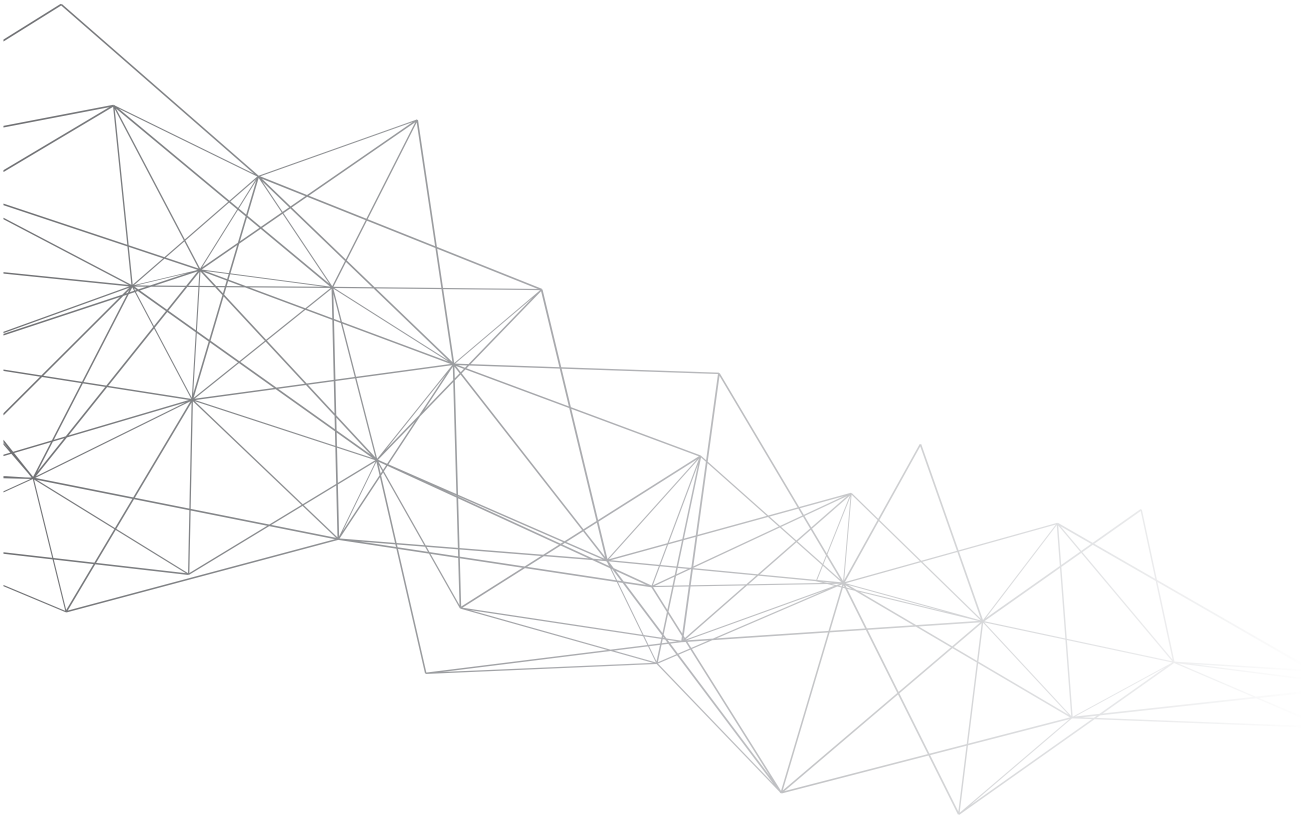
3 CHAPTER

Cutaneous allodynia as a predictor of migraine chronification



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Summary

Objectives
Cutaneous allodynia is a common feature accompanying migraine attacks and considered a clinical marker for central sensitization. In a longitudinal study, we wanted to investigate if allodynia in migraine patients is a predictor of increasing frequency of migraine days.

Methods
We included 3,029 well-defined, web-based migraine patients (86% female, mean age 42.8 ± 11.4 years, 61% migraine without aura). Questionnaires on migraine characteristics (including allodynia), depression and demographic factors were applied. The number of migraine days was measured twice. Multivariate regression models were used, with correction for other factors that are involved in the relation between allodynia and the number of migraine attacks or migraine days, with specific focus on depression.

Results
Of all 2,331 eligible migraine patients 1,624 (70%) had allodynia. Lifetime depression was an independent risk factor for allodynia (OR 1.52, 95% CI 1.26-1.84), as well as female gender, low age at onset, and high migraine attack frequency. Analysis of the longitudinal data (in migraineurs with a follow-up period of >6 months) showed that, apart from the known risk factors (low age at onset, high baseline number of migraine days, and depression), allodynia was an independent predictor for increase in number of migraine days over a mean follow-up period of 93 ± 30 weeks (median: 103 weeks, range: 26 – 160 weeks).

Conclusions
Cutaneous allodynia is a risk factor for migraine chronification and may warrant preventive treatment strategies.

