# The onset of the migraine attack

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# Chapter 3.

# Chronotypes and circadian timing in migraine

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## Abstract

### Background
It has been suggested that migraine attacks strike according to circadian patterns, and that this might be related to individual chronotype. Here we evaluated and correlated individual chronotypes, stability of the circadian rhythm, and circadian attack timing in a large and well-characterized migraine population.

### Methods
In 2,875 migraine patients and 200 non-headache controls we assessed differences in: (i) distribution of chronotypes, (Münich Chronotype Questionnaire); (ii) the circadian rhythm's amplitude and stability, (Circadian Type Inventory); and (iii) circadian timing of migraine attacks. Data were analysed using multinomial and linear regression models adjusted for age, gender, sleep quality and depression.

### Results
Migraineurs more often showed an early chronotype compared to controls (48.9% vs. 38.6%; adjusted OR 2.42 95% C.I. 1.58-3.69; $p$<0.001); as well as a late chronotype (37.7 vs 38.0%; adjusted OR 1.69 (95% C.I.: 1.10-2.61; $p$=0.016). Migraineurs, particularly those with high attack frequency, were more tired after changes in circadian rhythm (i.e. more languid; $p$<0.001) and coped less well with being active at unusual hours (i.e. more rigid; $p$<0.001) than controls. 961/2,389 (40.2 %) migraineurs reported early morning attack onset.

### Conclusion
Migraine patients are less prone to be of a normal chronotype than controls. They are more languid and more rigid when changes in circadian rhythm occur. Most migraine attacks begin in the early morning. These data suggest that chronobiological mechanisms play a role in migraine pathophysiology.

## Introduction

Several studies have suggested that migraine attacks show seasonal and circadian periodicity with attacks more likely to occur in the early morning, implicating chronobiological mechanisms in attack triggering and initiation [1-3]. Candidate mechanisms include those involved in (i) the later stages of the sleep cycle and/or the sleep/wake transition; (ii) various intrinsic circadian cycles and (iii) mechanisms functioning as *zeitgebers*, environmental signals such as the light modulating the biological clock [1-3].

Chronotype refers to an individual's endogenous circadian clock rhythm and how it synchronizes (entrains) to the 24h day. Chronotypes depend on sex, age, genetic and environmental factors [4], and are distributed normally in a given population. Some are very late (evening) people ('owls') while others are very early (morning) people ('larks') [5]. Early and late chronotypes have been associated several diseases. Early chronotypes have been associated with depression [6] and epilepsy [7], paroxysmal brain disorders with strong bidirectional comorbidity with migraine [8]. Late chronotypes have been associated with suicide attempts [9] and bipolar disorder [10], psychiatric disorders showing unidirectional comorbidity with migraine [9, 11]. Only a few small studies have investigated chronotype and migraine, with inconsistent results [2, 12]. Whether early or late chronotypes are associated with specific circadian timings of the onset of migraine attacks is unknown. Besides circadian phase (i.e. chronotype), low amplitude and high flexibility of circadian rhythm enable better coping with changes in sleep/wake pattern [13].

The present study has three aims. First, to analyse chronotypes in a large and well-defined migraine population. Second, to assess circadian rhythm amplitude and stability in relation to migraine. Finally, to study whether chronotype and circadian timing of migraine attacks are associated.

## Material and methods

### Subjects

Our study was conducted as a part of the Leiden University Medical Center Migraine Neuro Analysis (LUMINA) programme [14]. Participants were Dutch adults aged 18 to 74 years of age, both migraine patients and healthy controls. Patients with migraine with and without aura fulfilled the International Classification of Headache Disorders (ICHD-3b) criteria [15]. Controls did not suffer from migraine, cluster headache, chronic tension type headache or medication overuse headache. Both migraine patients and controls were recruited via public announcement, advertising in lay press and via the research website, and were considered eligible after a two-step inclusion process using validated questionnaires (see Supplementary Text 1 for details).

### Respondents and non-respondents in this study

Eligible subjects (both migraine patients and non-headache controls) within the LUMINA study were sent an invitation to participate in this study into chronotype by e-mail. A

reminder was sent twice. Subjects not having participated after two reminders were considered non-respondents. Baseline and demographic data of the non-respondents were available in the LUMINA study.

## Standard protocol approvals, registrations and patient consents

The study had been approved by the local medical ethics committee. All subjects provided written informed consent prior to the procedure.

## Design

In this observational and cross-sectional study, eligible subjects were sent an invitation to a digital questionnaire on sleep habits and sleeping problems. This included questions on phase, rhythm and stability of circadian chronotype as well as items on circadian timing of migraine attack onset. Questionnaires were filled out between September 2010 and September 2011. Non-responders were reminded twice per e-mail, and once per telephone.

