraine	5.2×10^{-5}
Migraine diagnosis class at baseline	5.1×10^{-5}
Presence of joint or pain comorbidities at baseline	3.1×10^{-5}

Note: Factors were identified by LASSO and random forest (presented in order of association).

Abbreviations: LASSO, least absolute shrinkage and selection operator; MIBS-4, Migraine Interictal Burden Scale-4; MIDAS, Migraine Disability Assessment; MSQ-EF, Migraine-Specific Quality of Life Questionnaire v2.1 Emotional Function; MSQ-RFP, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Preventive; MSQ-RFR, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Restrictive; MSSS, Migraine Symptom Severity Scale; OOB, out of bag.

as external validators. Finally, we did not examine biological correlates of progression such as changes in imaging or blood-based biomarkers. Ultimately, this work requires the mapping of clinical definitions of progression to biological underpinnings. We did use three well-justified definitions selected by clinical experts. The 1-year follow-up rate in the study was modest (19.7%), creating opportunities for information loss to follow-up. Participant dropout is a common problem in web surveys[21,56] but needs to be carefully considered when performing longitudinal analyses as this may lead to bias. Future research will examine predictors of dropping out. Of course, a web-based survey method and any methods of data capture that are entirely patient reported and subjective can be associated with biases around data accuracy and representation. However, migraine does not have objective known biomarkers associated with diagnosis or severity of impact; therefore, even when assessed by health-care professionals, most migraine data are based upon subjective patient report. The data in OVERCOME (US) were self-reported, and participants were required to have internet access and be able to read/write in English, which may have led to underrepresentation of populations who did not meet these criteria. Self-reported data may not provide an accurate representation of the true clinical picture, and by collecting survey data at baseline and 1-year follow-up, this study does not capture the dynamic nature of migraine progression in shorter or different time intervals. Future work may also look for biological evidence of changes in status, but that is beyond the scope of

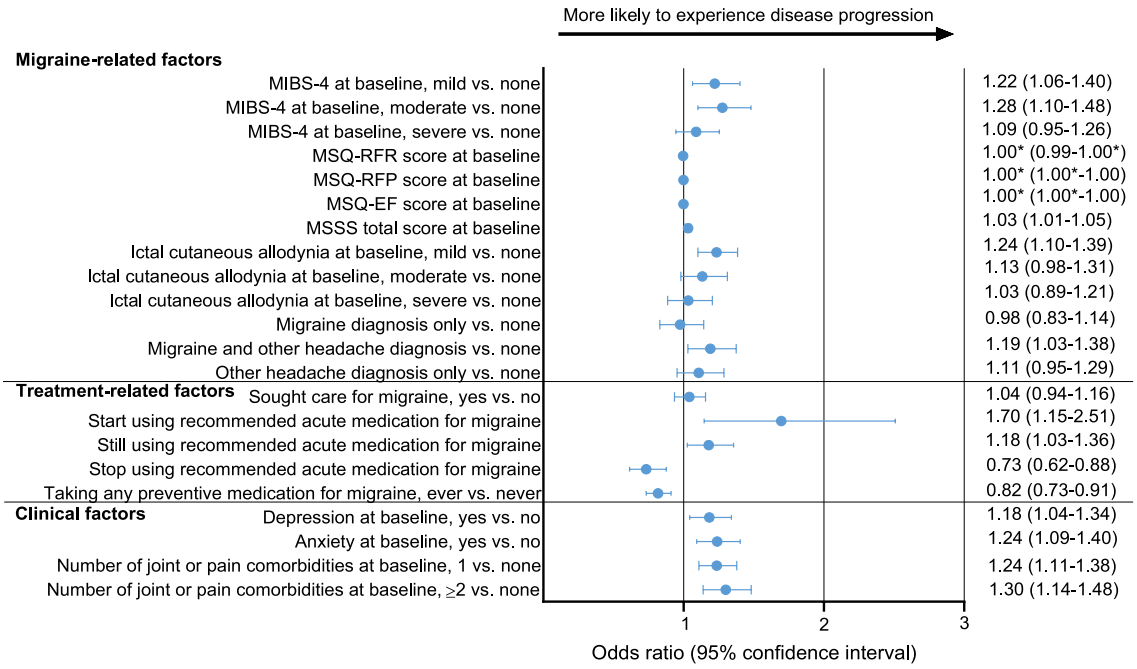

FIGURE 5 Factors associated with MIDAS progression. The factors most strongly associated with MIDAS progression at 1 year are shown in this forest plot. Continuous variables were standardized. Note that data points without evident error bars mean that the 95% CIs are contained within the width of the point shown. *Actual value is <1 but is rounded to two decimal places. CI, confidence interval; MIBS-4, Migraine Interictal Burden Scale-4; MIDAS, Migraine Disability Assessment; MSQ-EF, Migraine-Specific Quality of Life Questionnaire v2.1 Emotional Function; MSQ-RFP, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Preventive; MSQ-RFR, Migraine-Specific Quality of Life Questionnaire v2.1 Role Function-Restrictive; MSSS, Migraine Symptom Severity Scale; OTC, over the counter. [Colour figure can be viewed at wileyonlinelibrary.com]

the current report. While this study tested 67 unique variables as potential predictors of progression, there likely are other potential risk factors that were not included in this analysis or collected by the OVERCOME (US) study. As with all observational studies, there may be residual confounding, mediation, or effect modification not accounted for in these analyses.

In summary, this study assessed three definitions of migraine progression and determined rates of progression and risk factors for each definition. The definitions examined herein provide alternative broader ways to conceptualize the patient journey and define progression in clinical practice. The risk factors may inform clinical care if physicians use them to identify patients at high risk for progression. Our hope is to facilitate movement toward evidence-based, personalized approaches to preventing progression. As we move toward clinical trials designed to prevent progression, this research will inform the selection of operational definitions of progression that may be the primary outcomes of these studies. The risk factors provide a foundation for eligibility criteria to select individuals at high risk for progression and an inventory of remediable risk factors which may be targeted in future interventions. We recognize that this paper is an early step in the long journey toward developing clinically robust interventions that prevent progression.

AUTHOR CONTRIBUTIONS

Dawn C. Buse: Conceptualization; methodology; writing – original draft; writing – review and editing. **E. Jolanda Muenzel:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Anthony J. Zagar:** Formal analysis; writing – review and editing. **Ali Sheikhi Mehrabadi:** Formal analysis; writing – review and editing. **Robert E. Shapiro:** Methodology; writing – review and editing. **Gilwan Kim:** Methodology; writing – original draft; writing – review and editing. **Sait Ashina:** Conceptualization; methodology; writing – review and editing. **Robert A. Nicholson:** Conceptualization; methodology; writing – review and editing. **Richard B. Lipton:** Conceptualization; methodology; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Lilly will provide access to anonymized individual participant data collected during the study. The data will be available to request on vivli.org after the study team has completed analyses and publications. Access will be provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. After a proposal is approved, data and documents, including the study protocol, will need to be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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