Introduction

Cutaneous allodynia, the perception of pain in response to non-noxious stimuli to the normal skin, is a common feature accompanying migraine attacks. Migraine patients experience an increased sensitivity of the skin for common daily activities during attacks, such as combing of hair, taking a shower, touching the periorbital skin, shaving, or wearing earrings during migraine attacks. (1, 2) Prevalence estimates of allodynia in migraine patients range from 50 to 80%. (3)

Three distinct forms of allodynia have been described: thermal, static mechanical and dynamic mechanical allodynia. (4) Furthermore, a distinction between cranial and extra-cranial allodynia can be made. Allodynia is a marker for sensitization of nociceptive neurons in the trigeminal nucleus caudalis, which receive convergent input from the dura mater and the peri-orbital skin. (5) During a migraine attack, central sensitization of trigeminal neurons is elicited by persistent pain through activation of meningeal perivascular pain fibers. As a result of this sensitization, non-noxious stimuli of the peri-orbital skin are perceived as painful. Allodynia is a hallmark for success rate of acute headache medication treatment, because the success rate of rendering migraine patients pain-free increases dramatically if medication is taken before the establishment of allodynia and central sensitization. (6) Factors that have been reported to increase the likelihood of having allodynia during migraine attacks are: female gender, high Body Mass Index, headache specific features such as a low age at onset, high frequency of attacks, and comorbidity with depression and anxiety. (1, 2, 7-10) Extensive evidence is available on the comorbidity of migraine with depression, suggesting associations between migraine chronification, depression and medication overuse. (11-13) Because allodynia may be involved in these associations we evaluated the specific relationship between allodynia, depression and total migraine days in a large well-defined, web-based population of migraine patients. (14) This is the first study to assess if allodynia is an independent predictor of (i) migraine chronification (increase of the average number of migraine days per month) and (ii) overuse of acute headache medication.

Methods

Study design and population

Our study was conducted as a part of the LUMINA project, the details of which are reported elsewhere. (15) Participants were Dutch adults aged 18 to 74 years with migraine with or without aura according to the International Classification of Headache Disorders (ICHD-II) criteria. Our LUMINA study population was recruited via a dedicated, nation-wide website inviting migraineurs to participate

in migraine research. In addition, patients attending our dedicated headache clinic were also invited to participate in this survey. This group, however, comprises only 3.5% of the total LUMINA population. On the website, patients were asked to fill out a screening questionnaire that has been validated previously. (16) Firstly, if patients fulfilled the screening criteria, they were sent a web-based extended migraine questionnaire, based on the ICHD-II criteria. (15, 17) This questionnaire was validated before by performing a semi-structured telephone interview in 1038 patients who had filled out the extended migraine questionnaire. (15) The specificity of the questionnaire was 0.95. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, acute and prophylactic headache medication use, migraine attack frequency and migraine days, and allodynia. Participants without the needed internet skills were able to fill out the questionnaires on paper.

Secondly, all applicable migraine patients (n=3029) were selected for a web-based questionnaire on symptoms of (lifetime) depression. This depression questionnaire consisted of the Hospital Anxiety and Depression Scale (HADS-D), the Centre for Epidemiologic Studies Depression Scale (CES-D) and additional questions on lifetime depression: 'Have you ever used anti-depressants with as indication depression?' and 'Have you ever been diagnosed with a depression'? (18, 19) Only after having filled out the complete depression questionnaire, patients were enrolled in this study.

Thirdly, a questionnaire was sent to a large subset of participants for follow-up details on migraine days (defined as number of migraine headache days per month) and medication use. This allowed us to perform a longitudinal analysis on migraine days. Questions on demographic factors were part of this questionnaire. For the longitudinal analysis on migraine days only participants with a follow-up time of more than 6 months were selected (mean 93 ± 30 weeks, median 103 weeks, range: 26 – 160 weeks).

This LUMINA project was approved by the medical ethics committee of the Leiden University Medical Centre. All subjects provided written informed consent prior to the study.

Measurements

The extended migraine questionnaire included a 12-item questionnaire on symptoms of cutaneous allodynia (CA). These 12 items were similar to the items of the validated Allodynia Symptom Checklist (ASC). (2) CA was measured as a continuous variable, counting up the scores of all 12 allodynia items for each patient. Herewith "yes" was scored as 1, and "no", "not applicable" and "unknown" were scored as 0. Secondly, based on this continuous scale, we divided CA into