## Chronotype assessment

*Circadian chronotype phase*

Chronotype was assessed using a Dutch translation of the Munich Chronotype Questionnaire (MCTQ)[16,17]. The MCTQ obtains one's subjective self-reported chronotype (early, normal, or late). From the MCTQ, the 'timing of mid sleep on free days' is calculated. This timing is an objective measure of chronotype derived from the timing of mid-sleep on free days (MSF), the point of time exactly in the middle of the total sleep time on free days (individual sleep timing and duration are independent traits). For participants who indicated they were on shift-work at the moment of filling the questionnaire, additional questions on timing of sleep, going to bed etc. - separately for each of the different shifts - were visible and obliged to fill out. At the moment of our study the specific MCTQ that is validated for shift work[18] was not yet available.

*Chronotype, sleep duration, age and gender*

Both sleep duration and sleep timing on free days are influenced by the sleep-debt accumulated over the workweek[17]. These parameters were therefore corrected for the confounding effect of sleep-debt during the workweek, which were used in the analyses[17]. Analyses between migraineurs and controls were adjusted for gender and age, given its age and gender-dependency[17].

*Circadian rhythm amplitude and stability*

Amplitude and stability were assessed using the Circadian Type Inventory, a scale measuring individual capabilities and preferences regarding changes in sleep pattern[19]. The scale consists of two subscales. The languid-vigour scale reflects the individual capability to recover from a change in sleep-pattern and is linked to the amplitude of the circadian rhythm. The flexible-rigid scale reflects preferences regarding sleep pattern and is linked to the rhythm's stability. Each subscale contains 15 items, with 5 answer options (ranging from 1: 'practically never' to 5: 'practically always'), and total scores range from 15-75 per subscale. A higher score on languid-vigour indicates that an individual is more tired after changes in circadian rhythm (i.e. more languid: difficulty to overcome drowsiness and lethargy after

reduced sleep). A lower score on flexible-rigid indicates that an individual is coping less with being active or sleep at unusual hours (i.e. less flexible, more rigid).

### Circadian timing of attack onset

Migraineurs were asked to indicate on what time of the day attacks usually started, in 6 hour intervals (0.00-6.00 a.m.; 6.00-12.00 a.m.; 12.00-6.00 p.m.; 6.00-12.00 p.m.; or "can not indicate"). If 6-hour intervals were indicated, patients were asked to be more precise in 2-hour intervals, if possible.

### Migraine characteristics, demographics, data on sleep quality and depression

Within the LUMINA cohort, data on migraine characteristics were available. Of both migraineurs and controls demographics, data on intoxications, sleep medication and sleep data (Pittsburgh Sleep Quality Index; range 0-21, with score >5 indicative for poor sleep quality [20]) were collected. For depression, data from the HADS questionnaire [21] (Hospital Anxiety and Depression Scale with Anxiety and Depression subscales; total range 0-42, with HADS-D score ≥8 indicative for depression), CES-D (the Center for Epidemiologic Studies Depression scale; total range 0-60, CES-D>16 indicative for depression [22]), and a combined life-time depression algorithm [8] (HADS-D≥8 or CES-D>16 or physician-made diagnosis of depression or use of antidepressants with indication of depression) were used [23].

### Statistics

General characteristics were compared between migraineurs and controls using Student's t-tests for continuous variables, and Chi square tests for categorical data. To assess differences in chronotypes between patients and controls chi square tests and multinomial regression analyses were performed with chronotype as dependent variable (levels: early, normal, and late chronotype), adjusted for age and gender, and additionally for sleep quality and HADS depression score and shift work. Midsleep on free days corrected for sleep debt (MSFsc) was compared between patients and controls using a linear regression model, adjusted for age and gender. Continuous data on circadian rhythm's stability and amplitude were analysed using linear regression models (to identify determinants). The relationship between circadian timing of attack onset and chronotype was also assessed using Chi square tests and multinomial regression analyses. All data analyses were performed using SPSS 17.0 (SPSS inc., IBM, USA), with the statistical threshold at $p<0.05$.

## Results

### Study population

Questionnaires were sent to 2,875 migraineurs and 200 headache free controls. The total response was 2,578 (83.8%): 2,389 (83.1%) for migraineurs and 189 (94.5%) for controls. The characteristics are summarised in Table 1.

### Confounders

Compared to controls, migraineurs more frequently were female, had a lower educational level, and had a slightly higher body mass index (BMI). They consumed less units of alcohol

per week, had higher total scores on the Pittsburgh Sleep Quality Index and Hospital Anxiety and Depression Scale -Depression subscale (HADS-D), as well as a higher prevalence of life-time depression.