2 categorical classes, in concordance with the ASC. (2) Migraine patients were scored as allodynic when answering "yes" on ≥ 2 CA items. Exploratory cluster analysis was performed to determine whether the 12 items would fit in the known CA subgroups: thermal, static mechanic and dynamic mechanic. The analysis showed the expected clustering of i) resting the head on a pillow, exposure to heat and exposure to cold (thermal allodynia); ii) taking a shower, shaving the face and combing the hair (dynamic mechanic allodynia); iii) wearing contact lenses, wearing glasses, wearing a pony tail, wearing tight clothes, wearing earrings and wearing a necklace (static mechanic allodynia). This confirmed that our questionnaire, which was adapted from the ASC, covered well the construct of CA. Lifetime depression was measured as a dichotomous variable. We used validated cut-off scores, in combination with a previously used and published algorithm for depression and an additional question on lifetime depression: (Lifetime Depression = HADS-D ≥ 8 *OR* CES-D ≥ 16 *OR* use of antidepressants (with indication depression) *OR* diagnosis depression). (18-20) Although the HADS-D (depression subscale of the HADS) and CESD questionnaires focused only on the previous two weeks, we aimed to reliably measure lifetime depression by adding questions on antidepressant use and depression diagnoses. Validation of the depression diagnoses by performing a telephonic Composite International Diagnostic Interview (CIDI) in a subset of 102 randomly selected patients showed a sensitivity of 78% and a specificity of 64%. (21)

At baseline, we measured migraine frequency in two ways: number of migraine attacks and number of migraine days. For both we used five frequency classes, ranging from '1-2 per year' to 'more than 54 per year'. On follow-up we only assessed number of migraine days as continuous variable. We did this for two reasons: 1) definition of CM is arbitrary with cut off values of ≥ 15 headache days and ≥ 8 days migraine, 2) for purposes of statistical power (increased power when using continuous outcome measurement). (22) To assess change in migraine days over the follow-up period, we transformed the frequency classes at baseline into a continuous variable by using for each bracket the mean number of migraine days (i.e. 1-2 days per year -> 1,5 day per year). This was subtracted from the number of migraine days at follow up to obtain a continuous variable for change in number of migraine days per month.

In the follow-up measurement, patients were asked to fill in the number of days on which they had taken acute migraine medications like triptans and painkillers such as simple analgesics or NSAIDs for headache during the past 3 months.

Data analysis and statistics

Baseline characteristics were reported as mean ± standard deviations (SD) or percentages. Differences in means between groups were tested with

independent samples *t*-tests. Differences in proportions were tested using x^2 tests. Multivariate logistic regression models were used to test the association between CA and the following determinants: gender, age, BMI, age at onset of migraine, migraine subtype, the use of prophylactics, migraine attack frequency (categorical) and depression. Supplementary analysis was performed with migraine duration as substitute for age at onset. Results were reported as odds ratios with 95% confidence intervals (CI) and corresponding *p*-values. To test whether the association with migraine attack frequency differed between patients using prophylactics and patients not using prophylactics, the interaction between migraine attack frequency and prophylactics was added. To test whether the associations between CA and depression differed between males and females, the interaction between depression and gender was added.

Determinants of migraine days and number of medication days at follow-up were investigated using univariate and multivariate linear regression models. Because of the expected left-skewed distribution of migraine days, we used a log-transformation of this measure to prevent a skewed distribution of the residuals in the model. Determinants of change in migraine days were investigated using a multivariate linear regression model. For all models the following covariates were included: gender, age, BMI, age at onset of migraine, allodynia, migraine subtype, use of prophylactics, number of migraine days at baseline (categorical), depression and time of follow-up. Supplementary analyses were performed with migraine duration as substitute for age at onset. Results were reported as log-transformed regression coefficients (exp(B)) with 95% CI's, standardized regression coefficients (Beta) and corresponding *p*-values.

For all analyses *p*-values < 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS 17.0 (SPSS inc., IBM, USA).

Results

The total study flow is shown in figures 1 and 2. Of 3029 migraine patients who were sent depression questionnaires, 2331 (77.0%) were suitable for primary analysis. Participating (n=2331) versus non-participating (n=698) migraine patients were slightly older (42.8 vs. 39.6 years, $p<0.001$) but did not significantly differ in gender or migraine subtype. A total of 1992 (65.8%) migraine patients were suitable for secondary analysis. Participating (n=1992) versus non-participating (n=1037) patients were again slightly older (43.0 vs. 40.4 years, $p<0.001$) but did not significantly differ in gender or migraine subtype. Table 1 displays all baseline characteristics of the sample suitable for primary analysis, divided by the presence of CA. 1,624 migraine patients (69.7%) suffered from CA during migraine attacks. Of 2331 migraine patients 1423 (61.0%) had migraine without aura, being equally

divided over the groups with and without allodynia. Migraine patients with CA were more often females, had lower age at onset, longer disease duration, higher migraine attack frequency, used more often prophylactic agents, and had more lifetime depression (table 1).

In the first part of the analyses, determinants of allodynia were examined in a multivariate logistic regression analysis (table 2). The following determinants were significantly associated with CA: i) female gender, OR = 2.98 (95% CI 2.33-3.82); ii) lower age at onset, OR = 0.98 per year (95% CI 0.97-0.99); iii) longer migraine duration, OR = 1.02 per year (95% CI 1.01-1.03) iv) higher migraine attack frequency (for individual OR's of all contrasts see table 2); and v) lifetime depression, OR = 1.52 (95% CI 1.26-1.84). Interaction terms migraine attack frequency*prophylactics and lifetime depression*gender were not significant; final analyses were run without interaction terms.

In the follow-up study, associations between CA at baseline and the (log-transformed) number of migraine days at follow-up, with adjustment for several covariates were studied (table 3). The model showed that the following parameters were independent, statistically significant predictors for the number of migraine days at follow-up: i) having CA ($p<0.001$); ii) low age at onset ($p=0.03$); iii) higher migraine duration ($p=0.03$); iv) having migraine without aura ($p=0.008$); v) higher baseline number of migraine days (for individual p-values of all contrasts see table 3); and vi) having lifetime depression ($p<0.001$).

We studied the association between CA at baseline and the change in number of migraine days at follow up (mean duration of follow-up time was 93 ± 30 weeks, median: 103 weeks, range: 26 – 160 weeks). Table 4 presents multivariate linear associations between CA at baseline and the change in migraine days at follow-up, with adjustment for several covariates. The model showed that the following parameters were independent, statistically significant predictors of an increase in migraine days: i) having CA ($p<0.001$); ii) lower age at onset ($p=0.01$); iii) higher migraine duration ($p=0.01$); iv) using prophylactics ($p=0.05$); v) having a depression ($p=0.001$).

The association between CA at baseline and the (log-transformed) number of medication days at follow-up with adjustment for covariates are shown in table 5. The model showed that the following parameters were independent, statistically significant predictors for the number of medication days at follow-up: i) having CA ($p=0.002$); ii) low age at onset, ($p=0.002$); iii) higher migraine duration, ($p=0.002$); iv) using prophylactics, ($p<0.001$); v) higher baseline number of migraine days (for individual p-values for all contrasts see table 5); and vi) having a lifetime depression ($p<0.001$).

Discussion

This is the first longitudinal study demonstrating that cutaneous allodynia is an independent predictor of migraine chronification. Furthermore, we found independent associations of allodynia with several migraine specific determinants. Migraine patients are at increased risk of depression, and shared genetic factors may underlie this association. (20, 23) Comorbid depression is an important predictor of substance dependence and is very common in chronic migraine patients, in particular in those with overuse of acute headache medication. (24, 25) Thus a triad between migraine chronification, depression and medication overuse is suggested. (11-13) In this triad, cutaneous allodynia (CA) plays a role. Our data show that depression and high migraine attack frequency (as a marker of chronification) are independently associated with CA. We hypothesized that recurrent migraine with CA lead to a decreased threshold for subsequent migraine attacks. This statement is supported by the following findings: i) the association between CA and high migraine frequency (measured as migraine attack frequency in the cross-sectional part of the study and measured as migraine days in the longitudinal part of the study); ii) the association between low age at onset and CA; and iii) longer migraine duration is associated with CA in the same magnitude as low age at onset.

The clinical findings from this study correspond with the pathophysiological mechanism of CA. The underlying mechanism of migraine and allodynia is activation of the trigeminovascular neurons. (26) The activation of the trigeminovascular pathway contributes: i) to the headache phase of the migraine attack by sensitization of peripheral trigeminovascular neurons innervating the meninges; ii) to the cephalic allodynia by sensitization of second-order neurons in the spinal trigeminal nucleus (in the medullary dorsal horn) that receive input form the meninges, scalp and facial skin; and iii) to the development of extracephalic allodynia by third-order neurons in the posterior thalamic nuclei which receive input form meninges, facial and body skin. (26) Importantly, once established, sensitization of second order trigeminovascular neurons becomes activity independent, and maintains itself in the absence of sensory input later on. (26) The activity-independent form is the consequence of neurotransmitter and neuromodulator induced activation of multiple intracellular signaling pathways. Activity-independent sensitization develops slowly over several hours and lasts for a prolonged period of time. (27) This has important clinical implications, as late treatment with triptans during an attack is unsuccessful when this independent activity has occurred. (6) Finding out which critical thresholds are exceeded before central sensitization occurs will potentially lead to new medications preventing sensitization. Analyses of differences in brain structure and function, biochemical markers, and genetic profiles between migraine patients with and without CA will further enlighten the basic mechanisms behind CA, migraine chronification and depression.

A possible explanation for the association between CA and migraine frequency may be that repetitive activation of trigeminovascular neurons and consequently repetitive activation of modulatory pain pathways involving the periaqueductal gray may lead to impairment of function or neuronal cell damage in the periaqueductal gray (involved with migraine modulation) or eventually in other areas involved in migraine generation, thus leading to chronification of migraine. (1, 3) Another concept is that of nociception-induced plasticity, which has been demonstrated in animal experiments in the somatosenory cortex, thalamus, trigeminal brainstem neurons, and the cortico-limbic pathway. (28) This model suggests that kindling and related models of neuroplasticity can be used to describe ways in which exposure to a noxious stimulus may, under certain conditions, lead to a sensitized state, and to chronification of pain.