**Table 1. Baseline characteristics of study population**. Baseline characteristics of migraineurs (n=2,389) and non-headache controls (n=189). *p*-values depicted in bold indicate significant differences ($p<0.05$), using independent-samples t-tests and $\chi^2$ tests where appropriate. Y = years; F = female; BMI = body mass index; SD = standard deviation; PSQI = Pittsburgh Sleep Quality; HADS-D = Hospital Anxiety and Depression Scale, Depression sub-scale.

| Variable | Total (n=2,578) | Migraineurs (n=2,389) | Controls (n=189) | *p* |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age y, mean (SD) | 45.2 (11.9) | 45.1 (11.7) | 46.4 (14.2) | 0.23 |
| Gender F, n (%) | 2,149 (83.4%) | 2.047 (85.7%) | 102 (54.0%) | **<0.001** |
| BMI kg/m², mean (SD) | 24.5 (4.0) | 24.6 (4.1) | 24.1 (2.8) | **0.045** |
| Education level (%) | | | | **0.022** |
| Low | 163 (6.7%) | 151 (6.7%) | 12 (6.3%) | |
| Middle | 838 (34.72%) | 790 (35.0%) | 48 (25.4%) | |
| High | 1,447 (59.1%) | 1,318 (58.3%) | 129 (68.3%) | |
| Missing | 130 (5.0%) | 130 (7.6%) | 0 | |
| **Intoxications** | | | | |
| Nicotine, packyears, mean (SD) | 4.8 (9.1) | 4.9 (9.2) | 4.7 (8.3) | 0.84 |
| Alcohol; units/ week, mean (SD) | 3.1 (4.4) | 2.7 (3.8) | 6.9 (7.5) | **<0.001** |
| Caffeine; units/ day, mean (SD) | 5.9 (3.0) | 5.9 (3.0) | 5.6 (2.4) | 0.18 |
| **Other** | | | | |
| PSQI total score, mean (SD) | 6.3 (3.6) | 6.5 (3.6) | 4.2 (2.8) | **<0.001** |
| PSQI ≥6, % | 1,330 (51.6%) | 1,277 (53.5%) | 53 (28.0%) | **<0.001** |
| HADS-D, score, mean (SD) | 4.2 (3.6) | 4.3 (3.6) | 2.6 (3.0) | **<0.001** |
| Life-time depression | 1,046 (40.6%) | 1,017 (42.6%) | 29 (15.3%) | **<0.001** |
| Shiftwork ever, n (%) | 764 (29.6%) | 716/2.383 (30.0%) | 48/189 (25.4%) | 0.19 |
| Shiftwork last week, n (%) | 186/756 (24.6%) | 177/716 (24.9%) | 11/48 (22.9%) | 0.77 |
| Shiftwork history, y, mean (SD) | 10.7 (9.5) | 10.8 (9.6) | 8.5 (7.7) | 0.06 |

## Non-respondent data

Non-responder analysis in controls showed higher HADS-D score compared to responders due to one non-responder control who was an outlier with severe depression ($p=0.002$). In migraine patients, responders were slightly older ($p<0.001$), had a higher BMI ($p=0.03$), without differences in HADS-D scores ($p=0.09$) compared to non-responder migraineurs (data not shown).

## Chronotypes in migraineurs and controls

### *Self-reported chronotypes*

Chronotypes were distributed differently between groups (unadjusted proportions; $p<0.001$). Early chronotypes were more common in the migraine group (unadjusted: 1,167/2,387, 48.9% vs. 73/189, 38.6%), controls were more often normal chronotypes (44/189, 23.3% vs. 319/2.387, 13.4%). Late chronotypes did not differ (unadjusted: 901/2,387, 37.7%;

vs. 72/189, 38.1%). The adjusted odds ratio (OR) for a migraineur (vs. non-headache control) to have an early chronotype vs. a normal chronotype was 2.42 (95% C.I.: 1.58-3.69), and the OR for having a late vs. normal chronotype was 1.69 (95% C.I.: 1.10-2.61) (e-Table 1). In the overall model, there were significant effects of age ($p$<0.001), PSQI score ($p$=0.03) and HADS-D score ($p$=0.008), but not for gender ($p$=0.36) or shift work in the previous week ($p$=0.58). Sleep quality and HADS depression score were different between groups ($p$<0.05), but did not alter the difference between migraineurs and controls significantly.

*Self-reported chronotypes in migraine subtypes*

Earlier chronotypes were overrepresented in both migraine with aura and migraine without aura ($\chi$2-square test; $p$=0.002; $p$=0.01) vs. the non headache controls. Multinomial regression showed that both migraine subgroups were more likely to have both early and late chronotypes vs. the non headache controls (e-Table 1).

*Timing of mid sleep on free days corrected for sleep-debt (MSFc)*

MSFsc was not different between migraineurs and controls (mean ± SD): 3:39±0:58 vs. 3:43±0:59, adjusted for age and gender $p$=0.33 (e-Table 2).