Triptan induced allodynia has been studied in rats, proposing a biological mechanism between increased frequency of headache following triptan use. (29) However, there is no evidence for this phenomenon in humans. In our study, there was no association between triptan use and allodynia (OR 1.07, 95% CI 0.87 – 1.35). The potential role of hormonal use has not been investigated in this study.

Our study did not aim to define subjects as chronic migraineurs or episodic migraineurs. We measured the increase in the number of migraine days, as a marker of chronification. We did this for two reasons: 1) definition of CM is arbitrary with cut off values of ≥ 15 headache days and ≥ 8 days migraine, 2) for purposes of statistical power (increased power when using continuous outcome measurement). (22) We measured the average number of migraine attacks in the baseline measurement, whereas each migraine attack represents one occurrence of allodynia, independent from the duration of the attack.

The strengths of this study are the large sample size, the well-defined migraine status and detailed information on allodynia and depression characteristics. Most importantly, this is the first longitudinal study demonstrating that allodynia is a risk factor for migraine chronification. Possible limitations include the fact that our population might be younger and higher educated than the migraine population in general due to the recruitment of patients via the internet. However, we tried to limit this effect by enabling participants to fill out the questionnaires on paper. A minimum follow up of 6 months was chosen for pragmatic reasons to allow for sufficient statistical power. The median follow-up duration was 103 weeks, indicating that 50% of the study population had a follow up of two years or longer. In addition, one third had a follow up between one and two years, and 11% of subjects had a follow up of 6-12 months.

Although we previously described the LUMINA population as a clinical based cohort, we now feel that it is better to describe it as a 'well-defined, web-based

migraine population'. In our population 70% used triptans. Compared to other countries this may seem high but in the Netherlands and some Scandinavian countries the use of triptans in population based studies is amongst the highest. Furthermore, 87% was previously diagnosed with migraine by a physician, 26% is currently seen by a neurologist, 43% by a GP. The remaining 31% is not seen by a neurologist or a GP.

In conclusion, we found a longitudinal association between cutaneous allodynia and the number of migraine days. Secondly, we confirmed the association between allodynia and depression in the largest well-defined sample of migraine patients so far. In clinical practice, awareness that patients with migraine are at increased risk of chronification, especially when they suffer from a high migraine frequency, allodynia, medication overuse and depression is warranted. Future research should further elucidate these relationships and focus on prevention of allodynia, thereby protecting migraine patients from chronification.

Tables

Table 1. Baseline characteristics of migraine patients who suffer from allodynia (n=1624) versus migraine patients without allodynia (n=707).

	Total population n=2331	Allodynia n=1624	No allodynia n=707	p
Female	1994 (85.5%)	1461 (90.0%)	533 (75.4%)	**<0.001**
Age (years)	42.8 ± 11.4	42.7 ± 11.3	43.3 ± 11.7	0.23
BMI (kg/m^2)	24.5 ± 4.0	24.5 ± 4.1	24.6 ± 4.0	0.54
Age at onset migraine	19.4 ± 10.6	18.7 ± 10.2	20.8 ± 11.2	**<0.001**
Migraine without aura	1423 (61.0%)	991 (61.0%)	432 (61.1%)	0.97
Uses a triptan	1663 (71.3%)	1191 (73.4%)	472 (66.8%)	**0.001**
Uses migraine prophylaxis	875 (37.5%)	650 (40.0%)	225 (31.8%)	**0.001**
Migraine duration (years)	23.5 ± 13.0	23.9 ± 12.6	22.4 ± 13.7	**0.01**
Migraine attack frequency				**<0.001**
(attacks per year)*	98 (4.2%)	50 (3.1%)	48 (6.8%)	
1-2	322 (13.8%)	204 (12.6%)	118 (16.7%)	
3-6	709 (30.4%)	493 (30.4%)	216 (30.6%)	
7-12	991 (42.5%)	713 (43.9%)	276 (39.0%)	
13-54	213 (9.1%)	164 (10.1%)	49 (6.9%)	
more than 54				**<0.001**
Migraine days (per year)*	119 (5.1%)	76 (4.1%)	43 (6.1%)	
1-2	226 (9.7%)	134 (8.3%)	92 (13.0%)	
3-6	401 (17.2%)	269 (16.6%)	132 (18.7%)	
7-12	1060 (45.5%)	745 (45.9%)	315 (44.6%)	
13-54	525 (22.5%)	400 (24.6%)	125 (17.7%)	
more than 54				
Lifetime depression (% yes)	1036 (44.4%)	780 (48.0%)	256 (36.2%)	**<0.001**

Values are the absolute numbers with corresponding % or means ± SD. *P*-values depicted in bold indicate significant differences ($p<0.05$), using independent-samples t-tests and x^2 tests appropriately.
BMI: Body Mass Index

*Migraine attack frequency and number of migraine days per year were self-reported estimates. Few (n=21) patients reported more than one attack on one day, probably because migraine recurrences were counted as new attacks.

Table 2: Logistic associations between allodynia and possible determinants in 2331 participants with migraine.

	Odds Ratio	95% CI	*p*
Gender (F vs. M)	**2.98**	**2.33 - 3.82**	**<0.001**
Age (years)	1.01	1.00 - 1.02	0.17
BMI (kg/m^2)	1.00	0.98 - 1.02	0.84
Age at onset migraine (years)	**0.98**	**0.97 - 0.99**	**<0.001**
Migraine subtype (MA vs. MO)	1.06	0.87 - 1.27	0.61
Prophylactics (yes vs. no)	1.18	0.96 - 1.44	0.11
Migraine duration *	***1.02***	**1.01 - 1.03**	**<0.001**
Migraine frequency (attacks per year)			
3-6 vs. 1-2	**1.64**	**1.03 - 2.63**	**0.04**
7-12 vs. 1-2	**2.12**	**1.37 - 3.29**	**0.001**
13-54 vs. 1-2	**2.24**	**1.45 - 3.47**	**<0.001**
more than 54 vs. 1-2	**2.88**	**1.69 - 4.92**	**<0.001**
Depression (yes vs. no)	**1.52**	**1.26 - 1.84**	**<0.001**

Data are odds ratios (multivariate, adjusted for all mentioned covariates) with 95% confidence intervals and *p*-values. Values depicted in bold indicate significant findings. For further description of adjustments, see methods. Interaction terms migraine frequency*prophylactics and lifetime depression*gender were not significant; the final analyses were run without interaction terms. In the baseline measurement the number of migraine attacks was measured.
F: Female; M: Male; BMI: Body Mass Index; MO: Migraine without aura; MA: Migraine with aura

* *Migraine duration* was added in a different model, substituting 'age at onset'

Table 3: Linear associations between baseline migraine characteristics and the natural logarithm of migraine days at follow-up in 1992 persons with migraine (follow-up time > ½ year)

	1. Univariate exp(B)	95% CI	Beta	*p*	2. Multivariate exp(B)	95% CI	Beta	*p*
Allodynia (yes vs. no)	**1.32**	**1.23 - 1.43**	***0.157***	**<0.001**	**1.20**	**1.12 - 1.29**	**0.103**	**<0.001**
Gender (F vs. M)	**1.13**	**1.02 - 1.26**	**0.053**	**0.02**	1.00	0.90 - 1.10	-0.002	0.91
Age (years)	1.00	1.00 - 1.01	0.032	0.15	1.00	1.00 - 1.00	0.020	0.36
BMI (kg/m^2)	1.00	1.00 - 1.01	0.021	0.35	1.00	1.00 - 1.01	0.020	0.31
Age at onset (years)	1.00	0.99 - 1.00	-0.041	0.07	**1.00**	**0.99 - 1.00**	**-0.045**	**0.03**
*Migraine duration**	**1.00**	***1.00 - 1.01***	***0.061***	***0.01***	***1.00***	***1.00 - 1.01***	***0.055***	***0.03***
Migraine subtype (MO vs. MA)	**1.20**	**1.12 - 1.29**	**0.108**	**<0.001**	***1.09***	**1.02 - 1.17**	**0.054**	**0.008**
Prophylactics (yes vs. no)	***1.32***	**1.23 - 1.42**	**0.162**	**<0.001**	1.06	0.99 - 1.14	0.034	0.10
Baseline number of migraine days								
3-6 vs. 1-2 per year	1.14	0.96 - 1.35	0.048	0.14	1.14	0.97 - 1.36	0.050	0.12
7-12 vs. 1-2 per year	**1.57**	**1.34 - 1.84**	**0.208**	**<0.001**	**1.53**	**1.31 - 1.79**	**0.197**	**<0.001**
13-54 vs. 1-2 per year	**2.14**	**1.85 - 2.47**	**0.459**	**<0.001**	**2.03**	**1.75 - 2.34**	**0.426**	**<0.001**
> 54 vs. 1-2 per year	**3.50**	**3.00 - 4.08**	**0.623**	**<0.001**	**3.16**	**2.70 - 3.69**	**0.572**	**<0.001**
Depression (yes vs. no)	**3.94**	**2.55 - 6.07**	**0.138**	**<0.001**	**1.13**	**1.06 - 1.21**	**0.073**	**<0.001**
Follow-up time (years)	**0.86**	**0.80 - 0.92**	**-0.101**	**<0.001**	0.97	0.91 - 1.03	-0.021	0.31
Constant	.	.	.	.	**1.54**	**1.12 - 2.12**	.	**0.008**

Data are log transformed regression coefficients (exp(B)) with 95% confidence intervals, standardized regression coefficients (Beta) and *p*-values. Values depicted in bold indicate significant findings. For further description of adjustments, see Methods. For the follow-up measurement the number of migraine days was measured.
BMI: Body Mass Index; MO: Migraine without aura; MA: Migraine with aura

**Migraine duration* was added in a different model, substituting 'age at onset'

Table 4: Linear associations between baseline characteristics and the difference in migraine days between baseline and follow-up in 1992 persons with migraine.