## Amplitude and stability of the circadian rhythm

*Amplitude of the circadian rhythm*

Migraineurs were more languid (more tired after changes in sleep/wake pattern) compared to controls (mean ± SD): 48.9±0.6 vs. 46.1±1.3; $p$<0.001 (age and gender adjusted). Female gender, lower age and higher HADS-D score were correlated with greater languidnesss (higher scores) (Table 2). Higher attack frequency ($p$=0.009), but not migraine subtype ($p$=0.65), was associated with higher scores.

**Table 2. Predictors of higher scores on languid-vigour (LV) and flexible-rigid (FR) subscales in migraineurs and non-headache controls.** Higher score on LV scale reflects more languidness. On the FR scale, higher scores reflects more flexibility whilst lower scores reflect more rigidity. B = regression coefficient; SE = standard error; C.I. – confidence interval; MO = migraine without aura; F = female gender; HADS-D = Hospital Anxiety and Depression Scale, Depression subscale.

| Variable | Languid-vigour | | | | Flexible-rigid | | | |
|---|---|---|---|---|---|---|---|---|
| | B | SE | 95% C.I. | *p* | B | SE | 95% C.I. | *p* |
| **Total group** | | | | | | | | |
| Migraine diagnosis | 2.81 | 0.64 | 1.53 - 4.08 | **<0.001** | -3.00 | 0.51 | -4.00 - -2.00 | **<0.001** |
| Age (year) | -0.22 | 0.01 | -0.25 - -0.19 | **<0.001** | -0.06 | 0.01 | -0.09 - -0.04 | **<0.001** |
| Gender (F) | 2.43 | 0.46 | 1.53 - 3.33 | **<0.001** | -3.38 | 0.36 | -4.10 - -2.68 | **<0.001** |
| BMI (kg/m$^2$) | 0.03 | 0.04 | -0.06 - 0.11 | 0.52 | 0.11 | 0.03 | 0.05 - 0.17 | **0.001** |
| HADS-D score | 0.59 | 0.05 | 0.50 - 0.68 | **<0.001** | -0.36 | 0.04 | -0.43 - -0.29 | **<0.001** |
| **Migraineurs** | | | | | | | | |
| MO subtype | -0.17 | 0.36 | -0.87 - 0.54 | 0.65 | 0.46 | 0.28 | -0.09 – 1.00 | 0.10 |
| Attack frequency | 0.46 | 0.17 | 0.12 - 0.80 | **0.009** | -0.76 | 0.13 | -1.02 - -0.50 | **<0.001** |

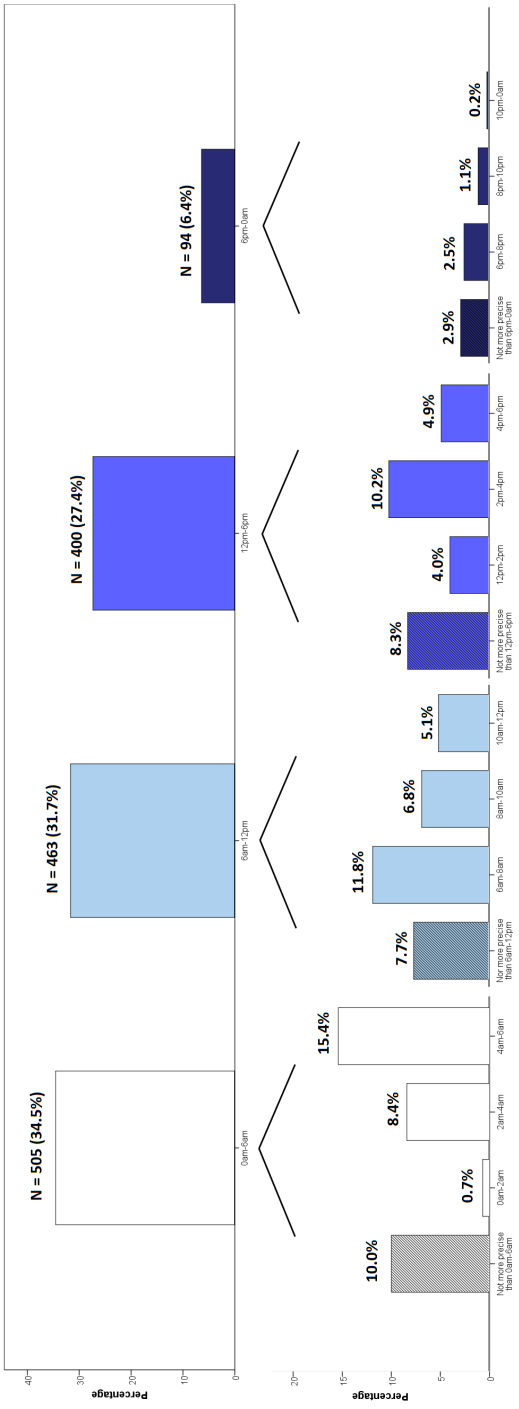


**Figure 1. Distribution of circadian preference periodicity of migraine attack onset in migraine patients.**
The upper panel depicts the timing of clinical onset of migraine attacks in 1,456/2,389 (61.0%) migraineurs who were able to specify the circadian timing of their attacks in 6h intervals. Attack most often began between 4 and 6 am (15.4% of total) or between 6 and 8 a.m (11.8% of total). In the lower panel, specifications into 2h intervals are depicted, with the bars accented in grey showing patients who could not further specify in 2h intervals. Percentages in the lower panel add up to 100%.

*Stability of the circadian rhythm*

Migraineurs were more rigid (less able to cope with changes in sleep/ wake pattern) than controls (reflected by lower scores): 48.0±0.6 vs. 51.0±1.0; $p$<0.001 (age and gender adjusted) (Table 2). Higher age, lower BMI, female gender and higher HADS-D score were associated with more rigidity (lower score). Higher attack frequency was correlated with lower scores ($p$<0.001).

## Circadian timing of attack onset in migraineurs

In total, 1,462/2,389 (61.0%) of migraineurs indicated a specific circadian timing for their migraine attacks, most often between 0.00-6.00 am (505/1,462; 34.5%), and between 6.00-12.00 am (463/1,456; (31.7%)). Out of these, 1,050/1,462 (71.2%) were able to indicate the usual timing of the onset of their attacks in 2h segments: 2.00-4.00 am and 4.00-8.00 am were reported most frequently (together: 399/1,050; 38.0%) (Figure 1).

## Patient chronotype linked to clinical migraine characteristics

Chronotypes were associated with attack time ($\chi$2-test; overall model $p$=0.003 (Figure 2)). Early attacks (0-6am) were most often reported by migraineurs with early chronotypes (57.6%), whereas patients with late chronotypes reported later attacks (12-6pm) more often (post-hoc; $p$<0.001). In patients, earlier circadian attack onset was related to higher age ($p$<0.001) and migraine without aura subtype ($p$=0.008) (using multinomial regression; overall model significance $p$<0.001). Early chronotypes were associated with higher age ($p$<0.001) as well as lower BMI ($p$=0.011), lower HADS-D scores ($p$=0.003), and worse sleep quality ($p$=0.004), compared to late chronotypes. Attack frequency and migraine subtype were not associated with chronotype (e-Table 3).

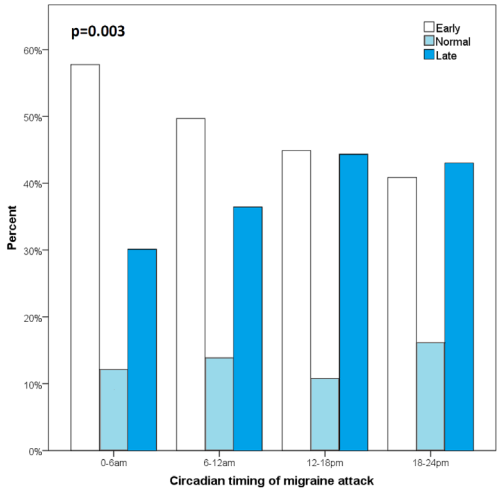


**Figure 2. Chronotype in relation to migraine attack onset.**

Early chronotypes are overrepresented among migraine patients with early attack onset. The proportion of migraine patients with early chronotype declines with advancing circadian attack onset time, whilst the proportion of late chronotypes increases. Normal chronotypes are evenly prevalent amongst subgroups with different attack onset times.

## Discussion

We found that migraineurs are less prone to be of a normal chronotype compared to healthy controls, and that they are less flexible in adapting to changes in the sleep/wake cycle. Migraine attack onset peaks in the early morning and is related to early chronotype. These findings suggest a different setting of the circadian clock in migraineurs and that mechanisms which are involved in the initiation of migraine attacks are linked to chronobiological pathways.