Variable	1. Multivariate B	95% CI	Beta	*p*
Allodynia (yes vs. no)	**11.12**	5.87 - 16.37	**0.07**	**<0.001**
Gender (F vs. M)	-3.06	-10.07 - 3.95	-0.01	0.39
Age (years)	**0.22**	**0.002 - 0.45**	**0.03**	**0.05**
BMI (kg/m^2)	0.46	-0.13 - 1.04	0.02	0.13
Age at onset (years)	**-0.30**	-0.54 - -0.06	**-0.04**	**0.01**
*Migraine duration **	***0.30***	0.06 - 0.54	***0.05***	***0.01***
Migraine diagnosis (MO vs. MA)	3.73	-1.15 - 8.62	0.02	0.13
Prophylactics (yes vs. no)	**5.07**	0.01 - 10.13	**0.03**	**0.05**
Baseline number of migraine days				
3-6 vs. 1-2 per year	-0.24	-12.55 - 12.07	-0.001	0.97
7-12 vs. 1-2 per year	5.36	-6.05 - 16.77	0.03	0.36
13-54 vs. 1-2 per year	-2.17	-12.83 - 8.49	-0.01	0.69
> 54 vs. 1-2 per year	**-137.31**	-148.80 - -125.83	**-0.74**	**<0.001**
Depression (yes vs. no)	**7.99**	3.19 - 12.78	**0.05**	**0.001**
Follow-up time (years)	-2.16	-6.65 - 2.33	-0.02	0.35
Constant	-1.12	-24.51 - 22.28	.	0.93

Data are regression coefficients (B) with 95% confidence intervals, standardized regression coefficients (Beta) and *p*-values. Values depicted in bold indicate significant findings. For further description of adjustments, see Methods. Interaction terms allodynia*prophylactics and allodynia*depression were not significant. Final analyses were run without interaction terms. For the follow-up measurement the number of migraine days was measured.
BMI: Body Mass Index; MO: Migraine without aura; MA: Migraine with aura

*Migraine duration was added in a different model, substituting 'age at onset'

Table 5: Linear associations between baseline migraine characteristics and the natural logarithm of number of headache medication use days at follow-up in 1992 persons with migraine (follow-up time > ½ year)

Variable	1. Univariate exp(B)	95% CI	Beta	*p*	2. Multivariate exp(B)	95% CI	Beta	*p*
Allodynia (yes vs. no)	**1.29**	**1.18 - 1.40**	**0.124**	**<0.001**	**1.15**	**1.05 - 1.25**	**0.067**	**0.002**
Gender (F vs. M)	**1.23**	**1.09 - 1.38**	**0.077**	**0.001**	1.11	0.99 - 1.25	0.040	0.07
Age (years)	1.00	1.00 - 1.01	0.020	0.37	1.00	1.00 - 1.01	0.025	0.29
BMI (kg/m^2)	1.01	1.00 - 1.02	0.043	0.06	1.01	1.00 - 1.02	0.041	0.06
Age at onset (years)	**0.99**	**0.99 - 1.00**	**-0.067**	**0.003**	**0.99**	**0.99 - 1.00**	**-0.070**	**0.002**
*Migraine duration **	***1.01***	**1.00 - *1.01***	***0.071***	**0.001**	**1.01**	***1.00 - 1.01***	***0.087***	***0.002***
Migraine diagnosis (MO vs. MA)	**1.10**	**1.02 - 1.20**	**0.052**	**0.02**	1.04	0.96 - 1.13	0.022	0.31
Prophylactics (yes vs. no)	**1.41**	**1.30 - 1.53**	**0.177**	**<0.001**	**1.19**	**1.10 - 1.30**	**0.092**	**<0.001**
Baseline number of migraine days								
3-6 vs. 1-2 per year	1.08	0.76 - 1.14	-0.024	0.48	0.94	0.77 - 1.15	-0.019	0.57
7-12 vs. 1-2 per year	**1.29**	**1.06 - 1.56**	**0.103**	**0.01**	**1.27**	**1.05 - 1.53**	**0.097**	**0.01**
13-54 vs. 1-2 per year	**1.65**	**1.38 - 1.97**	**0.267**	**<0.001**	**1.58**	**1.31 - 1.86**	**0.237**	**<0.001**
> 54 vs. 1-2 per year	**2.33**	**1.93 - 2.80**	**0.371**	**<0.001**	**2.06**	**1.70 - 2.49**	**0.317**	**<0.001**
Depression (yes vs. no)	**1.28**	**1.18 - 1.39**	**0.130**	**<0.001**	**1.16**	**1.07 - 1.25**	**0.078**	**<0.001**
Follow-up time (years)	0.94	0.87 - 1.02	-0.035	0.121	1.03	0.96 - 1.11	0.018	0.42
Constant	.	.	.	.	**1.80**	**1.22 - 2.64**	.	**0.003**