In contrast to two other, smaller studies which reported contrasting results, our study found that both migraine with and without aura patients are less prone to be of a normal chronotype. Gori et al. also reported overrepresentation of both morning and evening type subjects in 100 migraine without aura patients vs. 30 healthy controls[2]. In 93 patients with menstrual migraine, Cevoli et al found no differences in chronotype distribution compared to 85 controls[12]. We found that over 60% of patients reported circadian periodicity of their attacks, and that those migraine attacks showed a predilection for the early morning, mostly in patients with early chronotype. This is in line with earlier smaller studies[1-3]. Fox et al reported that migraine attacks started most frequently between 4-8am, based on 3,598 migraine attacks in 1,698 patients[1]. In a 11-month prospective study with 58 female patients, Alstadhaug et al. found that migraine attacks tended to peak around the middle of the day[3]. Amplitude (languid-vigour) and stability (flexible-rigid) of the circadian rhythm have not been studied before in relation to migraine. Our data show that migraine patients are more languid, indicating that they have more difficulty to overcome the effects of reduced sleep. They also have a more rigid circadian rhythm, i.e. they prefer to sleep and be active at set hours. Both effects are most pronounced among patients with high attack frequency. The effect sizes, however, are small and the exact clinical relevance needs to be further studied.

Our study has several strengths. The study sample is very large and the patients are well characterised. Non-headache controls and patients were recruited in exactly the same way, minimising the risk of inclusion bias. The use of validated instruments for migraine diagnosis and chronotype[5, 14] assured large populations of well characterised migraine patients and healthy subjects and detailed evaluation of circadian rhythmicity. Thirdly, the web-based questionnaire was easy to fill out and send in, resulting in high response rates in both groups.

Some limitations of the study can be addressed. There were some differences between the migraine and control groups. Migraine patients were more often female, had lower education levels and used less alcohol. They showed lower sleep quality and higher depression scores. Ideally, the differences between the migraine and the control groups would have been smaller. To minimize potential bias, the primary analyses were adjusted for the effects of age and gender. As an additional check, additional corrections were performed for the effects of sleep quality and depression. These, however, did not affect the differences between migraineurs and controls. Furthermore, we were not able to include the specific MCTQ shift-work version[18] in this study, since it was published after our data collection period. However, in participants who indicated that they were doing shift-work at the time of filling out the questionnaire, additional questions for each of the possible

shifts separately were included. Unfortunate as the number participant with recent shift work (last week) was very small no useful separate analysis could be made.

Although the number of control subjects in our study was considerably smaller than the number of migraine patients in our study, and smaller than numbers from population based studies, the distribution of chronotypes in the control group is similar to the general population. We believe the smaller size of the control group has hardly affected the statistical power of the study. The number of cases (n = 2,389) was high and the number of controls (n = 189) was still considerable, resulting in post-hoc power of 0.93 to detect the 12% difference in proportion of early chronotypes between both study groups at alpha 0.05. With regard to circadian rhythm amplitude and stability scales, post-hoc power to detect the differences we found was 1.0 (See supplementary text). Increasing the number of controls would have involved disproportionately large and in fact unnecessary efforts leading to only moderate increase in study power.

The subjects within the LUMINA study have partly been self-selected, since registration and participation via the study website was obligatory. The population we invited for participation was highly motivated as was reflected by the high response rates (over 80%). Although we can not rule out a self-selection bias, since both patients and controls have been recruited similarly, we feel this potential bias has affected both groups in a similar way. Since, in the LUMINA cohort, only 4% of subjects were included from our dedicated headache outpatient clinic and 87% of participants have been diagnosed with migraine previously by a physician, we feel these patients are representative of the migraine population in our country.

Overrepresentation of early chronotypes, early circadian attack onset and high circadian rigidity suggest that migraineurs have a different setting of the endogenous pacemaker in the suprachiasmatic nucleus, the main circadian rhythm initiator. This nucleus has extensive projections to the hypothalamus and the pineal gland and is pivotal in regulating wakefulness, the sleep/wake cycle [24], and various other body rhythms. The suprachiasmatic nucleus has been suggested to play an important role in the pathophysiology of episodic brain disorders such as cluster headache and migraine. It is unknown where, how, and why migraine attacks begin and the hypothalamus might be the site of initiation. Several observations and arguments support this hypothesis. Anatomically, the hypothalamic A11 dopaminergic nucleus facilitates and modulates trigeminovascular nociception [25], the underlying mechanism for headache in migraine. Clinically, hypothalamic involvement is suggested by the nature of the premonitory symptoms which frequently occur several hours to even days before the headache and other features of the migraine attack begin; the circadian rhythmicity of migraine attacks [1,2]; the temporal relationship between fluctuations in female hormone levels (menarche, menstruation, pregnancy and menopause) and onset, recurrence and disappearance of migraine attacks in women, and changes in several other hormones [26]. Altered hypothalamic activation during spontaneous migraine attacks has also been detected in a positron emission tomography study [27]. More recently, a functional imaging study covering three untreated migraine attacks in one patient showed, in addition to hypothalamic activation, altered functional coupling to the trigeminal spinal nuclei prior

to an attack. Functional changes in the hypothalamo-brainstem coupling might be an important driver for attack initiation [28].

Early chronotypes are also overrepresented in depression and epilepsy [29]. These paroxysmal brain disorders show strong bidirectional comorbidity with migraine, suggesting overlapping pathophysiologic mechanism, possibly shared genetic factors [8]. These might predispose to early and late chronotypes and circadian rigidity. This hypothesis is further supported by observations in two rare genetic conditions, in which migraine is associated with marked changes in sleep pattern or biorhythm. First, in familial advanced sleep phase syndrome, a very rare, highly penetrant autosomal disorder caused by a mutation in the casein kinase 1-delta *(CK1-δ)* gene, patients suffer from extreme chronotype shifts leading to advanced sleep onset and offset. Patients in two of these families also have migraine with aura [30]. Second, transgenic mouse models expressing the R192Q *CACNA1A1* mutation that in humans causes familial hemiplegic migraine lack the physiological retardation in circadian adaptation to phase advance shifts (east-bound jetlag) [31].

In conclusion, most migraineurs are early birds and have difficulties in coping with (acute) changes in the sleep/wake cycle. Attack preferentially strike in the early morning. These observations underscore an important role for chronobiological mechanisms in migraine attack initiation.

## Clinical Implications

- Migraine patients are less prone to be of a normal chronotype and they are more languid and more rigid when changes in circadian rhythm occur.
- 60% of migraine patients report diurnal periodicity of headache attacks, of which one third reports attack beginning between midnight and 6 am, and one third between 6 am and noon
- Taken together, these data suggest that chronobiological mechanisms play a role in migraine pathophysiology.

## Acknowledgements

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# Supplementary material

## Supplementary text

### Subject inclusion within the LUMINA study

Both migraine patients and controls were recruited via nationwide public announcement, advertising in lay press and via the research website, and were considered eligible after a two-step inclusion process using validated questionnaires via the especially designed LUMINA website. Additionally, patients from our outpatient headache clinic were invited to participate by a letter. On the website, patients were asked to fill out a screening questionnaire that has been validated previously. Firstly, if patients fulfilled the screening criteria, they were sent a web-based extended migraine questionnaire, based on the ICHD-II criteria [14, 15]. This questionnaire was validated before by performing a semi-structured telephone interview in 1,038 patients who had filled out the extended migraine questionnaire [14]. The specificity of the questionnaire was 0.95. We consider the cohort a well-defined web-based cohort, with 4% of subjects included from our dedicated headache outpatient clinic, 87% of the participants having been diagnosed as migraineurs previously by a medical doctor. 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 allodynia. Participants without the needed internet skills were able to fill out the questionnaires on paper. Non-headache individuals willing to participate had to pass a screening questionnaire online via the research website. If this screening questionnaire did not show any indication for having migraine, cluster headache, chronic tension type headache or medication overuse headache, individuals were sent a subsequent in depth questionnaire. This second questionnaire again assessed possible headache complaints, together with demographic variables. Only individuals that fulfilled both the criteria of 'non-headache' in the screening and in depth questionnaire were considered eligible controls and were approached for this questionnaire study. Since recruitment of control subjects started at a later point in time and inclusion rate was slower, the number of migraine patients included exceeds the number of controls included in our study.

### Respondents and non-respondents in this study

Eligible subjects (both migraine patients and non-headache controls) within the LUMINA study were sent an invitation to participate in this study into chronotype by e-mail. A reminder was sent twice. Subjects not having participated after two reminders were considered non-respondents. Baseline and demographic data of the non-respondents were available in the LUMINA study.

### Sample size

The control group in our study was considerably smaller than the case group but, we believe, this has hardly affected the statistical power of the study. The number of cases (n = 2,389) was high and the number of controls (n = 189) was still considerable, resulting in a post-hoc power of 0.93 to detect the 13% difference in proportion of early chronotypes between both

study groups at alpha 0.05 (and a post-hoc power of 0.76 to detect a 10% difference). With regard to circadian rhythm amplitude stability, we have a post-hoc power of 100% to detect a difference of 2.0 (amplitude scale) and 3.0 (stability scale) between groups at alpha 0.05. Increasing the number of controls would have involved disproportionately large and in fact unnecessary efforts leading to only moderate increase in study power.

## Supplementary tables

**e-Table 1. Determinants for chronotype distribution in migraineurs and non-headache controls.**

| Variable | Early vs. normal chronotype | | | Late vs. normal chronotype | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% C.I. | *p* | Odds ratio | 95% C.I. | *p* |
| Migraine (vs. controls) | 2.42 | 1.58-3.69 | **<0.001** | 1.69 | 1.10-2.61 | **0.016** |
| Migraine without aura (vs. controls) | 2.14 | 1.37-3.34 | **0.001** | 1.54 | 0.96-2.43 | 0.06 |
| Migraine with aura (vs. controls) | 2.76 | 1.71-4.43 | **<0.001** | 2.01 | 1.23-3.28 | **0.005** |
| Age (year)* | 1.01 | 1.00-1.02 | 0.11 | 0.98 | 0.96-0.99 | **<0.001** |
| Gender (F)* | 0.88 | 0.62-1.19 | 0.37 | 0.98 | 0.70-1.38 | 0.92 |
| PSQI score* | 0.96 | 0.92-0.99 | 0.01 | 0.98 | 0.94-1.01 | 0.19 |
| HADS-Depression score* | 0.99 | 0.95-1.02 | 0.17 | 1.02 | 0.99-1.07 | 0.19 |
| Shift work last week* | 0.88 | 0.55-1.41 | 0.59 | 1.05 | 0.65-1.01 | 0.84 |