Data are log transformed regression coefficients (exp(B)) with 95% confidence intervals, standardized regression coefficients (Beta) and *p*-values. Values depicted in bold indicate significant findings. For further description of adjustments, see Methods. BMI: Body Mass Index; MO: Migraine without aura; MA: Migraine with aura

*Migraine duration was added in a different model, substituting 'age at onset'

Figures

Figure 1: Study flow primary analysis

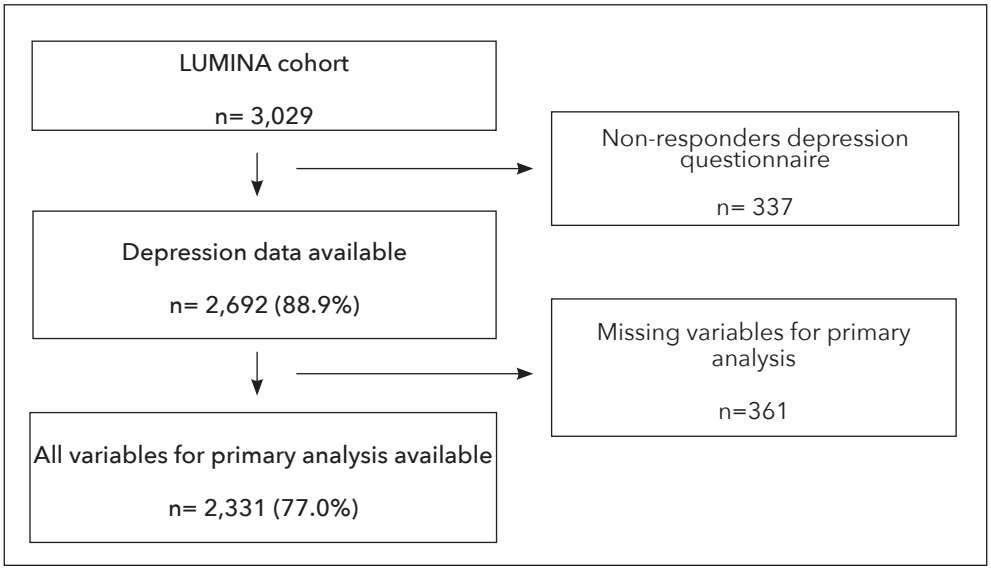
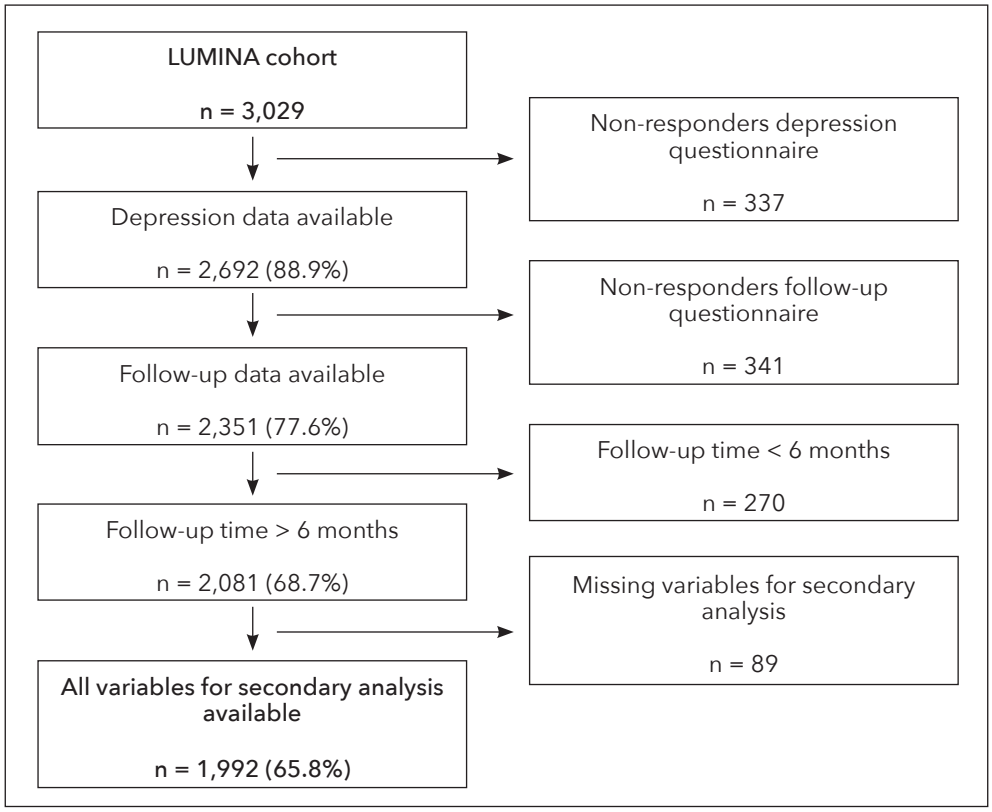


Figure 2: Study flow secondary analyses



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