F = female gender; C.I. = confidence interval. All analyses were adjusted for age, gender, PSQI and HADS score. Outcome of multinomial regression. * overall model significance was $p<0.001$ (age), $p=0.36$ (gender), $p=0.03$ (PSQI score); $p=0.008$ (HADS Depression score) and $p=0.58$ (shift work last week).

**e-Table 2. Mid sleep and sleep duration in migraineurs and non-headache controls.** Data are depicted for total group and for strata based on age and gender. MSFsc = Mid sleep on free days (clock time), corrected for accumulated sleep debt; SD = standard deviation. Higher age predisposed for earlier MSFsc ($p$<0.001), but gender was not associated ($p$=0.10).

| | Controls | | | | Migraineurs | | | |
|---|---|---|---|---|---|---|---|---|
| | n | *Work days* Ø ± SD | *Free days* Ø ± SD | *MSFsc* Ø ± SD | n | *Work days* Ø ± SD | *Free days* Ø ± SD | *MSFsc* Ø ± SD |
| **Mid sleep time, h:min±SD** | | | | | | | | |
| < 21 years of age | 189 | 3:04±42' | 3:57±69' | 3:43±59' | 2.389 | 3:02±46' | 3:51±68' | 3:39±58' |
| 21-30 years of age | 4 | 3:31±23' | 5:15±74' | 4:48±54' | 12 | 3:51±26' | 5:25±58' | 5:07±63' |
| > 30 years of age | 32 | 3:12±38' | 4:45±77' | 4:18±76' | 285 | 3:17±53' | 4:40±60' | 4:19±61' |
| Women | 153 | 3:01±43' | 3:46±62' | 3:34±52' | 2,092 | 2:59±44' | 3:44±65' | 3:33±55' |
| Men | 102 | 3:04±37' | 4:01±72' | 3:49±63' | 2,047 | 3:03±45' | 3:51±67' | 3:39±57' |
| | 87 | 3:04±47' | 3:53±67' | 3:48±63' | 342 | 2:57±50' | 3:50±66' | 3:39±63' |
| **Sleep duration, h:min±SD** | | | | | | | | |
| < 21years of age | 189 | 7:04±61' | 7:41±83' | | 2.389 | 7:05±69' | 7:36±92' | |
| 21-30 years of age | 4 | 8:14±55' | 9:30±71' | | 12 | 7:48±52' | 8:41±65' | |
| >30 years of age | 32 | 7:20±47' | 8:32±61' | | 285 | 7:31±67' | 8:31±81' | |
| Women | 153 | 6:57±63' | 7:28±82' | | 2,092 | 7:01±69' | 7:28±91' | |
| Men | 102 | 7:18±64' | 7:54±89' | | 2,047 | 7:07±69' | 7:37±93' | |
| | 87 | 6:48±55' | 7:27±64' | | 342 | 6:56±71' | 7:32±86' | |

**e-Table 3. Demographics and clinical characteristics in different chronotypes among migraineurs.** BMI = Body Mass Index; MO = migraine without aura; AF = attack frequency; PSQI = Pittsburgh Sleep Quality Index; HADS-D = Hospital Anxiety and Depression Scale; Depression subscale.

| Variable | Early | Normal | Late | *p* |
|---|---|---|---|---|
| Age y, mean (SD) | 46.9 (11.0) | 46.0 (12.1) | 42.4 (11.9) | **<0.001** |
| BMI, mean (SD) | 24.3 (3.9) | 24.6 (3.9) | 24.9 (4.4) | **0.011** |
| MO, n (%) | 695/1.167 (59.6%) | 203/319(63.6%) | 561/901 (62.3%) | 0.28 |
| AF≤4 / months, n (%) | 1.075/1.167 (92.1%) | 287/319 (90.0%) | 827/901 (91.6%) | 0.47 |
| PSQI, mean (SD) | 6.3 (3.5) | 7.0 (4.1) | 6.6 (3.5) | **0.004** |
| HADS-D, mean (SD) | 4.1 (3.4) | 4.6 (3.8) | 4.6 (3.7) | **0.003** |